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Aciclovir
A Reappraisal of its Antiviral Activity, Pharmacokinetic Properties and Therapeutic Efficacy

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Summary

Synopsis

Aciclovir (acyclovir) is a nucleoside analogue with antiviral activity in vitro *against the herpes simplex viruses (HSV), varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV) and human herpesvirus 6 (HHV-6).*

Topical, oral or intravenous aciclovir is well established in the treatment of ophthalmic, mucocutaneous and other HSV infections, with intravenous aciclovir the accepted treatment of choice in herpes simplex encephalitis. The efficacy of aciclovir is increased with early (preferably during the prodromal period) initiation of treatment but, despite significant clinical benefit, viral latency is not eradicated, and pretreatment frequencies of recurrence usually continue after episodic acute treatment is completed. Intravenous administration has also shown benefit in the treatment of severe complications of HSV infection in pregnancy, and neonatal HSV infections. Recurrence of HSV has been completely prevented or significantly reduced during suppressive therapy with oral aciclovir in immunocompetent patients.

Use of oral aciclovir is effective but controversial in the treatment of otherwise healthy individuals with varicella (chickenpox), and in some countries it has been recommended for use only in cases which may be potentially severe. The development of rash and pain associated with herpes zoster (shingles) is attenuated with oral or intravenous aciclovir therapy, ocular involvement is prevented, and post-herpetic neuralgia appears to be decreased. Similarly, in a few patients with zoster ophthalmicus, oral aciclovir has reduced the frequency and severity of long term ocular complications and post-herpetic neuralgia, and herpes zoster oticus is improved with intravenous aciclovir.

Oral aciclovir has prevented recurrence of HSV genital or orofacial infections during suppressive therapy in > 70% of immunocompetent patients in most clinical trials. Suppression of latent HSV, VZV and CMV infections has been achieved in many immunocompromised patients receiving the oral or intravenous formulations. Aciclovir also appears to offer partial protection from invasive CMV disease in CMV-seropositive bone marrow transplant recipients.

The few comparative trials published have shown aciclovir to be at least as effective as other investigated antivirals in the treatment of HSV infections in immunocompetent patients, and more effective than inosine pranobex in the prophylaxis of genital herpes. Similarly, in isolated clinical trials, oral aciclovir appears as effective as topical idoxuridine and oral brivudine in some parameters in immunocompetent patients with VZV infections, and the intravenous formulation appears at least as effective as oral brivudine and intravenous vidarabine in treating these infections in immunocompromised patients. Investigations of a regimen of aciclovir plus zidovudine in patients with acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC) suggest some advantage for the combination over zidovudine monotherapy in reducing the incidence of opportunistic infections and mortality. However, patient numbers were limited and these preliminary results require substantiation.

Aciclovir is well tolerated. Mild gastrointestinal effects may occur with the oral formulation in a few patients, and acute reversible renal failure and neurotoxicity has been associated with high peak plasma aciclovir concentrations, usually in patients receiving intravenous administration.

Thus, aciclovir in intravenous, oral and to a lesser extent topical formulations retains its secure position as an effective agent in the therapy and prophylaxis of HSV and VZV infections in immunocompetent and immunocompromised patients, with no clear advantages shown for newer agents over aciclovir in limited comparisons. The role of aciclovir in the prevention of CMV infections in immunocompromised patients is also generally accepted, but its use in diseases caused by other herpes viruses such as EBV and HHV-6 has not been supported in clinical investigations to date. Nonetheless, there appears to be potential for further growth in the role of aciclovir if combination regimens become more accepted in the treatment of viral infections, and if its efficacy in reducing opportunistic infections and associated mortality in patients with AIDS or ARC is confirmed.

Antiviral Activity

Aciclovir (acyclovir) selectively inhibits DNA replication of herpes viruses, with low host cell toxicity. The antiviral is preferentially activated in infected cells; initial phosphorylation occurs via viral thymidine kinase, and aciclovir triphosphate (the active derivative obtained from the monophosphate via host cell enzymes) inhibits viral DNA polymerase more readily than the cellular enzyme, thus preventing viral replication. Although Epstein-Barr virus (EBV) appears to have only minimal thymidine kinase activity, EBV DNA polymerase is very susceptible to inhibition by aciclovir triphosphate. Since cytomegalovirus (CMV) does not code for thymidine kinase, and CMV DNA polymerase is poorly inhibited by aciclovir triphosphate formed by cellular enzymes, CMV is less susceptible to aciclovir than are herpes simplex virus (HSV), varicella zoster virus (VZV) and EBV.

In descending order of susceptibility, the viruses against which aciclovir exhibits *in vitro* antiviral activity are HSV-1 and 2, VZV, EBV, human herpesvirus 6 (HHV-6) and CMV. The *in vitro* activity of aciclovir was generally similar to or greater than that of most other antiviral agents tested against HSV and VZV; ganciclovir, idoxuridine and vidarabine are more potent than aciclovir against CMV; ganciclovir and foscarnet appear to be more potent against HHV-6; and aciclovir appears to have greater activity than penciclovir against EBV. Combination of aciclovir with various antiviral compounds has resulted in synergistic or additive antiviral activity *in vitro* against HSV, VZV and CMV. Although part of the latent HSV reservoir is eradicated by aciclovir in ganglionic or tissue cultures and replication is readily interrupted, reversion to latency occurs after several days of exposure.

The *in vivo* activity of aciclovir was demonstrated in animal models of HSV ocular, cutaneous, genital, CNS and neonatal infections. Initiation of aciclovir administration within 24 hours of viral challenge can reduce the establishment of viral latency following primary infection, but eradication of established latent virus has not been achieved. Activity as a prophylactic agent has been demonstrated in rabbits with HSV keratitis. Combination with other antiviral agents, such as vidarabine, ribavirin or ribonucleotide reductase inhibitors, has resulted in synergistic effects against HSV infections in animals.

Most aciclovir-resistant strains of HSV and VZV have mutations in the thymidine kinase gene which result in little or no production of the enzyme. Resistant HSV strains occur infrequently in immunocompetent patients, and reactivation of these strains from latency is rare. However, aciclovir-resistant HSV strains causing clinical disease are becoming increasingly common among the immunocompromised population. Reports of aciclovir-resistant strains of other herpes viruses are comparatively rare.

Pharmacokinetic Profile

The pharmacokinetic disposition of intravenous aciclovir is not affected by dose, duration or frequency of administration. Steady-state plasma aciclovir concentrations in immunocompromised patients

(6.7 to 20.6 mg/L after intravenous doses of 2.5 to 15.0 mg/kg every 8 hours) are similar to those obtained with equivalent single doses. Absorption of oral aciclovir is slow and variable, with a bioavailability of 15 to 30%. There is no systemic absorption of topical aciclovir from the ointment, but 30 to 50% of the drug reaches the basal epidermis in cutaneous infections treated with the cream formulation, and substantial intraocular penetration occurs with the ophthalmic ointment.

Orally or intravenously administered aciclovir is distributed to a wide range of tissues and fluids, crosses the placenta and accumulates in breast milk. Plasma protein binding is 9 to 33%, and is independent of plasma aciclovir concentrations. Drug interactions appear to be scarce. Area under the plasma concentration-time curve values and elimination half-life are increased when aciclovir and probenecid are coadministered.

The main metabolite, 9-carboxymethoxymethyl guanine, accounts for about 14% of a dose and is pharmacologically inactive. Since the main route of elimination is via renal excretion, kidney dysfunction affects plasma concentrations, extent of metabolism and rate of elimination of the drug. The elimination half-life in adults with normal renal function is 2 to 3 hours, extending to about 20 hours in patients with end-stage renal failure. The half-life in dialysis patients is 6 to 10 hours, but is prolonged to 13 to 18 hours during continuous ambulatory peritoneal dialysis. In neonates, total body clearance is reduced and elimination half-life is increased to up to 5 hours.

Therapeutic Efficacy

In Immunocompetent Patients

Double-blind placebo-controlled studies in immunocompetent patients have demonstrated the efficacy of intravenous (5 mg/kg 3 times daily), oral (200mg 5 times daily) and topical (applied 4 to 6 times daily) aciclovir initiated within 4 days of the first symptoms of HSV perigenital infection. The duration of viral shedding and time to complete healing of lesions are significantly reduced, particularly in the primary episode. Topical aciclovir is less effective in ameliorating symptoms than are the other formulations. Comparison of topical aciclovir and intramuscular interferon-α has demonstrated no significant differences in the treatment of primary genital herpes infection, with a trend in favour of aciclovir in parameters involving time to healing, pain, and viral response. The rate of recurrence of infection is not affected by initial treatment with aciclovir.

Most well-controlled trials have shown complete suppression of genital herpes recurrence in 71 to 88% of immunocompetent patients, using prophylaxis with oral aciclovir 800 to 1000 mg/day for up to 2 years. Pretreatment recurrence rates returned on discontinuation of aciclovir. Complete suppression of recurrence for 5 years has been achieved in 20% of patients on aciclovir prophylaxis (800 to 1600 mg/day). Two well-controlled trials have demonstrated a clear advantage for oral aciclovir over oral inosine pranobex in the suppression of recurrent genital HSV infection.

Oral aciclovir therapy causes significant improvements in recurrent orofacial and cutaneous infections if begun as early as possible after reactivation. Prophylaxis with topical, and especially oral, aciclovir reduces the severity and frequency of orofacial and cutaneous HSV recurrence during treatment. Reductions in symptoms are small with topical treatment of recurrent orofacial herpes in immunocompetent patients.

Aciclovir 3% ophthalmic ointment 5 times daily eliminates 95 to 100% of herpetic dendritic corneal ulcers in 5 to 9 days, and is at least as effective as idoxuridine 0.5 and 1.0%, trifluridine 2% and vidarabine 3% ointments. The ophthalmic ointment is also as effective as vidarabine in treating geographic corneal ulcers. Combination of aciclovir with topical interferon-α shortens the time to healing of superficial herpetic keratitis by several days compared with aciclovir alone. Oral administration of aciclovir appears to be equivalent or superior to topical administration in the treatment of herpetic disciform keratitis. Addition of topical corticosteroids to the ophthalmic ointment has proved effective in treating herpetic disciform keratitis and necrotising stromal keratitis unresponsive to single agent therapy.

Aciclovir ophthalmic ointment is as effective as vidarabine ophthalmic ointment in herpetic disciform keratitis and trifluridine ophthalmic solution in herpetic kerato-uveitis, when corticosteroids are included in the regimens. However, corticosteroids may not be necessary in patients

with HSV uveitis previously untreated with corticosteroids if oral aciclovir is added to topical aciclovir therapy. Prophylaxis with oral aciclovir 800 to 1000 mg/day for 12 to 15 months completely prevented HSV keratitis recurrence in all patients undergoing penetrating keratoplasty, compared with a recurrence rate of 44% in an untreated group.

The treatment of choice for HSV encephalitis, intravenous aciclovir 10 mg/kg every 8 hours for at least 10 days, improves survival rates and reduces the incidence of serious sequelae to infection. Addition of interferon-β to the regimen provided no advantage in most patients. A placebo-controlled trial of oral aciclovir prophylaxis (800 mg/day for 26 weeks) in HSV erythema multiforme has substantiated previous reports of efficacy. Case studies have reported successful intravenous aciclovir treatment and prophylaxis in patients with HSV meningitis, and successful treatment of HSV-associated encephalitis, disseminated infection and hepatitis in pregnant women, followed by survival of mothers and infants without complications. Intravenous aciclovir and vidarabine appear equally effective in the treatment of neonatal HSV infections including mucocutaneous infection, encephalitis and disseminated disease.

There is some controversy over the role of aciclovir in treating varicella (chickenpox) in otherwise healthy individuals, since the disease is usually self-limiting. Nonetheless, oral aciclovir initiated within 24 hours of the appearance of the rash associated with varicella (chickenpox) has resulted in decreased numbers of lesions, duration of new lesion formation, severity or duration of pruritus, time to healing and duration of fever in otherwise healthy children, adolescents and adults in several well-designed studies. Clinical improvement has been noted in a few adults with varicella pneumonia receiving intravenous aciclovir, and maternal mortality rates associated with this complication have been decreased during pregnancy.

In patients with herpes zoster (shingles), intravenous (5 mg/kg every 8 hours for at least 5 days) or oral (4000 mg/day for 7 days) aciclovir treatment begun within 72 hours of exanthem onset attenuates the development of rash and pain, offers protection against ocular involvement and appears to decrease the duration of post-herpetic neuralgia. Topical idoxuridine was superior to oral aciclovir in some parameters in one double-blind study, but efficacy was similar in time to disappearance of papulopustules, appearance of first scabs, loss of all scabs, and disappearance of erythema or pain. Oral brivudine was associated with significantly greater reductions in pain and new lesion formation compared with intravenous aciclovir in elderly cancer patients with severe herpes zoster, but there were no differences in time to loss of vesicles or time to full crusting.

Although the immediate efficacy of aciclovir ophthalmic ointment in the treatment of zoster ophthalmicus is equivocal, oral aciclovir begun within 72 hours of skin eruption produces significant reductions in the longer term (up to 12 months) in frequency and severity of ocular complications such as dentriform keratopathy, stromal keratitis and anterior uveitis in these patients.

Case reports and one small placebo-controlled trial have demonstrated rapid improvement of facial function grade in patients with herpes zoster oticus treated with intravenous aciclovir, and success is also reported in isolated cases of patients with herpes zoster-associated encephalitis, myelitis, idiopathic vocal cord paralysis and Rosai Dorfman disease. Recurrence of severe almost constant aphthae has been prevented or decreased with oral aciclovir 1600 mg/day for 10 weeks.

Although trends towards faster improvement have been recorded in 2 double-blind trials of aciclovir versus placebo in patients with infectious mononucleosis, no statistically significant differences were seen. Addition of aciclovir to interferon-α therapy in patients with chronic hepatitis B appears to offer some advantages over monotherapy, but no significant differences in the rate of seroconversion were demonstrated. Aciclovir has prevented postsurgical recurrence of laryngeal papillomatosis in 3 children and improved symptoms of epilepsia partialis continua in 4 patients.

In Immunocompromised Patients

The efficacy of intravenous (250 mg/m^2 every 8 hours) or oral (2000 mg/day) aciclovir is well established in the treatment of immunocompromised patients with HSV infections. Severe infections refractory to normal dosages of aciclovir (such as HSV hepatitis, or infections caused by viruses deficient in thymidine kinase activity) may respond to higher dosages, as demonstrated in case reports. Topical administration (5% in polyethylene glycol) reduced the period of viral shed-

ding in renal transplant recipients, but the value of topical aciclovir is limited in severely immunocompromised patients.

Viral shedding and/or scabbing time, deterioration in clinical condition and progression of the disease are reduced in immunocompromised patients with VZV infections treated with intravenous aciclovir (500 mg/m^2 every 8 hours for 5 to 8 days). In this setting aciclovir appears as effective as oral brivudine and at least as effective as intravenous vidarabine. Oral aciclovir is also effective in promoting healing and preventing dissemination of varicella in immunocompromised patients, and topical aciclovir reduced time to pustulation, crusting and healing in immunocompromised patients with localised herpes zoster.

Virtually complete suppression of latent HSV or VZV infections during intravenous or oral aciclovir prophylaxis has been demonstrated in most patients at increased risk of recurrence because of bone marrow transplantation, radiotherapy or cytotoxic chemotherapy, while up to 50% of infections which did recur involved asymptomatic viral shedding only. While protection was confined to the period of therapy in most patients, there is evidence that long term prophylaxis may also result in a reduction in the rate of HSV infections, compared to that seen in placebo recipients, after discontinuation of therapy. Oral aciclovir prophylaxis has provided protection against HSV and VZV infections in patients receiving renal transplants, and against HSV infections in liver and heart transplant recipients, with complete suppression of clinical symptoms during treatment in most patients. The incidence of HSV infection was also reduced in renal and heart transplant patients for up to 12 months following withdrawal of aciclovir prophylaxis.

High dose oral or continuous infusion of intravenous aciclovir have resulted in resolution of EBV infections such as oral hairy leucoplakia in immunocompromised patients, but reactivation of latent infection occurs frequently on discontinuation of the drug. Similarly, although aciclovir treatment of symptomatic CMV infection in immunocompromised patients has generally resulted in little clinical improvement, continuous infusion has resolved the infection in isolated cases.

Aciclovir prophylaxis appears to decrease CMV shedding, and reduce the incidence of clinically evident and invasive CMV disease, and possibly that of associated mortality, in immunocompromised patients with haematological disorders, despite decreased activity compared with prophylaxis against HSV and VZV. The rate of CMV infection after treatment was decreased in some patients. The incidence of CMV infection was reduced by about half (to 36%) during 1 year of observation after a 12-week course of oral aciclovir prophylaxis (800 to 3200 mg/day) in a double-blind trial in renal transplant recipients, and by half to two-thirds (to 18.3 to 30.8%) in liver transplant recipients after a 12-week course of oral aciclovir (2000 to 3200 mg/day) in several trials. Oral aciclovir plus CMV-specific immunoglobulin prophylaxis appears to offer some advantage in preventing CMV infection in patients receiving heart or lung transplants but controlled double-blind trials have not been performed in this patient population.

The effects of aciclovir alone or combined with zidovudine on laboratory measures of human immunodeficiency virus infection are equivocal, but recent double-blind studies have suggested that combined therapy may offer an advantage over zidovudine monotherapy in terms of survival and incidence of opportunistic infections in patients with acquired immunodeficiency syndrome (AIDS) or AIDS-related complex.

Tolerability

Aciclovir is well tolerated whether administered by ocular, topical, oral or intravenous routes. Adverse reactions to topical preparations have been mainly limited to mild local effects. The incidence of most adverse events, such as gastrointestinal symptoms, rash and headache, occurring during oral aciclovir therapy is similar to that seen in patients receiving placebo. There have been occasional reports of acute, usually reversible, renal failure and neurotoxicity associated with the oral formulation, but these occur more often with intravenous administration, usually in patients with high peak plasma aciclovir concentrations. Slow infusion rates, adequate hydration and lower dosages of aciclovir are recommended in patients with renal dysfunction. The effects of aciclovir on immune function have not yet been clarified. Depression of the immune response to herpesvirus antigens associated with oral and intravenous aciclovir treatment or prophylaxis in some studies is postulated to be a result of viral inhibition rather than a direct immunosuppressant effect.

Dosage and Administration

Therapy with aciclovir should be initiated as soon as possible after the onset of signs or symptoms. For dosage recommendations in specific herpesvirus infections see table XI on page 192. Dosage reductions proportional to the degree of impairment are necessary in patients with moderate to severe renal dysfunction.

Aciclovir (acyclovir) is an acyclic analogue of the natural nucleoside 2′-deoxyguanosine (fig. 1) with antiviral activity against herpes DNA viruses. The pharmacology and therapeutic efficacy of this agent were first reviewed in the Journal by Richards et al. (1983) and subsequently re-evaluated by O'Brien and Campoli-Richards (1989). This review re-examines the role of aciclovir in the treatment and prevention of herpesvirus and other viral infections in both immunologically competent and immunologically compromised patients in the light of recently published literature.

1. Antiviral Activity

The antiviral activity of aciclovir has been discussed in depth in the two previous reviews in the Journal (Richards et al. 1983; O'Brien & Campoli-Richards 1989) and the reader is referred to these for further details. This section provides an overview of the previous findings and evaluates data published since the last review.

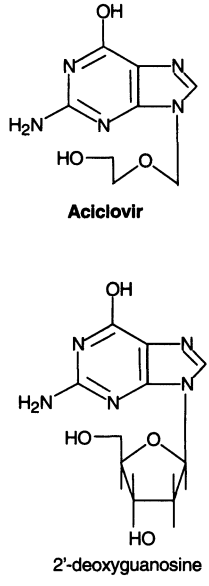

Fig. 1. Chemical structure of aciclovir and 2′-deoxyguanosine.

Aciclovir selectively inhibits DNA replication of herpes viruses (fig. 2) with low host cell toxicity. Uptake of aciclovir is enhanced in herpesvirus-infected cells, and phosphorylation of the drug to aciclovir monophosphate occurs via herpesvirus-coded thymidine kinase. Subsequent conversion to the active metabolite, aciclovir triphosphate, is catalysed by host cell enzymes. Aciclovir triphosphate functions as a substrate for and preferential inhibitor of viral, rather than cellular, DNA polymerase. It binds to herpes simplex virus (HSV) DNA polymerase in competition with the natural nucleoside, is incorporated into viral DNA, and prevents further elongation of the chain (see reviews by O'Brien & Campoli-Richards 1989; Reardon & Spector 1991).

Since thymidine kinase-negative HSV mutants and cytomegalovirus (CMV) do not code for thymidine kinase, monophosphorylation of aciclovir does not occur readily in cells infected with these viruses. CMV DNA polymerase has low susceptibility to inhibition by aciclovir triphosphate and the virus subsequently has low susceptibility to aciclovir. Epstein-Barr virus (EBV) may have reduced thymidine kinase activity, but EBV DNA polymerase is susceptible to inhibition by aciclovir triphosphate formed by cellular enzymes, which may account for some of the drug's activity against this virus (Datta & Pagano 1983).

The antiviral spectrum of aciclovir activity was extensively studied in the early stages of it's development. Later investigations have focused on the activity of aciclovir in combination with other antivirals and interferons, and the monitoring of drug

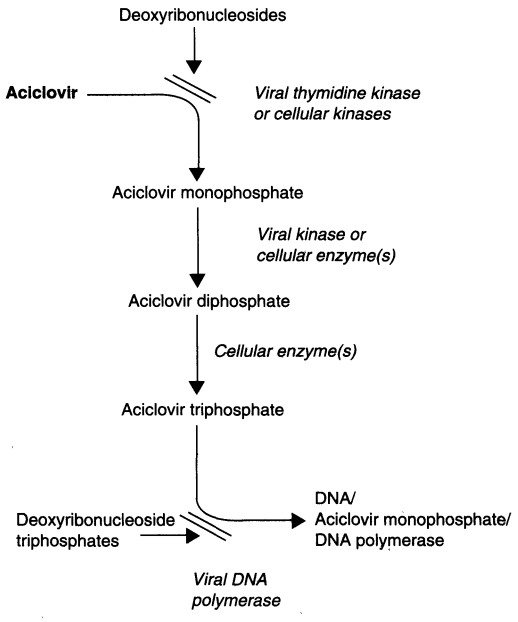

Fig. 2. Aciclovir inhibition of the viral DNA biosynthetic pathway. Aciclovir competes with deoxyribonucleosides for viral thymidine kinase or cellular kinases. In addition to competitively inhibiting the association of deoxyribonucleoside triphosphates with viral DNA polymerase, aciclovir triphosphate incorporates into the growing viral DNA chain, leading to the termination of DNA synthesis because of its lack of a 3'-hydroxyl moiety.

resistance, although some studies continue to report the susceptibility to aciclovir of the less thoroughly investigated herpes viruses.

1.1 Antiviral Activity *In Vitro*

In vitro findings should be interpreted with caution, since information obtained from *in vitro* culture systems does not necessarily correlate with the clinical efficacy or toxicity of an antiviral agent (Richards et al. 1983), and the immune status of the host is not considered in *in vitro* susceptibility testing (Pulliam et al. 1986).

The results of antiviral susceptibility tests vary with the assay method, the substrate cell type and the viral strain employed (O'Brien & Campoli-Richards 1989). Upadhyay et al. (1991) postulated that the rate of viral replication may also affect susceptibility to antiviral chemotherapy. They found that while both aciclovir and trifluridine suppressed *in vitro* HSV-1 viral replication at 36.5°C, only aciclovir continued to suppress replication at a temperature of 26°C, when viral replication and cell metabolism are reduced. This suggests that the antiviral activity of aciclovir is retained in cells with a low metabolic rate in which viral replication is slow, for example in viral corneal stromal disease.

Of the human herpes viruses, herpes simplex types 1 and 2 are the most susceptible to aciclovir in cell culture, followed in descending order of general susceptibility by varicella zoster virus (VZV), EBV, human herpesvirus 6 (HHV-6) and CMV (see table I). The activity of aciclovir is generally similar to or greater than that of most other antiviral agents tested against HSV and VZV, greater than that of penciclovir against EBV, less than that of ganciclovir, idoxuridine and vidarabine against CMV and less than that of ganciclovir and foscarnet against HHV-6 (table I).

Aciclovir does not appear to exhibit *in vitro* antiviral activity against viruses outside the herpes group. Hepatitis B virus replication may be inhibited by aciclovir, but *in vitro* information is limited to one study showing decreasing viral polymerase activity with increasing aciclovir concentration (0.5 to 150 mg/L; Galle & Theilmann 1990).

The effects of subinhibitory doses of aciclovir on HSV and VZV were investigated *in vitro* by Shiraki et al. (1989), who found that aciclovir enhanced plaque formation without compromising inhibition at higher doses.

1.1.1 Activity of Aciclovir Combined with Other Antivirals

It is postulated that combination therapy employing aciclovir and other selective antiviral agents will achieve inhibition of infectivity and replication of some viruses at concentrations better tolerated and more easily attained *in vivo*, and should also reduce the incidence of emergent resis-

Table I. Summary of *in vitro* antiviral activity of aciclovir

Virus	IC_{50}a (mg/L)	Comparative activity								Reference
		brivudine	FIAC	foscarnet	ganciclovir	idoxuridine	interferon-α	penciclovir	vidarabine	
HSV-1	0.01-2.7	=	−/=	+	−/=	+	+	+/=	+	4,5,7,9,10,11,12, 14,15
HSV-2	0.01-4.4	+	+/=	+	−/=	+	+	+/=	+	4,5,9,10,11,12, 14,15
VZV	0.17-26	−		+	+	=		=	+/=	9,11,12,14
EBV	1.5-8.8							+		9,12
HHV-6	3-25			−	−					1,2,6,13
CMV	1.82-68			+	−	−		+	−	3,8,9,11,12

a Concentration of aciclovir inhibiting viral-induced cytopathogenicity or viral plaques by 50%.

Abbreviations and symbols: CMV = cytomegalovirus; EBV = Epstein-Barr virus; FIAC = 2′-fluoro-5-iodoarabinosylcytosine; HHV-6 = human herpesvirus-6; HSV = herpes simplex virus; VZV = varicella zoster virus; + indicates antiviral activity of aciclovir greater than that of comparative antiviral; − indicates antiviral activity of aciclovir less than that of comparative antiviral; = indicates antiviral activity of aciclovir similar to that of comparative antiviral.

Reference key: 1 Agut et al. (1989, 1991); 2 Åkesson-Johansson et al. (1990); 3 Andrei et al. (1991); 4 Boivin et al. (1993); 5 Brisebois et al. (1989); 6 Burns & Sandford (1990); 7 Charles & Gray (1990); 8 Fletcher et al. (1991); 9 Littler et al. (1993); 10 Menage et al. (1990); 11 O'Brien & Campoli-Richards (1989); 12 Richards et al. (1983); 13 Russler et al. (1989); 14 Vere Hodge (1993); 15 Weinberg et al. (1992).

tant viral strains (O'Brien & Campoli-Richards 1989).

Combination of aciclovir with other antiviral agents has resulted in additive or synergistic antiviral activity against HSV, VZV and CMV (table II). It has been hypothesised that interferon-mediated alterations of nucleoside metabolism in virus-infected cells may be involved in the synergistic action between aciclovir and the interferons (O'Brien et al. 1990). Interferon treatment of HSV-infected cells resulted in decreased concentrations of the natural nucleoside thymidine, and of all deoxyribonucleoside 5′-triphosphates, particularly deoxyguanosine triphosphate (dGTP). Since aciclovir triphosphate competes with dGTP in the production of viral DNA, an increase in the aciclovir triphosphate : dGTP ratio would be expected to contribute to the antiviral synergy.

Virus-specific ribonucleotide reductase inhibitors may be useful in combination with aciclovir. A 2-acetylpyridine thiosemicarbazone inhibitor of ribonucleotide reductase (A723U) has been shown to potentiate the antiviral activity of aciclovir against HSV (Karlsson & Harmenberg 1988) and a 2-acetylpyridine thiocarbonohydrazone (348U87) produced synergistic inhibition of VZV with aciclovir (Spector 1993; table II). As with interferon, it has been suggested that virus-encoded ribonucleotide reductase inhibitors decrease the size of the dGTP pool against which aciclovir triphosphate competes as substrate for viral DNA polymerase, but inhibitors of ribonucleotide reductase also increase the concentrations of aciclovir triphosphate in herpesvirus-infected cells, thus increasing the aciclovir triphosphate : dGTP ratio further (Reardon & Spector 1991). Support for potential synergy is also provided by the finding that HSV mutants defective in ribonucleotide reductase activity are hypersensitive to aciclovir (Coen et al. 1989).

1.1.2 Effects on Latent Infection

Replication of HSV in ganglion explant or tissue culture is readily interrupted during incubation with aciclovir; reversion to latency is noted after several days of exposure to the drug. Aciclovir appears to eradicate only part of the latent viral reservoir, as assessed by the reactivation rate after

Table II. Antiviral agents causing synergistic or additive antiviral activity *in vitro* in combination with aciclovir (references are encoded in parentheses)

Virus	Synergy	Additive activity
HSV	Acemannan (7) A 723U (8) Chlorhexidine (11) Interferon-α (1,5,6,10,23) Interferon-β (9,21) Interferons, cloned α-hybrid (3) Ribavirin (12,15) Vidarabine (4)	Brivudine (13) Interferon-α (6) Penciclovir (22) Trifluridine (13) Vidarabine (13,14)
VZV	348U87 (20) Interferon-α (1,10)	Brivudine (2) Idoxuridine (2) Trifluridine (2)
CMV	GS-504 (17) Interferon-α (16) Trifluridine (16)	Interferon-α (10) Interferon-β (18) Trifluridine (18) Vidarabine (19)

Abbreviations: CMV = cytomegalovirus; HSV = herpes simplex virus; VZV = varicella zoster virus.

Reference key: 1 Baba et al. (1984); 2 Biron & Elion (1982); 3 Crane & Milne (1985); 4 Crane et al. (1984); 5 Hammer et al. (1982); 6 Hanada et al. (1989); 7 Kahlon et al. (1991); 8 Karlsson & Harmenberg (1988); 9 Kawaguchi et al. (1986); 10 Levin & Leary (1981); 11 Park et al. (1991); 12 Pancheva (1991); 13 Schinazi & Nahwias (1982); 14 Schinazi et al. (1982); 15 Shishkov & Pancheva (1990); 16 Smith et al. (1983); 17 Snoeck et al. (1992); 18 Spector et al. (1982b); 19 Spector & Kelly (1985); 20 Spector (1993); 21 Stanwick et al. (1981); 22 Sutton et al. (1992); 23 Taylor et al. (1989).

drug removal. Alternate exposure of ganglion explants to aciclovir-containing and drug-free media has been associated with statistically significant reductions in the proportion of reactive virus, dependent on the frequency and duration of alternating exposures and the number of latently infected neurons present (see review by O'Brien & Campoli-Richards 1989).

1.2 Antiviral Activity *In Vivo*

1.2.1 Animal Models

Since animal models of herpesvirus infections other than HSV are mostly of limited use as predictors of clinical efficacy in humans (Collins 1983), this discussion is largely restricted to herpes simplex models. The *in vivo* antiviral efficacy of aciclovir against HSV-1 and 2 has been summarised by O'Brien and Campoli-Richards (1989). Efficacy has been demonstrated in animal models of ocular, cutaneous, genital, CNS and neonatal infections. The efficacy of aciclovir was influenced by factors such as animal species, size of viral inoculum, drug dosage, route and frequency of administration, and rapidity of initiation of therapy following viral inoculation.

Initiation of topical or systemic aciclovir within 24 hours of viral challenge has prevented the establishment of viral latency following primary infection, and reductions in the number of reactive latent herpes simplex foci have been observed with aciclovir treatment in some studies, but eradication of established latent virus from neuronal ganglia has not been achieved.

Aciclovir appears to be generally at least as effective as other nucleoside analogues *in vivo*, although some compounds such as the 2′-fluoropyrimidines and 5′-vinylpyrimidines may offer greater protection in certain models (see review by O'Brien & Campoli-Richards 1989). Oral aciclovir and oral penciclovir had similar antiviral activity in mice infected with HSV (Sutton & Boyd 1993) and in other animal models of HSV infection (Littler et al. 1993), but penciclovir was more active when given in discrete subcutaneous doses (Sutton & Boyd 1993). Aciclovir has also been shown to be effective as a prophylactic agent *in vivo*, preventing the re-emergence of postoperative herpes simplex type 1 keratitis in rabbits after penetrating keratoplasty (Beyer et al. 1989).

Combination of aciclovir with antiviral agents such as vidarabine, 2′-fluoro-5-methylarabinosylcytosine (FIAC), and 2′-fluoro-5-methylarabinosyluracil (FMAU), has resulted in marked synergistic effects against herpes simplex encephalitis in the mouse model (Schinazi et al. 1986) and ribavirin potentiated the antiviral effects of aciclovir in a herpes simplex keratitis model in rabbits (Pancheva 1991). Similarly, the addition of immunotherapy with human immune globulin to aciclovir treatment soon after infection in mice re-

sulted in synergistic antiviral effects, presumably reflecting the importance of cellular immunity in the control of HSV infections (Hilfenhaus et al. 1987). However, the combination of aciclovir and recombinant interferon-α was associated with toxicity in newborn or weanling mice (Connell et al. 1985; Crane & Sunstrum 1988).

Confirming *in vitro* findings (section 1.1.1), synergistic activity has been demonstrated *in vivo* for aciclovir plus inhibitors of HSV ribonucleotide reductase in cutaneous murine infections caused by both aciclovir-susceptible and aciclovir-resistant strains of HSV (Ellis et al. 1989; Lobe et al. 1991; Spector et al. 1992).

A model employing VZV adapted to cells in congenitally hairless guinea pigs has been used to demonstrate the amelioration of exanthem by subcutaneous aciclovir (Myers & Stanberry 1991).

High dose oral aciclovir (700 mg/kg/day) was effective in preventing B virus (herpesvirus simiae) disease in infected rabbits, and a similar regimen has been suggested for prophylaxis when humans are occupationally exposed to this potentially fatal infection (Zwartouw et al. 1989).

1.2.2 In Humans

Asymptomatic shedding of HSV during aciclovir prophylaxis has been recorded (Straus et al. 1989). The rate of symptomatic shedding was decreased from 95 to 6 positive cultures per 1000 cultures during treatment, but the rate of asymptomatic shedding remained constant at an average of 8 per 1000 cultures. A relatively high rate of asymptomatic viral shedding (7 of 48 patients) was seen in a study of aciclovir 800 mg/day as prophylaxis for recurrent genital herpes (Bowman et al. 1990). However, noncompliance may have triggered the episodes in question, and further well designed trials are required to determine the effect of various aciclovir dosages on this parameter.

Measurement of the *in vivo* survival time of EBV-infected cells in long term virus carriers with no history of immune deficiency demonstrated that viral shedding in the oropharynx was inhibited by aciclovir treatment (800mg 5 times daily for 28 days) and returned on withdrawal of the drug, but the incidence of virus-infected B cells in the blood remained constant (Yao et al. 1989). The level of virus carriage in the blood was thus presumed to be maintained for at least 4 weeks despite inhibition of virus replication in the oropharynx with aciclovir.

1.3 Viral Resistance to Aciclovir

Aciclovir-resistant strains of HSV and VZV arise chiefly from the selection of variants with altered thymidine kinase, and are readily produced *in vitro*. Resistance can occur through deletion of the viral thymidine kinase gene, alteration of viral thymidine kinase resulting in less efficient phosphorylation of aciclovir, or alteration of viral DNA polymerase resulting in decreased inhibition by aciclovir triphosphate. Clinically, aciclovir-resistant strains are most commonly reported in severely immunocompromised patients receiving extended courses of the drug, and most are thymidine kinase negative. Loss of viral thymidine kinase gene expression has been associated with a decrease in virulence and ability to reactivate from latent infections in animal models and man. However, mutants which retain the thymidine kinase phenotype appear also to retain varying degrees of virulence (O'Brien & Campoli-Richards 1989). This has been corroborated in 2 surveys of the emergence of resistant HSV isolates over a period of 15 years (Collins & Ellis 1993b). Thymidine kinase-negative isolates were avirulent and failed to reactivate from latent infection, while the more limited number of isolates with variations in DNA polymerase or altered thymidine kinase showed only slight attenuation of virulence and continued to reactivate from latency.

The emergence of resistant HSV strains after prolonged treatment with aciclovir appears to be infrequent in immunocompetent patients (O'Brien & Campoli-Richards 1989). Hill et al. (1993) reported an incidence of aciclovir-resistant HSV in immunocompetent patients of 6.3% (8 of 127), while Ketchum et al. (1991) [who developed a rapid screening method for detecting the presence

of thymidine kinase activity in HSV infected cells] reported an incidence of 2.9% (1 of 34) and Collins and Ellis (1993a) 0.7% (2 of 287). When recurrences occur they are almost always resolved on administration of therapeutic or increased dosage of aciclovir, consistent with the failure of thymidine kinase-deficient viruses to reactivate from latency (Boivin et al. 1993; Charles & Gray 1990; Englund et al. 1990b; Kroon et al. 1989; Rabalais et al. 1989).

The degree of immunosuppression in patients infected with HSV will influence the degree of inhibition of viral replication by host factors and may thus influence the degree of development of resistance to aciclovir. In studies by Englund et al. (1990b) and Gray et al. (1989), resistant HSV strains occurred in 4.7 to 5.7% of patients who were severely immunocompromised (as a result of treatment for malignancy, rejection following organ transplantation or infection with human immunodeficiency virus [HIV]) and none of those less severely affected or immunocompetent. However, in a survey in the United Kingdom, Collins and Ellis (1993a) found that of 81 severely immunocompromised patients studied because of poor response to aciclovir, 18 (22.2%) developed resistant isolates, compared with 0.7% of 287 immunocompetent patients.

Case reports of the development of clinically aggressive aciclovir-resistant HSV strains in immunocompromised patients receiving aciclovir therapy are becoming increasingly common (Bevilacqua et al. 1991; Birch et al. 1990; Erlich et al. 1989; Gateley et al. 1990; Gray et al. 1989; Ljungman et al. 1990; Marrero et al. 1991; Sacks et al. 1989).

In a retrospective incidence cohort study by Englund et al. (1990b), progressive clinical disease, more severe in children, was reported in all 7 immunocompromised patients seen over 1 year who had aciclovir-resistant viral strains (4.7% of the total number of immunocompromised patients). All patients had received previous aciclovir therapy. Similarly, in a 2-year survey monitoring the occurrence and characterisation of aciclovir-resistant HSV isolates, 12 of 785 patients screened (1.5%) had resistant strains (Nugier et al. 1992). Of these 12 patients (all of whom had received aciclovir therapy), 10 were immunocompromised (5.4% of the total number of immunocompromised patients) and 5 (one of whom was immunocompetent) had clinically significant disease associated with the resistant strains.

The development of viral host cell resistance to aciclovir during long term exposure may also be a factor in the failure of HSV infection to respond to treatment. Cinatl et al. (1992) established a culture of monkey kidney cells able to survive in 45 mg/L aciclovir. Aciclovir doses required to reduce HSV yield were 5 to 50 times larger than those required for similar reductions of HSV in nonresistant host cells.

Reports of aciclovir-resistant strains of other herpes viruses are relatively rare. Recently, 2 groups of investigators have recorded the emergence of aciclovir-resistant VZV in 5 patients with acquired immunodeficiency syndrome (AIDS) after long term treatment with the drug (Jacobson et al. 1990; Linnemann et al. 1990). The virus was initially susceptible to intravenous or oral aciclovir in all patients, but persistent lesions developed despite administration of suppressive oral aciclovir dosages of 400 to 4000 mg/day. The resistant viruses were deficient in thymidine kinase activity. Conversely, although aciclovir-resistant strains of CMV exist, prophylactic high dosage (3.2 g/day) oral aciclovir for 3 months did not induce resistant CMV in 53 renal allograft patients (Fletcher et al. 1991).

2. Pharmacokinetic Profile

This overview of the pharmacokinetic properties of aciclovir draws upon previous reviews (O'Brien & Campoli-Richards 1989; Richards et al. 1983), incorporating significant additional information provided by more recent studies. Table III summarises the results of pharmacokinetic investigations.

The pharmacokinetics of intravenously administered aciclovir are best described by a 2-compart-

ment open model (de Miranda & Blum 1983). The pharmacokinetic disposition of the drug is not affected by dose, duration or frequency of administration. Mean plasma aciclovir concentrations at steady state (6.7 to 20.6 mg/L) after intravenous administration to immunocompromised patients (2.5 to 15 mg/kg every 8 hours) are similar to the peak plasma concentrations obtained with equivalent single doses (Whitley et al. 1982b).

Absorption of oral aciclovir across the small intestine appears to be passive (Tanna et al. 1992) and is incomplete, resulting in 15 to 30% bioavailability and mean peak plasma concentrations (C_{max}) 1.5 to 2.5 hours post dose (table III). Transcutaneous penetration of aciclovir in topical preparations varies with the formulation used, and has been improved with the addition of skin penetration enhancing agents (Gonsho et al. 1990; Loftsson et al. 1989; Park et al. 1992). However, delivery of the drug to the basal epidermis (the site of HSV infections) after topical application was 30 to 50% of that achieved with oral administration (Parry et al. 1992), and systemic absorption has not been detected with topical doses of 5% ointment every 4 to 6 hours (table III). Aciclovir ophthalmic ointment significantly penetrates through the intact epithelium of a healthy cornea, whereas trifluorothymidine and vidarabine only achieve useful concentrations in the interior chamber if the cornea is ulcerated (Poirier et al. 1982).

Plasma protein binding occurs in a range of 9 to 33%, irrespective of plasma aciclovir concentration (de Miranda et al. 1982a; data on file, Wellcome Foundation Ltd). Aciclovir appears to be distributed to a wide range of tissues and fluids in humans after oral and intravenous administration (table III). Chavanet et al. (1990a) have suggested that meningeal penetration may be enhanced by the addition of probenecid, which has also been shown to increase the area under the plasma concentration-time curve and prolong the elimination half-life of aciclovir (Laskin et al. 1982a). Although aciclovir appears to accumulate in breast milk, exposure of the nursing child is estimated to be less than 1 mg/day, presenting a low theoretical risk (Meyer et al. 1988). Recent data suggest that transfer of aciclovir through the human placenta occurs passively at a considerably lower rate than that of a fully diffusible marker, phenazone, and that placental aciclovir metabolism does not occur (Henderson et al. 1992).

The elimination half-life ($t_{1/2}$) of aciclovir after intravenous administration is 2 to 3 hours, and the mean total body clearance (CL) 15.6 L/h/1.73m^2 (table III). The main metabolite of aciclovir, 9-carboxymethoxymethyl guanine, is pharmacologically inactive and accounts for up to 14% of an aciclovir dose in recipients with normal renal function. A minor metabolite, 8-hydroxy-9-(2-hydroxyethoxymethyl) guanine, represents less than 0.2% of a dose (Richards et al. 1983). The main route of elimination of aciclovir is via renal excretion, with 45 to 79% of an intravenous dose recovered unchanged in the urine, which decreases with reduced creatinine clearance. In neonates, $t_{1/2}$ is slightly longer (2.5 to 5.0 hours) and CL is about one third of that of an adult with normal renal function (table III). In infants aged ≥1 year, the pharmacokinetics of aciclovir are generally comparable with those of adults (Blum et al. 1982).

As the kidneys are the principal route of aciclovir elimination, renal impairment affects the plasma concentrations, extent of metabolism and rate of elimination of the drug. In patients with end-stage renal failure who are administered aciclovir, mean C_{max} values are nearly doubled, mean $t_{1/2}$ is increased 7-fold to approximately 20 hours, and mean CL is decreased 10-fold compared with patients with normal renal function (Richards et al. 1983).

Aciclovir is readily haemodialysable, with a $t_{1/2}$ in dialysis patients of about 6 to 10 hours (Burgess & Gill 1990; Laskin et al. 1982c). During continuous ambulatory peritoneal dialysis $t_{1/2}$ ranges from 13 to 18 hours (O'Brien & Campoli-Richards 1989; Burgess & Gill 1990), while in a patient undergoing continuous arteriovenous haemofiltration/dialysis it was 19.6 hours (Jones & Alderman 1991).

Table III. Pharmacokinetic profile of aciclovir

Parameter/ medium	Aciclovir route and dosage (duration)	Value	Reference
Absorption			
C_{max}		Varies with IV dose in approximate linear fashion	6,7,17,23
t_{max}	Oral	1.5-2.5h	2,8,26
C^{ss}	IV 2.5-15.0 mg/kg q8h	6.7-20.6 mg/L (similar in neonates)	12[a],28
	Oral 200mg q4h 400mg q4h	0.52-0.56 mg/L 0.79-1.22 mg/L	8,25,26
Time to C^{ss}	Oral	1-2d	8
Bioavailability	Oral	15-30%	25
Topical absorption	5% ointment q6-q4h (5-7d)	Undetectable systemically	5,21
	3% ointment q5h (4-6 doses)	1.7 mg/L in aqueous humour	22
Distribution			
Kidney	IV 400-1200 mg/m^2 q8h	1000% of plasma values	27
Lung, liver, heart		Approx. 130% of plasma values	
Brain, spinal cord		25-70% of plasma values	
CSF	IV infusion	50% of plasma values	1,28
	IV infusion 50 mg/kg + oral probenecid 1g per week	82% of plasma values	3
	Oral 800mg q8h	13-52% of plasma values	19
Saliva	Oral 200 or 400mg	13% of plasma values	26
Tears	Oral 2000 mg/d	18% of plasma values	4
Aqueous humour	Oral 400mg (5 doses in 24h)	30-50% of plasma values (about 50% of topical values)	13
VZV vesicles	IV 7.2-43.2 mg/kg/d	100% of plasma values	24
	Oral 200-400mg q4h	100% of plasma values	26
Placental cord blood	Treatment or suppression of HSV infections during pregnancy: oral 200-400mg q8h	< 0.1-0.7 mg/L (60-99% of maternal plasma values)	10,11,14
Amniotic fluid		< 0.1-2.6 mg/L (300-600% of maternal plasma values	
Breast milk	Oral 1000 mg/d	Up to 324% of maternal plasma values	18,20
Vd		48 (range 22.5-101) L/1.73m^2	1
Plasma protein binding	IV, resulting in plasma aciclovir concentrations of 0.4-5.1 mg/L	9-33% independent of plasma aciclovir concentration	7,29
Metabolism and Elimination			
$t_{1/2}$	IV 0.5-15.0 mg/kg	2-3h	6,7,16,17,23
$t_{1/2}$ neonates		2.5-5.0h independent of dose	9,12
$t_{1/2}$ breastmilk	Oral 1000 mg/d	2.8h	20
$t_{1/2}$ CSF	IV infusion 50 mg/kg + oral probenecid 1g per week	28h	3
Renal excretion	IV	45-79% of dose	6,16,17,23,24
CL		15.6 (range 5.5-30.2) L/h/1.73m^2	1
CL neonates		3.5-10.1 L/h/1.73m^2	12,15

Table III. Contd

Parameter/ medium	Aciclovir route and dosage (duration)	Value	Reference
CL_R		75-80% of CL	15
Mean % of dose recovered unchanged in urine		45-79%, decreasing with decreased creatinine clearance	6,16,17,23,24

a In neonates.

Abbreviations: C_{max} = peak plasma aciclovir concentration; C^{ss} = steady-state plasma concentration; CL = total body clearance; CL_R = renal clearance; CSF = cerebrospinal fluid; d = days; h = hours; HSV = herpes simplex virus; IV = intravenous; q = every; t_{max} = time to peak plasma concentration; $t_{1/2}$ = elimination half-life; Vd = volume of distribution; VZV = varicella zoster virus.

Reference key: 1 Blum et al. (1982); 2 Brigden et al. (1980); 3 Chavanet et al. (1990a); 4 Collum et al. (1985); 5 Corey et al. (1982); 6 de Miranda et al. (1979); 7 de Miranda et al. (1982a); 8 de Miranda et al. (1982b); 9 Englund et al. (1991); 10 Frenkel et al. (1991); 11 Haddad et al. (1993); 12 Hintz et al. (1982); 13 Hung et al. (1984); 14 Kingsley (1986); 15 Laskin (1983); 16 Laskin et al. (1982a); 17 Laskin et al. (1982b); 18 Lau et al. (1987); 19 Lycke et al. (1989); 20 Meyer et al. (1988); 21 Niimura et al. (1990a); 22 Poirier et al. (1982); 23 Spector et al. (1981); 24 Spector et al. (1982a); 25 Straus et al. (1982); 26 Van Dyke et al. (1982); 27 Wade et al. (1982b); 28 Whitley et al. (1982b); 29 Data on file, Wellcome Foundation Ltd.

3. Therapeutic Efficacy in Immunologically Competent Patients

3.1 Herpes Simplex Virus Infections

3.1.1 Perigenital Infections

Genital herpes is usually a result of HSV-2 infection, but HSV-1 is estimated to be the causative agent in 10 to 40% of cases of primary infection, depending on geographical area (Sacks 1987). First or initial clinical episodes of genital herpes infection are termed primary when serological testing at the time of presentation fails to reveal antibodies specific for HSV in patients with no previous history of genital sores. Initial nonprimary infections are first episodes in patients whose sera are positive for HSV antibodies. In an untreated primary infection the incubation period is 5 to 6 days, viral shedding lasts for 11 to 12 days, and mucocutaneous lesions heal fully in about 18 to 22 days (Corey et al. 1983; Mindel & Sutherland 1983). Recurrent episodes are milder, with a mean pain duration of 4 to 6 days, viral shedding time of about 4 days, and a healing time of about 9 to 11 days (Corey et al. 1983; Thin 1988). Recurrences develop more frequently when the initial infection is caused by HSV-2 rather than HSV-1 (Barton et al. 1984; Corey et al. 1983; Kinghorn et al. 1986; Mertz et al. 1984).

Treatment of Initial and Recurrent Episodes

The efficacy of aciclovir treatment in *initial* genital herpes infection of immunocompetent patients is well established (Richards et al. 1983; O'Brien & Campoli-Richards 1989). Double-blind, placebo-controlled studies have shown that intravenous (5 mg/kg 3 times daily), oral (200mg 5 times daily) and, to a lesser extent, topical aciclovir therapy (5% in polyethylene glycol ointment or propylene glycol cream, applied 4 to 6 times daily), initiated within 4 days of the first appearance of signs or symptoms, produces significant reductions in the duration of viral shedding and time to complete healing of lesions in this type of infection. Although efficacy was evident in subsequent recurrences of the infection, statistically significant amelioration of the course of infection was particularly apparent in the more severe primary or initial episode. Pain and dysuria tended to be less responsive to treatment with topical aciclovir, and the ointment formulation appeared less able to significantly reduce new lesion formation.

Oral aciclovir (400mg 5 times daily for 10 days) also reduced the duration of viral shedding and rectal lesions ($p < 0.05$) in initial rectal HSV infection of 29 patients in a double-blind placebo-controlled randomised trial (Rompalo et al. 1988).

The efficacy of topical aciclovir (5% ointment applied every 4 hours for 7 days) has been investigated in a double-blind comparison with intramuscular recombinant interferon-α for the treatment of initial genital herpes infection in 105 patients (Levin et al. 1989). Although there were

Table IV. Summary of double-blind, placebo (P)-controlled studies of prophylactic oral aciclovir (A) in patients with recurrent genital herpes

Reference	No. of patients (% female)	Dosage	Duration of therapy (weeks)	Results: A *vs* P[a]		
				median time to first recurrence (days)	recurrence-free patients (%)	mean monthly recurrence rate
Baker et al. (1989)[b]	261 (65)[c]	400mg bid	52	274* *vs* 19	46* *vs* 5	0.15* *vs* 0.73
Douglas et al. (1984)	143 (55)	200mg bid	12	120* *vs* 18	65* *vs* 6	0.14* *vs* 0.86
		200mg 5xd	12	120* *vs* 18	71* *vs* 6	0.13* *vs* 0.86
Halsos et al. (1985)[d]	31 (0)	200mg qid	12	84* *vs* 14	77* *vs* 10	0.17* *vs* 0.87
Kroon et al. (1989)[d]	24 (38)	400mg bid	12	>84* *vs* 13	71* *vs* 0	
Mertz et al. (1988b)[be]	950 (NR)	400mg bid	52	246** *vs* 18	44* *vs* 2	0.15** *vs* 0.95
Mindel et al. (1984)	56 (61)	200mg qid	12	100** *vs* 14	86** *vs* 4	0.05** *vs* 1.4
Velasco et al. (1991)[f]	51 (35)	400mg bid	24		88 *vs* 4	

a * $p < 0.001$; ** $p < 0.0001$.

b Multicentre study.

c Subset of patients in Mertz et al. (1988).

d Crossover study.

e Recurrences were treated with aciclovir 200mg 5 times daily for 5 days.

f All patients received aciclovir 200mg 5 times daily for 10 days before beginning trial medication.

Abbreviations: bid = twice daily; qid = 4 times daily; 5xd = 5 times daily; NR = not reported.

no statistically significant differences between therapies, there was a trend in favour of aciclovir in time to healing, decreased pain, and viral response (negative cultures) for infections caused by HSV-1 or 2. Further, unlike aciclovir, interferon-α was associated with significant toxicity.

Aciclovir treatment of first episode genital herpes infection does not alter the rate of recurrence of the infection after drug withdrawal. Although new lesion formation and viral shedding are inhibited and the duration of episodes is reduced by 1 to 2 days with early oral aciclovir treatment of *recurrent* infections, the beneficial effects are less dramatic than those seen in the longer initial episodes. Topical application of aciclovir in recurrent infections has produced conflicting results. In some placebo-controlled studies the 5% cream has shown some clinical efficacy, while the 5% ointment has shown little or no clinical effect (reviewed by O'Brien & Campoli-Richards 1989).

Oral Prophylaxis for Suppression of Frequently Recurring Episodes

Prophylactic oral administration of aciclovir at dosages of 800 to 1000 mg/day for up to 1 year suppresses recurrence of genital herpes in 71 to 88% of patients, as evidenced by most double-blind placebo-controlled trials (table IV). Baker et al. (1989) found similar results when assessed quarterly (69 to 76% suppression during each 3-month period), and observed an overall suppression rate of 46% for the year of therapy. According to Goldberg et al. (1993) this lower figure was obtained from analysis of a subset of the patients investigated by Mertz et al. (1988b), who reported a suppression rate of 44% during one year of therapy.

Monthly recurrence rates were decreased significantly with aciclovir treatment to a mean of 0.13 (range 0.05 to 0.17) for patients with recurrent

genital herpes, compared with a mean of 0.95 (range 0.73 to 1.4) in patients receiving placebo in 5 well-controlled studies (see table IV). However, recurrence rates returned to pretreatment frequencies after discontinuation of aciclovir.

In an extended multicentre trial conducted in 950 patients, of whom > 500 were treated with oral aciclovir 400mg twice daily (increased up to 800mg twice daily in 23 patients in the second and third years) as prophylaxis for recurrent genital HSV infection (table V), Mertz et al. (1988b) reported 44% of aciclovir recipients to be recurrence-free in the first year of prophylaxis. In the second year, when the study was changed to provide nonblinded suppressive aciclovir therapy in all patients, about 49% of aciclovir recipients were recurrence free (Mertz et al. 1988a). During the third (Kaplowitz et al. 1991) and fourth (Goldberg et al. 1989) years, the incidence of recurrence-free patients approached or exceeded 60% each year. This increase in percentage of recurrence-free patients with time is possibly associated with the withdrawal of nonresponders as the trial proceeded. 25.4% of those receiving aciclovir prophylaxis for 3 years (Kaplowitz et al. 1991) and 20% of those receiving aciclovir for 5 years (Goldberg et al. 1993) experienced no recurrence for the entire time.

Similarly promising results were obtained by Rooney et al. (1992) in a double-blind placebo-controlled crossover trial of oral aciclovir prophylaxis in patients with ultraviolet light-induced reactivation of HSV-2 (200mg 5 times daily from 1 day before to 5 days after exposure). Recurrences developed in 8% of aciclovir recipients, and in 36% of placebo recipients ($p = 0.004$).

The efficacy of oral aciclovir (800 mg/day for 12 to 24 weeks) has been compared with that of oral inosine pranobex (1 to 4 g/day) in the suppression of recurrent genital HSV infection in 2 well controlled studies (table VI). Both studies showed a clear advantage for aciclovir in the number of recurrence-free patients during treatment, the monthly recurrence rate and the time to first recurrence after withdrawal of treatment.

Continuous prophylactic aciclovir treatment of patients with recurrent attacks of genital HSV infection is effective but drug acquisition costs are high (Whatley & Thin 1991). Dosage reduction and episodic treatment have been investigated as possible means of reducing costs and increasing patient compliance. Oral aciclovir 200mg 2 to 3

Table V. Summary of data from an extended multicentre investigation of patients with recurrent genital herpes receiving oral aciclovir (A) 400 to 800mg twice daily[a]

Reference	Year of trial	No. patients completing each year	Trial design	Mean yearly recurrence rate[b]	Recurrence-free patients (%)		
					per quarter	per year[b]	cumulative
Mertz et al. (1988b)	1	A 519 P 431	db,r	1.8*** 11.4		44** 2	44
Mertz et al. (1988a)	2	A 348 P/A 276	nb	1.4 1.9		49 39	29.1
Kaplowitz et al. (1991)	3	A 289 P/A 236	nb	0.99* 1.4		63 56	25.4
Goldberg et al. (1989)[c]	4	A+P/A 433	nb		80-89	63	
Goldberg et al. (1993)	5	A+P/A 389	nb	0.8	86-89	69	20

a Recurrences in all groups were treated with aciclovir 200mg 5 times daily for 5 days.

b * $p < 0.05$; ** $p < 0.001$; *** $p < 0.0001$.

c Abstract.

Abbreviations: P = placebo; P/A = placebo for the first year, then aciclovir; db = double-blind; nb = nonblinded; r = randomised.

Table VI. Summary of double-blind randomised trials of oral prophylaxis with aciclovir (A) versus inosine pranobex (I) or placebo (P) in patients with frequently recurring genital herpes

Reference	No. of patients	Dosage	Duration (weeks)	Results		
				recurrence-free patients (%)	mean monthly recurrence rate	time to first recurrence post treatment (days)
Kinghorn et al. (1992)	A 53	400mg bid	24	69*	0.11*	143.7*
	I 49	500mg bid		4	0.59	40.5
	P 24			21	0.42	56.2
Mindel et al. (1989)	A 14	200mg qid	12	64**	0.16***	A<I***[a]
	I 17	1g qid		0	1.22	

a Values not reported.

Abbreviations and symbols: bid = twice daily; qid = 4 times daily; < indicates fewer days with aciclovir; * $p < 0.05$ *vs* I and P; ** $p < 0.001$; *** $p < 0.0001$.

times daily prevented recurrence of genital HSV infection in 65 to 70% of patients (Douglas et al. 1984; Kroon et al. 1990). Selection of HSV strains with clinically lowered sensitivity to aciclovir was not apparent in the nonblinded dose-titration study by Kroon et al. (1990). The effects of different dosage regimens on recurrent attacks using episodic treatment begun on initiation of the prodromal symptoms were compared by Whatley and Thin (1991) in another nonblinded study. Dosages of aciclovir 200mg 5 times daily for 5 days and 400mg twice daily for 5 days aborted 44% and 60% of recurrences, respectively, and shortened the duration of 38% and 17% of recurrences by ≥ 50%. However, this regimen would be restricted to patients with a clearly recognisable prodrome.

The use of oral aciclovir 200mg 4 times daily from 1 week before term for an average of 10 days was investigated in a preliminary report of a nonblinded comparative study in pregnant women with a history of recurrent genital HSV infection (Stray-Pedersen 1990). Symptomatic recurrences and asymptomatic viral shedding were completely suppressed in all 92 treated women, whereas 12 such episodes (26%) occurred in the 46 untreated control patients < 10 days before or during delivery ($p < 0.001$). No infants were infected and no adverse events were noted. However, evaluation of the impact of this study should take into consideration the occurrence of asymptomatic shedding despite aciclovir therapy in some patients (section 1.2.2), and also the increased risk of infection in infants if the mothers have primary rather than recurrent infections (Brown & Baker 1989).

3.1.2 Orofacial and Cutaneous Infections

In a randomised trial of patients with herpes labialis, a decrease in mean duration of pain by 36% ($p = 0.02$) and mean healing time to loss of crust by 27% ($p = 0.03$) were noted with oral aciclovir (400mg 5 times daily for 5 days) versus placebo administered in the prodromal or erythema lesion stage (Spruance et al. 1990). The mean maximum lesion size and the frequency of aborted lesions were unaffected by aciclovir therapy, but the frequency of positive viral cultures was significantly decreased in aciclovir versus placebo recipients ($p = 0.004$).

In a more recent double-blind trial in 20 patients with a history of sun-induced herpes labialis, oral therapy with aciclovir 200mg 5 times a day for 5 days starting 48 hours after ultraviolet radiation exposure provided statistically significant improvements in mean maximum lesion area, mean healing time to loss of crust, and mean healing time to normal skin ($p \leq 0.05$) compared with placebo recipients ($n = 20$) [Spruance et al. 1991]. The frequency of aborted lesions, the mean duration of pain and the frequency of positive viral cultures were not affected.

Systemic aciclovir is also effective for therapy of mucocutaneous (other than orofacial) HSV in-

fections. Oral aciclovir 2000 mg/day for 10 days, begun as early as possible after reactivation, reduced the mean duration of clinical symptoms ($p = 0.008$), local and systemic signs of infection ($p = 0.024$) and viral positivity ($p = 0.01$) in a double-blind placebo-controlled crossover study of recurrent HSV-2 infection of the hand (Gill & Bryant 1991). Individual case studies have also reported the successful treatment of HSV whitlow with intravenous and oral aciclovir, and also successful prophylaxis in such patients with orally administered drug (O'Brien & Campoli-Richards 1989).

Prophylaxis with oral aciclovir (800 mg/day) reduces the severity (Rooney et al. 1993; Thomas et al. 1985) and frequency of orofacial and cutaneous HSV recurrence during treatment (table VII). However, it appeared to have no effect on the rate of recurrence after discontinuation of treatment.

Outbreaks of orofacial HSV infection can occur among children in closed communities. An investigation of short term prophylaxis with oral aciclovir in preventing the spread of infection and limiting clinical symptoms in such a community demonstrated its efficacy (Kuzushima et al. 1992).

Table VII. Summary of randomised double-blind placebo (P)-controlled studies of aciclovir (A) prophylaxis in patients with recurrent orofacial or cutaneous HSV infections

Reference	Number of patients	Dosage of aciclovir	Duration of therapy (follow up)	Results (A *vs* P)[a]			
				recurrence-free patients during treatment (%)	mean monthly recurrence rate during treatment	time to first recurrence during treatment (days)	time to first recurrence after treatment (days)
Topical Prophylaxis							
Gibson et al. (1986)[b]	23	5% cream qid	16w (16w)	13 *vs* 4	0.1 *vs* 0.3*	41 *vs* 43	
Raborn et al. (1990)[c]	A 95 P 96	5% cream 5x daily	From 12h before exposure for ≤ 7d (4d)	77 *vs* 57**		A = P[d]	
Spruance et al. (1991)[e]	A 45 P 45	5% cream every 2h while awake	From time of exposure for 7d	51 *vs* 60			
Oral Prophylaxis							
Rooney et al. (1993)[b]	20	400mg bid	16w (to recurrence after withdrawal)	50 *vs* 15	0.21 *vs* 0.45**	118 *vs* 46*	28 *vs* 28
Spruance et al. (1991)[e]	A 33 P 33	200mg 5x daily	From time of exposure or 7d before, for 7-14d	82 *vs* 61 (100 *vs* 64 for delayed recurrences***)[f]			
Thomas et al. (1985)[b]	11	200mg qid	12w[g] (to recurrence after withdrawal)	82 *vs* 18*		53 *vs* 34	39 *vs* 28

a * $p \leq 0.05$; ** $p < 0.01$; *** $p < 0.001$.

b Crossover trial design.

c Skiers with sun-induced herpes labialis were exposed to sunlight.

d Values not reported.

e Patients with sun-induced herpes labialis were exposed to experimental ultraviolet light.

f In placebo recipients, a small percentage of lesions developed within 48h of exposure, the remainder were delayed to 2-7d after exposure.

g Changed to alternate regimen if recurrence occurred.

Abbreviations: d = days, h = hours, w = weeks, bid = twice daily, qid = 4 times daily.

Aciclovir 30 to 60 mg/kg/day was administered to 37 children aged up to 3 years, for 7 days from the first signs of the outbreak. The rate of seroconversion to HSV (27 *vs* 91%) and the incidence of symptomatic disease (0 *vs* 82%) were significantly decreased in patients receiving aciclovir prophylaxis compared with untreated controls (n = 22).

Short term prophylaxis is also of potential use in recurrent sun-induced HSV infections. In an experimental model of this disorder, oral aciclovir prophylaxis completely inhibited the development of lesions developing 2 to 7 days after ultraviolet radiation exposure, but not those developing within 12 to 24 hours of exposure (Spruance et al. 1991; table VII).

Aciclovir 5 or 10% ointment has mostly proved ineffective for the treatment of recurrent orofacial herpes in immunocompetent patients. However, the 5% ointment was superior to the 1% ointment (rated "effective" by 88 *vs* 55% patients) in a comparative trial of topical aciclovir treatment of cutaneous HSV infections (Niimura et al. 1992). The 5% cream appears to be superior to the ointment formulation in recurrent orofacial infection outbreaks, but reductions in symptoms remain small (reviewed by O'Brien & Campoli-Richards 1989), even with vehicle formulations offering improved absorption (Raborn et al. 1989). This finding, however, may reflect delayed application, since outcome appears to improve if the cream is applied during the prodromal phase. There were no significant differences in subjective or objective parameters measured between 5% aciclovir cream and 1% tromantadine gel in a randomised double-blind trial in patients with recurrent orofacial herpes (Ostheimer et al. 1989).

Prophylactic topical aciclovir (5% cream) from the time of exposure did not significantly decrease lesion frequency or severity in an experimental model of recurrent sun-induced HSV infections (Spruance et al. 1991). However, the frequency of orofacial HSV infection recurrence was reduced in skiers receiving topical aciclovir prophylaxis 12 hours before exposure (Raborn et al. 1990) and severity and frequency of herpes labialis recurrence was reduced in patients receiving topical prophylaxis for 16 weeks (Gibson et al. 1986; table VII).

3.1.3 Ocular Infections

As reviewed by Richards et al. (1983) and O'Brien and Campoli-Richards (1989) and subsequently confirmed by Vajpayee et al. (1989), 95 to 100% of herpetic dentritic corneal ulcers are resolved in 5 to 9 days with aciclovir 3% ophthalmic ointment applied 5 times daily. This formulation is at least as effective as idoxuridine 0.5% and 1.0% ointments, trifluridine 2% ointment (since confirmed by Høvding 1989) and vidarabine 3% ointment, and possibly takes effect more rapidly than these antivirals. Geographic corneal ulcers also respond to aciclovir ophthalmic ointment, which appears to have similar efficacy to that of vidarabine in this indication. When combined with human interferon-α, aciclovir 3% ophthalmic ointment shortens the time to healing of superficial herpetic keratitis (dendritic or geographic ulcers) by approximately 3 days, from the 7 to 9 days required by aciclovir plus placebo (Colin et al. 1983; de Koning et al. 1983; Meurs & van Bijsterveld 1985).

Aciclovir 3% eyedrops (2 drops in the inferior conjunctival sac 5 times daily) were successful in treating dendritic keratitis caused by HSV and punctate keratitis caused by adenovirus in a preliminary investigation (Cabezas 1991). Remission of symptoms occurred in 4.2 and 6.8 days, respectively, and all 13 patients were healed in 2 weeks, without adverse effects. Further investigation of this formulation is merited.

Some results obtained with oral aciclovir (400mg 5 times daily) in superficial herpetic keratitis have been seen as equivocal, possibly because of insufficient duration of therapy (O'Brien & Campoli-Richards 1989). However, in a nonblind study of oral (400mg 5 times daily) versus topical (3% ophthalmic ointment 5 times daily) aciclovir, administered until healing occurred (mean about 25 days) in 39 patients with active herpetic disciform keratitis, oral therapy was equivalent or superior to topical therapy (Porter et al. 1990). No significant differences were found between the groups

in rates of resolution of most clinical symptoms; times to resolution of conjunctivitis, stromal infiltration and oedema, and uveitis; time to complete healing; decrease in intraocular pressure; and recurrence rates in the 3-year follow-up. There was a significantly greater improvement in lacrimation (resolved in 12.1 *vs* 27.6 days) and visual acuity scores in tablet versus ointment recipients ($p = 0.02$).

The combination of aciclovir 3% ophthalmic ointment with topical corticosteroids has proved effective in the treatment of herpetic disciform keratitis and necrotising stromal keratitis (Vajpayee et al. 1989) where the antiviral alone has been ineffective. Power et al. (1992) demonstrated in a double-blind comparative trial that healing occurred significantly more quickly in patients with first episode (i.e. no previous steroid exposure) disciform keratitis when treated with 3% aciclovir ointment plus 0.1% betamethasone drops 5 times daily continued for 14 days after healing, than in patients receiving aciclovir alone ($p < 0.05$). As reviewed in O'Brien and Campoli-Richards (1989), aciclovir 3% ophthalmic ointment appears to be as effective as vidarabine ophthalmic ointment when both are combined with a topical corticosteroid in the treatment of herpetic disciform keratitis, and as effective as trifluridine 1% ophthalmic solution in herpetic kerato-uveitis, with patients in both groups receiving local injections of dexamethasone as required. However, corneal ulcers may heal more quickly in trifluridine recipients.

Colin et al. (1991) found that HSV uveitis in 13 of 14 patients who were previously untreated with corticosteroids, and receiving topical (3% ophthalmic ointment 5 times daily) plus oral (200mg 5 times daily) aciclovir for 2 weeks, healed in a mean of 3.6 weeks, while only 10 of 18 patients who had received corticosteroids previously were healed with this regimen, in a mean of 4.7 weeks. All remaining patients responded to additional corticosteroid treatment. The authors suggest that topical plus systemic aciclovir may be considered as first-line treatment in such patients, thus avoiding the problems associated with corticosteroids. Similarly, the combination of intravenous aciclovir (5 mg/kg every 8 hours) and trifluridine eyedrops (every 3 hours) may be of use in patients with herpetic keratoconjunctivitis associated with eczema herpeticum (Margolis & Ostler 1990).

No recurrences of herpes simplex keratitis developed during prophylaxis with oral aciclovir 800 or 1000 mg/day in 4 or 5 divided doses for 12 to 15 months beginning prior to penetrating keratoplasty or on the first postoperative day in 13 patients (14 eyes), compared with recurrences in 4 of 9 untreated patients (9 eyes; $p < 0.05$) [Foster & Barney 1992].

3.1.4 Other Herpes Simplex Virus Infections

Large collaborative studies comparing intravenous aciclovir and vidarabine have established aciclovir 10 mg/kg every 8 hours, administered for at least 10 days, as the treatment of choice for biopsy-proven HSV encephalitis (O'Brien & Campoli-Richards 1989). Aciclovir was particularly beneficial in improving overall survival rates and reducing the incidence of serious sequelae to infection. The efficacy of intravenous aciclovir plus interferon-β was recently shown to be equivalent to that of aciclovir alone in a retrospective study of 214 children with HSV encephalitis (Wintergerst & Belohradsky 1992). However, in a subgroup of children with low-density areas in the temporal lobes in cranial computed tomography scans, the development of defects and mortality was significantly lower in those receiving the combination ($p = 0.014$).

Case reports of intravenous aciclovir treatment of HSV-2-induced meningitis in 2 patients (5 and 10 mg/kg 3 times daily for 7 and 10 days, respectively) and oral prophylaxis for recurrent meningitis in 3 patients (200mg 3 or 4 times daily either continuously or intermittently at onset of perigenital lesions) have provided promising but preliminary results (Bergström & Alestig 1990). Intravenous aciclovir treatment (500mg every 8 hours) of HSV meningitis was also beneficial in a previous report (Levy & Sagar 1984).

There is also an instance of successful treatment of HSV-associated exacerbation of Crohn's disease

with aciclovir 200mg 5 times daily, repeated every 3 weeks for 5 cycles (Rüther et al. 1992). Surgery was no longer necessary as a consequence of the subsequent changes in the morphological and clinical findings.

HSV encephalitis (Frieden et al. 1990), disseminated HSV infections (Cox et al. 1986; Grover et al. 1985) and HSV hepatitis (Chazotte et al. 1987; Klein et al. 1991; Lagrew et al. 1984) during pregnancy have been successfully treated with intravenous aciclovir according to several case studies. There is only one reported case in which a (possibly immunocompromised) pregnant woman with HSV encephalitis did not survive after aciclovir therapy, although the infant was saved (Berger et al. 1986). In contrast, attempts to treat HSV infections during pregnancy using other methods have often resulted in failure. Frieden et al. (1990) report the deaths of 4 pregnant women with HSV encephalitis and 3 of the fetuses despite treatment with idoxuridine, antituberculous treatment, septic shock treatment or phenothiazines plus dexamethasone (possibly reflecting the difficulties inherent in diagnosis of the disease). Similarly, of 10 women receiving treatments other than aciclovir for HSV hepatitis in pregnancy reported by Klein et al. (1991), only 4 mothers (including 2 of 3 receiving vidarabine) and 4 infants (including 1 of 3 whose mothers received vidarabine) survived.

Neonatal HSV infections appear to respond clinically to intravenous aciclovir therapy with little associated toxicity. In a blinded randomised comparative trial of intravenous aciclovir and vidarabine (both 30 mg/kg/day for 10 days) in 202 neonates with HSV infection, there were no significant differences in morbidity or mortality after a year (Whitley et al. 1991). No infant with infections of the skin, eyes or mouth died, and 88% and 98% of vidarabine and aciclovir recipients, respectively, were developing normally after a year. Of the 71 infants with encephalitis, 14% in each treatment group died, with normal development in 43% and 29%, respectively, of the survivors after a year. Of the 46 with disseminated disease, mortality was 50% in vidarabine recipients and 61% in aciclovir recipients, and 58% and 60%, respectively, of the survivors were developing normally after a year. The authors stated a preference for aciclovir treatment because of its ease of administration, and suggested that higher doses of aciclovir for longer treatment periods may be useful in refractory cases. Continued use of aciclovir from birth to 3 years of age (initially intravenously and then orally) has been reported for a preterm infant who developed HSV meningitis and/or localised infection on each attempt to discontinue therapy (Bergström & Trollfors 1991). The child developed normally during the period of prophylaxis.

Previous case reports (O'Brien & Campoli-Richards 1989) of prevention of frequently recurring herpes simplex-associated erythema multiforme with oral aciclovir (400 to 1000mg daily administered prophylactically for up to 12 months) have been substantiated in a double-blind placebo-controlled trial of 400mg twice daily for 26 weeks in 19 patients (Tatnall et al. 1991). A significant reduction in the mean number of attacks was observed with active treatment, and in 2 patients disease remission was complete. In a review of these results and other patients receiving short oral aciclovir courses (1000 mg/day for 5 days) or continuous suppressive oral aciclovir treatment, 54% of patients experienced either partial or complete suppression (Schofield et al. 1993). Successful suppression of erythema multiforme with very low dose aciclovir (200mg daily) for 11 months in 1 patient (Williams & Lever 1991) suggests that this regimen offers a potential advantage for cost reduction over extended prophylaxis with the higher dosage.

3.2 Varicella Zoster Virus Infections

3.2.1 Varicella (Chickenpox)

Varicella, or chickenpox, is the primary infection caused by VZV. Although in many otherwise healthy children the disease is not severe, the associated costs to parents and the community may be reduced by returning the children to school more quickly, and the use of aciclovir treatment in these patients has recently been under discussion. As-

Table VIII. Summary of randomised double-blind placebo (P)-controlled trials of oral aciclovir (A) in otherwise healthy immunocompetent patients with varicella

Reference	Patient age (years) [initial occurrence in household]	Dosage (duration in days)	Interval from rash onset to start of treatment (hours)	Number of patients	Results: A *vs* P[a]				
					number of lesions	duration of new lesion formation (days)	time to healing (days)	duration of fever (days)	severity/ duration of pruritus
Adults									
Andreoni et al. (1992)	18-25	800mg 5xd (5)	≤ 48	A: 50 P: 50	A = P	A = P	A = P[b]	A < P**[c]	A < P*
Wallace et al. (1992)	17-33	800mg 5xd (7)	≤ 24	A: 38 P: 38	A < P* (268 *vs* 500)	A < P* (2.7 *vs* 3.3)	A < P***[d] (5.6 *vs* 7.4)	A < P* (2.4 *vs* 2.7)	A < P*[e]
			> 24 to 72	A: 36 P: 36	A > P* (233 *vs* 158)	A > P* (3.0 *vs* 2.3)	A = P[d] (7.0 *vs* 6.8)	A = P (2.0 *vs* 2.1)	A = P
Adolescents									
Balfour et al. (1992)	13-18	800mg qid (5)	≤ 24	A: 31 P: 31	A < P* (397 *vs* 421)	A < P*** (2.7 *vs* 3.2)	A < P* (22.7 *vs* 92.7)[f]	A < P*	
Children									
Balfour et al. (1990)	5-16 [86%]	10-20 mg/kg[g] qid (5-7)	≤ 24	A: 50 P: 52	A < P* (336 *vs* 500)	A = P (3 *vs* 3)	A < P***[h] (3 *vs* 4)	A < P*** (1 *vs* 2)	A = P
Dunkle et al. (1991)	2-12 [55%]	20 mg/kg[g] qid (5)	≤ 24	A: 367 P: 357	A < P*** (294 *vs* 347)	A < P ***	A < P*** (13 *vs* 33)[f]	A < P***	A < P***
Ghirga et al. (1992)	4-8 [100%]	5 mg/kg qid (2)	NR	A: 30 P: 30	A < P* (80 *vs* 130)		A < P[h] (2 *vs* 3.5)	A < P (0.5 *vs* 1)	

a * $p < 0.05$; ** $p < 0.01$; *** $p \leq 0.001$.

b % crusted by day 6.

c On day 1.

d Time to 100% crusting.

e On day 5.

f Mean number of residual lesions on day 28.

g Oral suspension.

h Median time to decrease in number of lesions.

Abbreviations: A < P = values for aciclovir recipients less than those for placebo recipients; A=P = values for aciclovir and placebo recipients similar; A > P = values for aciclovir recipients greater than those for placebo recipients; NR = not recorded; qid = 4 times daily; 5xd = 5 times daily.

pects such as the effects of aciclovir on immune function, the drug's acquisition costs, the recommendation that it be administered within 24 hours of illness, the possible development of antiviral resistance, and the possible adverse effects (despite the good tolerability profile to date) of such potential widespread therapy are also of concern.

Several well-designed studies have investigated the efficacy of oral aciclovir in the treatment of children, adolescents and adults with varicella (table VIII). Initiation of treatment within 24 hours of appearance of the rash was associated with a significant decrease in the total number of lesions (by 6 to 46%), time to healing of lesions (by 1 to 2 days) and duration of fever (by 0.5 to 1 day) with aciclovir therapy compared with placebo (Balfour et al. 1990, 1992; Dunkle et al. 1991; Wallace et al. 1992). Time to cessation of new lesion formation

was also significantly decreased (by about 0.5 days) [Balfour et al. 1992; Dunkle et al. 1991; Wallace et al. 1992], as was severity or duration of pruritus (Andreoni et al. 1992; Dunkle et al. 1991; Wallace et al. 1992), in several trials. Similar results were reported in a noncomparative study in 31 adolescents and adults (Feder 1990) and several case reports (Marino & McDonald 1991). When aciclovir treatment was initiated later than 24 hours after the appearance of the rash, results were equivocal (Andreoni et al. 1992; Wallace et al. 1992).

There has been little information on the treatment of varicella in neonates, but there are isolated reports that clinical improvement occurred in 10 infants who developed uncomplicated varicella soon after birth and were treated with intravenous aciclovir 5 to 15 mg/kg/day for 5 to 8 days (Kavaliotis 1992; Wirth et al. 1987). Disseminated VZV disease in an infant treated with VZV immunoglobulin (2 days after birth) and intravenous aciclovir (1500 mg/m^2/day for 7 days) from the fifth day of illness (after dissemination had occurred), however, resulted in fatality (King et al. 1986).

A nonblinded study which assessed 25 nonrandomised age-matched controls, investigated the prevention of clinical symptoms of varicella with oral aciclovir (40 or 80 mg/kg/day for 7 days) in 25 children exposed to an index case in the family (Asano et al. 1993). The children were previously unexposed to varicella, and therapy was begun 7 to 9 days after the onset of illness in the index case. Four (16%) aciclovir recipients developed mild symptoms of varicella, and one of these developed fever. All control group children developed moderate to severe symptoms, with fever in 17 ($p < 0.01$).

Complications of Varicella

Although few varicella cases occur in adults, this group accounts for a large proportion of the hospitalisations and deaths associated with the disease. The most frequent complication of varicella in adults is varicella pneumonia (Haake et al. 1990). In a retrospective study, intravenous aciclovir (3 to 10 mg/kg every 8 hours for 5 days) was begun within 36 hours of admission in 11 patients, followed by oral aciclovir in 6, and was compared with no treatment in 27 patients. Significantly lower mean temperatures and respiratory rates, and greater improvement in oxygenation, were evident within 5 to 6 days of hospitalisation in aciclovir recipients (Haake et al. 1990). Good therapeutic responses to intravenous aciclovir therapy (5 mg/kg every 8 hours) were also noted in another retrospective study of 7 patients with varicella pneumonia (Garcia Quintana et al. 1992).

Maternal mortality rates as high as 41% have been reported for pregnant women with varicella pneumonia when not treated with antivirals (Lotshaw et al. 1991). Several case reports of intravenous aciclovir therapy (15 to 45 mg/kg/day for 4 to 10 days), plus oral therapy in some patients, have appeared in the literature in the past few years (Broussard et al. 1991; Smego & Asperilla 1991). Of the 22 mothers evaluated, 3 died of uncontrolled infection or complications. Neither congenital varicella syndrome nor active perinatal varicella occurred in any child.

Oral aciclovir (200mg 4 times daily for 7 days) has been successfully employed in the treatment of peripheral chorioretinitis developing as a complication of varicella in an adult (Kelly & Rosenthal 1990).

3.2.2 Herpes Zoster (Shingles)

Recrudescence of previous VZV infection results in cutaneous expression as herpes zoster or shingles. Intravenous (5 to 10 mg/kg 3 times daily for 5 days) and oral (800mg 5 times daily for 7 to 10 days) aciclovir therapy beginning within 72 hours of exanthem onset attenuated the development of rash and pain in 9 double-blind placebo-controlled studies involving a total of 1044 immunocompetent patients with acute herpes zoster, and appeared to offer protection against ocular involvement in patients with trigeminal zoster (see review by O'Brien & Campoli-Richards 1989; and Morton & Thomson 1989). Therapeutic efficacy was maximised with early initiation of therapy.

Post-herpetic neuralgia occurs in 13 to 40% of patients aged > 60 years (McKendrick et al. 1989).

Results of earlier double-blind placebo-controlled studies assessing the effects of oral aciclovir (2000 to 4000 mg/day for 5 to 10 days) in this condition have been equivocal. No significant difference in the incidence of post-herpetic neuralgia was seen in two studies of 2000 mg/day and one of 4000 mg/day between aciclovir and placebo groups (Huff et al. 1988; McKendrick et al. 1984; Wood et al. 1988), but a lower incidence in patients receiving 4000 mg/day ($p<0.05$) was reported (Huff et al. 1988).

Surman et al. (1990) investigated the effect of aciclovir 4000 mg/day given orally for 12 weeks in a small group of patients with a history of herpes zoster and with post-herpetic neuralgia of > 2 months' duration. While pain was significantly decreased during treatment in aciclovir recipients, during follow-up of 2 months there were no differences in this variable between aciclovir (n = 11) and placebo (n = 9) groups.

In contrast, a double-blind placebo-controlled study has demonstrated a significant and more sustained decrease in the monthly prevalence of pain and other post-herpetic neuralgia symptoms in patients with acute herpes zoster receiving oral aciclovir 800mg 5 times daily for 7 days (Morton & Thomson 1989). At one month, pain was reported by 60% of placebo versus 33% of aciclovir recipients ($p = 0.026$) and the difference remained significant for the second ($p = 0.011$) and third ($p = 0.0082$) months. Other post-herpetic neuralgia symptoms (numbness, itching etc.) were present in significantly fewer aciclovir recipients from the third to the sixth months ($p = 0.043$).

In a reanalysis of the combined results of 3 of these trials (Huff et al. 1988; Morton & Thomson 1989; Wood et al. 1988) plus a trial investigating aciclovir in zoster ophthalmicus (Harding & Porter 1991; see next section), the duration of post-herpetic neuralgia (time to first cessation of pain) was shorter in aciclovir recipients but the difference did not reach statistical significance. However, when the definition of post-herpetic neuralgia was extended to include the time to complete cessation of pain, thus excluding the results from 364 patients in the trial by Wood et al. (1988) for whom this parameter was not recorded, a significant decrease in the duration of pain was demonstrated (from mean 86 to 49 days, $p < 0.001$; Crooks et al. 1991).

The efficacy of oral aciclovir (800mg 5 times daily for 7 days) has been compared with that of topical idoxuridine (40% in dimethylsulfoxide once daily for 4 days) in a randomised double-blind trial of patients with uncomplicated herpes zoster infection (Aliaga et al. 1992). The outcome of this trial may have been affected by the inclusion of patients up to 4 days after the appearance of lesions and by possible differences between the 2 treatment groups in initial disease characteristics. However, topical idoxuridine appeared to be superior to aciclovir in reducing the time to drying of vesicular lesions (7.1 *vs* 8.3 days, $p < 0.05$), preventing new lesion formation during treatment (24 to 28% *vs* 43 to 50% of patients, $p < 0.01$) and time to resolution of pruritus (8.9 *vs* 12.0 days, $p < 0.05$) and hyperaesthesia (5.6 *vs* 11.0 days, $p < 0.05$). Aciclovir was as effective as idoxuridine in time to disappearance of papulopustules, appearance of first scabs, loss of all scabs, disappearance of erythema and disappearance of pain, but analgesic drugs were discontinued earlier in the idoxuridine group (9.3 *vs* 12.4 days, $p < 0.01$). Six of 85 patients receiving idoxuridine developed erythema (1 withdrawn) compared with none of the 86 aciclovir recipients. There was no significant difference between the groups in the number of patients developing post-herpetic neuralgia (5 receiving idoxuridine and 12 aciclovir).

Severe herpes zoster in 47 elderly patients with cancer was treated with intravenous aciclovir (10 mg/kg 3 times daily for 5 days) or oral brivudine (125mg 4 times daily for 5 days) in a randomised double-blind trial (Wutke et al. 1991). There were significantly greater reductions in mean pain score and time to the last new lesion with brivudine treatment ($p = 0.02$), but no significant differences in time to loss of vesicles or time to full crusting, and neither therapy appeared to influence post-herpetic neuralgia. No severe adverse effects occurred with either drug.

Zoster Ophthalmicus

Results of comparative trials investigating the effects of 3% aciclovir ophthalmic ointment in the treatment of VZV infection of the ophthalmic division of the trigeminal nerve have been equivocal. McGill and Chapman (1983) found corneal epithelial lesions resolved significantly more quickly with aciclovir ointment than with topical steroids, while there were no differences between treatments in stromal, uveal or scleral responses. However, Marsh and Cooper (1991) concluded that topical aciclovir alone was insufficient in severe inflammation, and that combination with steroids may be appropriate in these patients. The latter trial included patients treated up to 3 weeks after the appearance of the skin rash, which may have compromised the efficacy of aciclovir (Herbort 1992).

In marked contrast, placebo-controlled trials of oral aciclovir (600 to 800mg 5 times daily for 10 days) for zoster ophthalmicus, initiated within 72 hours of skin eruption, provide clear evidence of long term benefit. Cobo et al. (1985, 1986) reported reductions in ocular complications over 12 months of follow-up which were statistically significant for dentriform keratopathy (occurred in 14% of 36 aciclovir recipients *vs* 31% of 35 placebo recipients, $p < 0.05$), stromal keratitis (25 *vs* 56%, $p < 0.01$) and anterior uveitis (19 *vs* 49%, $p < 0.05$). Similarly, Harding and Porter (1991) reported a significant reduction with oral aciclovir (800mg 5 times daily for 10 days) in the frequency of active intraocular disease after 6 months of follow-up (5% of 24 aciclovir recipients had chronic uveitis *vs* 42% of 22 placebo recipients, $p < 0.01$), and nonsignificant reductions in the frequency (aciclovir 30 *vs* placebo 51%) and severity of complications during the trial (treated with topical aciclovir ointment and mydriatics). Mean pain scores (recorded using a visual analogue scale) were significantly lower in aciclovir recipients from week 5 (1.9 *vs* 13.6mm, $p = 0.02$) to the last follow-up at 6 months (1.0 *vs* 9.3mm, $p = 0.03$), suggesting a positive effect on post-herpetic neuralgia. Extending the treatment period of aciclovir 800mg 5 times daily from 7 to 14 days provided no improvement in the outcome of zoster ophthalmicus in a double-blind comparative trial (Hoang-Xuan et al. 1992).

Other Zoster Complications

In several case reports, intravenous aciclovir treatment (5 to 10 mg/kg every 8 hours) of herpes zoster-associated encephalitis and herpes zoster oticus resulted in rapid resolution of infection (O'Brien & Campoli-Richards 1989). Success with intravenous or oral aciclovir has been subsequently documented in the treatment of herpes zoster myelitis (Chotmongkol & Phankingthongkum 1992), herpes zoster-associated idiopathic vocal cord paralysis (Benninger 1992), and Rosai Dorfman disease associated with VZV infection in a patient with negative EBV capsid antigen results (Baildam et al. 1992). Recent reports of aciclovir treatment of herpes zoster oticus have been positive in most cases. In a randomised study of intravenous aciclovir (10 mg/kg every 8 hours)/prednisolone versus placebo/corticosteroid, 5 of 8 patients versus 3 of 7 ($p < 0.05$) improved in facial function grade (Ramos Macias et al. 1992). Of 5 patients with atraumatic facial palsy, 4 completely recovered and 1 improved after oral aciclovir therapy (200 to 400 mg 5 times daily for 5 days) in a series of case reports by Albeck and Ninn-Pedersen (1989). In 5 similar but severely affected patients, the initial facial function grades improved (final function 70 to 90%) after intravenous aciclovir (5 mg/kg every 8 hours for 5 to 8 days) followed by oral therapy in 3 patients (400mg 5 times daily for 7 days) [Uri et al. 1992].

The prevention of recurrence of severe almost constant aphthae [suggested to be caused by reactivation of latent VZV (Pedersen 1989)] was achieved with oral aciclovir therapy (800mg twice daily for 10 weeks) in 2 of 8 patients, with occasional recurrences in a further 4; however the remaining 2 patients received no benefit (Pedersen 1992). In an earlier report using a lower dosage (400mg twice daily for a year), there was no significant difference in prevention of recurrent aphthae between patients receiving constant aciclovir ($n = 25$, 18 with a history of aphthae) and

those receiving intermittent treatment (200mg 5 times daily for 5 days; n = 19, 13 with a history of aphthous ulcers) for genital HSV outbreaks (Wormser et al. 1988). 20% of those receiving continuous aciclovir therapy had fewer attacks than before treatment, 24% had more attacks, there was no difference in 48%, and the remainder were unevaluable.

3.3 Other Viral Infections

The addition of intravenous aciclovir (250mg 3 times daily) to intravenous immunoglobulin and hydrocortisone, as described in a recent case report of a patient with infectious mononucleosis and severe thrombocytopenia, resulted in an immediate response and normalisation of the thrombocyte count within 3 days (Hugo et al. 1989). Two randomised double-blind trials of intravenous (10 mg/kg every 8 hours for 7 days, n = 31; Andersson et al. 1986) or oral (600mg 5 times daily for 10 days, n = 120; van der Horst et al. 1991) aciclovir monotherapy in infectious mononucleosis have demonstrated only nonsignificant trends towards more rapid improvement with aciclovir than with placebo.

The estimated 200 to 300 million carriers of hepatitis B virus (HBV) worldwide risk severe liver disease if the infection is left unchecked (Main 1991). The efficacy of aciclovir in treating patients with chronic hepatitis B is uncertain. Two randomised comparative studies of intravenous aciclovir 45 mg/kg/day for 4 weeks failed to show a statistically significant effect on the rate of seroconversion (Alexander et al. 1987; Guarascio et al. 1986a). However, small noncomparative studies have suggested some additional effects when aciclovir is added to interferon-α treatment (Guarascio et al. 1986b, 1990; Schalm et al. 1985). In a randomised comparative trial (Berk et al. 1992), 44 patients with chronic hepatitis B received intravenous aciclovir (2000 mg/day) for two 2-week courses during treatment with subcutaneous interferon-α for 16 weeks. Although at 1-year follow-up there was no statistically significant difference in rate of seroconversion (25%) compared with that in 43 similar patients who received no treatment (14%), a partial response was reported for 30 versus 5% of patients in these respective cohorts ($p < 0.05$).

It has been suggested (Trépo et al. 1986) that aciclovir efficacy in chronic active hepatitis is greater in patients with low levels of HBV replication before treatment. This view was supported in a noncomparative pilot study of oral aciclovir (600 mg/day for 4 weeks) in 10 patients (Minuk et al. 1992). Aciclovir was administered after a 4-week tapered course of oral prednisone on the premise that thymidine kinase activity increases during the regenerative response to steroid-induced hepatitis. The results were encouraging: 7 patients lost at least one, and 2 of these lost all, serological markers of HBV replication, either transiently or during the entire 6-month follow-up period. Most patients had had hepatitis since childhood and were of Southeast Asian origin or were homosexual (HIV-negative), factors thought to indicate reduced response to antiviral therapy. Comparative clinical trials are required to investigate these results further, as it is possible that the response reflected steroid withdrawal alone.

It is considered likely that papilloma of the larynx is of viral aetiology, probably caused by the DNA virus, human papillomavirus. The disease tends to recur after surgical removal of the tumour. In one child with laryngeal papillomatosis, surgical excision of the tumour was followed by recurrence of the disease within 3 months. The tumour was again excised and intravenous aciclovir (300 mg/day for 5 days) was initiated. Two other children with laryngeal papillomatosis received oral aciclovir (500 to 600 mg/day for 5 to 6 months) prophylaxis on removal of the tumours. No recurrence occurred in any of the 3 children for follow-up periods of 18 to 42 months (Lopez Aguado et al. 1991). A study to investigate these effects is presently underway.

The childhood syndrome epilepsia partialis continua, involving continuous partial motor seizures, has been treated in 4 patients with aciclovir 30 mg/kg/day, administered intravenously initially

and then orally, for long periods (duration not stipulated; Ragazzo et al. 1991). The condition was interrupted in all patients after 1 to 2 weeks of treatment, isolated partial motor seizures previously occurring when the patients were not experiencing status epilepticus reduced by 10 to 50% of initial frequency, and neurological status improved.

4. Therapeutic Efficacy in Immunologically Compromised Patients

4.1 Treatment of Established Infections

4.1.1 Herpes Simplex Virus

The efficacy of intravenous or oral aciclovir in the treatment of immunocompromised patients with HSV infections is well established. Intravenous (250 mg/m^2 8-hourly) and oral (400mg 5 times daily) aciclovir administration significantly accelerates the resolution of viral shedding and pain, and reduces time to healing in these patients. Topical administration of aciclovir 5% ointment was effective in reducing the period of pain and viral shedding in recurrent cutaneous orofacial infections in one study of renal transplant recipients (Whitley et al. 1982a). However, the usefulness of the topically applied drug is limited to patients with solely external mucocutaneous lesions, with no benefit for those with intraoral or intravaginal infection or those with viscerally disseminated disease (see reviews by Meyers 1985; O'Brien & Campoli-Richards 1989; Richards et al. 1983).

A combination of aciclovir 5% and the ribonucleotide reductase inhibitor 348U87 3% was applied topically as a cream every 3 hours for 14 to 42 days to the lesions of 10 HIV-infected patients with anogenital HSV infections resistant to aciclovir (Safrin et al. 1993). Although the lesion areas decreased during the first 14 days of therapy in 7 patients, complete healing of the area occurred in only 1. Seven patients reported reduction of pain and 8 noted decreased erythema during therapy.

Severe infections refractory to normal dosages of aciclovir may respond to higher dosages. Severe HSV-associated hepatitis developing 24 days after high dose chemotherapy and autologous bone marrow transplantation in a patient treated with oral aciclovir (200mg 5 times daily) from 7 days preoperatively was successfully treated with high dosage intravenous aciclovir (10 mg/kg 3 times daily; Hayashi et al. 1991). Although drugs such as foscarnet (Safrin et al. 1991) are commonly used in patients with infection caused by resistant strains of HSV, high-dose aciclovir may also be useful in these patients. HSV infections refractory to intermittent intravenous aciclovir (30 to 40 mg/kg/day for 13 to 21 days) in 3 immunocompromised patients resolved with continuous infusion of aciclovir 1.22 to 6.25 mg/kg/hour for 8 to 46 days (Fletcher et al. 1989). The isolates from all 3 patients were deficient in thymidine kinase activity. Continuous infusion of aciclovir at 1.5 to 2.0 mg/kg/hour for 6 weeks was also successful in the treatment of 2 immunocompromised patients with ulcerative proctitis caused by HSV resistant to intravenous aciclovir 10 mg/kg every 8 hours as a result of viral mutation (Engel et al. 1990).

4.1.2 Varicella Zoster Virus

VZV infections occur often in immunocompromised patients and may be severe. Painful skin lesions and post-herpetic neuralgia are common complications, and mortality rates of 6 to 17% have been associated with disseminated disease from primary (varicella) or recurrent (herpes zoster) infection (Shepp et al. 1986). A discussion of the morbidity and mortality of VZV infection in these patients is provided by O'Brien & Campoli-Richards (1989).

Several placebo-controlled or comparative trials have examined the effect of aciclovir in the treatment of VZV infections in immunologically compromised patients. In double-blind placebo-controlled trials of intravenous aciclovir (500 mg/m^2 every 8 hours for 5 to 8 days) in patients with cutaneous dissemination of herpes zoster or children with varicella, reductions in duration of viral shedding and/or scabbing time were statistically significant for aciclovir versus placebo (Balfour et al. 1983; Nyerges et al. 1988), or were similar in both groups (Prober et al. 1982). Deterioration of patient condition and progression of the disease were significantly reduced in

aciclovir recipients in all 3 trials compared with placebo.

Intravenous aciclovir was as effective as oral brivudine in reducing the time to scabbing and duration of new lesion formation in immunocompromised children with VZV infections, although patient numbers were small (table IX). Similarly, intravenous aciclovir was mostly at least as effective as intravenous vidarabine in reducing time to scabbing, duration of new lesion formation (in the majority of trials) and duration of viral shedding, and was significantly more effective in reducing time to healing, in immunocompromised children and adults with VZV infections (table IX).

Four of 5 patients with cystic fibrosis and VZV infections who received intravenous aciclovir (10 mg/kg every 8 hours for 7 days) within 24 hours of appearance of the rash, had clinical improvement within 72 hours and stable forced expiratory volume during 1 year's follow-up (Ong et al. 1991).

Disseminated herpes zoster in a woman 14 weeks pregnant was successfully treated with intravenous aciclovir (5 mg/kg every 8 hours for 10 days) about 12 months after bone marrow transplantation; a healthy infant was delivered at full term (Horowitz & Hankins 1992). In another case report, a child with leukaemia received successful intravenous aciclovir treatment (17 to 20 mg/kg every 8 hours for 10 weeks) for multifocal leucoencephalitis caused by VZV (Carmack et al. 1993).

In a randomised nonblinded trial of intravenous (250 mg/m^2 3 times daily for 7 days, n = 13) versus oral (800mg 5 times daily in adults and 400mg 5 times daily in children for 7 days, n = 14) aciclovir, treatment was begun within 3 days of appearance of the rash in bone marrow recipients with localised herpes zoster (Ljungman et al. 1989). There were no differences between the groups in duration of new lesion formation (median 2, range 0 to 4 days for both groups), time to healing [intravenous 5 (2 to 8) days, oral 6 (3 to 10) days] or time with pain [intravenous 3 (0 to 21) days, oral 4 (0 to 14) days]. Similar results were achieved in a trial using high dose oral aciclovir suspension (800mg 5 times daily for 7 days), which was significantly superior in healing and preventing the dissemination of varicella in immunocompromised children than placebo in historical controls (Mészner et al. 1993). Oral administration of aciclovir, if proved as effective as intravenous administration in further comparative studies, may offer potential cost advantages over the parenteral route in patients not requiring hospitalisation (Gnann & Whitley 1991).

In a double-blind investigation, topical aciclovir in polyethylene glycol ointment base proved significantly superior to placebo clinically (reduced time to pustulation, crusting and healing), but duration of viral shedding and pain resolution were unaffected, in immunocompromised patients with localised herpes zoster (Levin et al. 1985). As with HSV infections, use of topical aciclovir formulations in immunocompromised patients appears to be limited.

4.1.3 Epstein-Barr Virus

Clinical response of EBV infection to aciclovir therapy has been limited, despite the susceptibility of this organism to the drug in pharmacodynamic studies. Reactivation of latent infection occurs frequently on discontinuation of aciclovir administration, especially in immunocompromised patients (reviewed by O'Brien & Campoli-Richards 1989). Recent case reports (Glick & Pliskin 1990; Naher et al. 1990) and nonblinded studies (Brockmeyer et al. 1989; Herbst et al. 1989) of high-dose oral aciclovir in the treatment of patients with oral hairy leucoplakia provide evidence of efficacy during drug administration, but also demonstrate the inevitable recurrence of disease on drug withdrawal. Continuous infusion of aciclovir (1.46 to 9.7 mg/kg/hour for 5 to 21 days) resulted in resolution of EBV infection previously refractory to intermittent therapy (30 mg/kg/day intravenously or 100 mg/kg/day orally for 5 to 12 days) in 2 of 4 immunocompromised patients (Fletcher et al. 1989).

4.1.4 Cytomegalovirus

Despite transient effects on viraemia and possibly viral titre in the target organ, aciclovir treat-

Table IX. Summary of comparative clinical trials of intravenous aciclovir (A) and intravenous vidarabine (V) or oral brivudine (B) in immunocompromised patients with VZV infections

Reference	Maximum pretreatment duration of infection (days)	Dosage (duration in days)	Type of infection (no. of patients)	Results (A *vs* V or B)[a]				
				scabbing time (days)	duration of new lesion formation (days)	duration of viral shedding (days)	time to healing (days)	comments
Heidl et al. (1990, 1991)[b] (in children)	≥2 in 9A & 7B patients	A 1500 mg/m²/d (≥5) B 5 mg/kg q8h (≥5)	Varicella (8A/6B) Herpes zoster (14A/15B)	A = B[c] (12 *vs* 10)	A = B (4 *vs* 5)			Disseminated disease before treatment: 7A/3B Treatment failures: A = B (2 *vs* 2)
Kunitomi et al. (1989)[b] (in children)	A 4; V 5	A 5-10 mg/kg q8h (4-7) V 10 mg/kg/d (3-5)	Varicella (5A/8V)	A = V (8.2 *vs* 6.1)	A ≥ V (4.0 *vs* 2.1)	A = V 5.4 *vs* 3.3		
			Herpes zoster (4A/8V)	A ≤ V (6.8 *vs* 10.1)	A = V (2.3 *vs* 3.0)	A = V (4.3 *vs* 5.3)		
Shepp et al. (1986)[b]	3	A 500 mg/m² q8h (7) V 10 mg/kg/d (7)	Varicella (11A/11V)	A < V***[e] (7 *vs* 17)	A < V* (3 *vs* 6)	A < V** (4 *vs* 7)	A < V** (17 *vs* 28)	Cutaneous dissemination: A < V* (0/10 *vs* 5/10)[d] Treatment failures: A < V (0/11 *vs* 4/11) Recurrence of herpes zoster: 5w (1/11 *vs* 0/11)
Vildé et al. (1986)[b]	3, or if new lesions still forming	A 10 mg/kg q8h (5)[e] V 30 mg/kg/d (5)[e]	Varicella (10A/8V)		A = V (3.9 *vs* 4.7)	A ≤ V[f]		Recurrence of varicella: 3d (2/10 *vs* 0/8)
			Disseminated herpes zoster (10A/10V)		A = V (2.6 *vs* 2.9)	A ≤ V[f]		
Whitley et al. (1992)[g]	A 5.9; V 5.4	A 10 mg/kg q8h (≥7) V 10 mg/kg/d (≥7)	Disseminated cutaneous herpes zoster (37A/36V)	A = V (40-50% by day 7)	A = V (2.2 *vs* 1.7 for primary dermatome)		A < V*[h] (8.7 *vs* 11.9)	Post-herpetic neuralgia: A = V (40% *vs* 50% at 6 months)

a * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.
b No controls for bias included.
c Crusting time.
d Patients entering with localised dermatomal disease.
e Two vidarabine-treated patients and 3 aciclovir-treated patients received therapy for 7 days due to the severity of illness.
f Virus was isolated from 9 aciclovir and 10 vidarabine recipients.
g Double-blind trial.
h During hospitalisation.

Abbreviations and symbols: d = days; q8h = 8-hourly; = indicates equivalence; w = weeks: ≤ indicates non-statistically significant tendency in favour of aciclovir; ≥ indicates tendency in favour of comparative drug; < indicates significant advantage for aciclovir ($p < 0.05$).

ment of symptomatic CMV infection in immunocompromised patients has resulted in little clinical improvement, and has not generally improved survival rates (reviewed by O'Brien & Campoli-Richards 1989), although intravenous aciclovir (45 mg/kg/day) has been effective in isolated cases (Sugiura et al. 1991). Six immunocompromised patients who had not responded to intermittent intravenous aciclovir (10 to 30 mg/kg/day for 4 to 7 days) were given continuous aciclovir infusion (0.45 to 3.3 mg/kg/hour) for 2 to 29 days with resolution of the infection in 2 recipients (Fletcher et al. 1989).

4.1.5 Human Immunodeficiency Virus

The role of herpesvirus infections in the transmission of HIV and development of AIDS is as yet incompletely understood. Disruption of the mucosal epithelium may result in increased spread of infection by HIV seropositive patients with genital ulceration, and increased seroconversion in HIV-negative patients with genital ulceration who are exposed to HIV (Kreiss et al. 1988). It has recently been demonstrated that HHV-6 alone can target and kill natural killer cells (Lusso et al. 1993). Infection with HHV-6 can cause expression of CD4 antigen on natural killer cells, thus predisposing the cell to HIV infection. Holmberg et al. (1988) mentions *in vitro* studies suggesting that some herpes viruses may act as cofactors in HIV disease by reactivating latent HIV. Webster et al. (1989) reported that CMV- and HIV-positive patients were more than twice as likely to progress to HIV disease as CMV-negative HIV-positive patients. Although an association between herpes viruses and the development of AIDS was not supported by data reported by Holmberg et al. (1988) or Barnass et al. (1989), the consequences of nontreatment of herpesvirus infections may be more serious than previously suspected.

The effects of aciclovir on laboratory parameters indicating HIV infection are equivocal. Intravenous aciclovir (50 mg/kg up to 3.5g) was given as a once-weekly infusion (plus 1g oral probenecid) in 24 mildly symptomatic HIV-positive patients for 4 months in a double-blind randomised trial (Chavanet et al. 1990b). The mean changes in CD4+ cell counts (+68 *vs* −105 cells/μl with placebo; nonsignificant) and β_2-microglobulin levels (−0.27 *vs* +0.63 mg/L with placebo; $p < 0.025$) suggested a delay in disease progression. However, several nonblinded comparative studies in HIV-positive patients who were asymptomatic or had AIDS-related complex (ARC) found the addition of high-dose oral aciclovir to zidovudine therapy was associated with no significant difference in laboratory parameters including p24 antigen levels or CD4+ cell counts (Brockmeyer et al. 1989; Collier et al. 1990; Weber et al. 1991). These results were substantiated by Pedersen et al. (1992) in a double-blind randomised trial in 197 patients with AIDS or ARC, in which oral aciclovir (800mg every 6 hours) had no additional effect on p24 antigen levels to that provided by zidovudine.

Recent evidence, however, suggests a potential benefit of combined therapy on survival, and incidence of associated infections, in patients with AIDS or ARC (table X). Cooper et al. (1991) reported a significant difference in time to development of AIDS-defining opportunistic infections in patients with ARC who received 6 months' treatment with aciclovir plus zidovudine compared with those receiving placebo alone. There was no significant difference between the group receiving zidovudine monotherapy and that receiving placebo in this parameter. The patient groups were stated to be comparable. Although the placebo group had slightly higher (not significant) CD4+ counts than the other groups, the authors considered that this did not affect the outcome. No effect on survival was seen during the 6 months of this trial.

The 134 patients receiving active treatment in the trial by Cooper et al. (1991) were included in an extended study by the same group (Cooper et al. 1993) along with 131 patients with AIDS. Opportunistic infections occurred in fewer patients receiving combination versus monotherapy (not significant). The incidence of herpesvirus infections was decreased in patients receiving aciclovir/zidovudine therapy versus those receiving zidovu-

Table X. Summary of multicentre randomised trials of oral aciclovir (A) plus oral zidovudine (Z) versus zidovudine alone in patients with AIDS or ARC

Reference	ARC/AIDS	No. of patients	Dosage (duration in weeks)	Incidence of opportunistic infections (%)	Incidence of herpes virus infection (%)	Survival (% alive at end of therapy)
Cooper et al. (1991)[a]	ARC	A+Z 67 Z 67 P 65	A 800mg q6h Z 250-500mg q6h (24)	A+Z 7* Z 9 P 18	A+Z 7 Z 18 P 22	A+Z 99 Z 96 P 94
Cooper et al. (1993)[a]	ARC	A+Z 67 Z 67	A 800mg q6h Z 250-500mg q6h (48)[b]	A+Z 13 Z 15	A+Z 13 Z 21	A+Z 97* Z 88
	AIDS	A+Z 62 Z 69		A+Z 45 Z 52	A+Z 10 Z 28	A+Z 79* Z 59
Lobato-Mendizábal & Ruiz-Argüelles (1992)[c]	ARC/AIDS	A+Z 15 Z 11	A 200mg tid Z 100mg tid (156)	A+Z 33 Z 36		A+Z 93* Z 55

* $p < 0.05$ versus zidovudine monotherapy except in Cooper et al. (1991) study where $p < 0.05$ versus placebo.

a Double-blind trial.

b Continuation of Cooper et al. (1991) study.

c Nonblinded trial.

Abbreviations: AIDS = acquired immunodeficiency syndrome; ARC = AIDS-related complex; P = placebo; q6h = every 6 hours; tid = 3 times daily.

dine alone and mortality was significantly lower in the combination therapy group over the year of treatment (fig. 3).

These results were similar to those achieved by Lobato-Mendizábal and Ruiz-Argüelles (1992), who reported significantly lower mortality in the group receiving aciclovir/zidovudine for up to 3 years than in those receiving zidovudine monotherapy (table X). In patients with initial CD4+ counts > 200/μl, the response to the antiviral combination was also superior in terms of improvements in Karnofsky score, bodyweight and CD4+ cell counts, and the incidence of infection, cancer and anaemia secondary to treatment.

The effects of aciclovir on survival in HIV-positive patients were again positive in a randomised double-blind study in patients with advanced HIV infection (Youle et al. 1993). Twenty-seven of 153 patients receiving oral aciclovir (800mg 4 times daily for 48 weeks) died during the 1-year follow-up, compared with 43 of 149 placebo recipients (probability of death 0.23 *vs* 0.39; $p = 0.018$). The survival benefit was apparent in patients receiving concomitant zidovudine for ≥ 60 days during the study (probability of death 0.12 *vs* 0.29; $p = 0.029$).

4.2 Viral Infection Prophylaxis

4.2.1 Patients with Haematological Disorders

Several well-designed placebo-controlled studies, in patients considered at increased risk of herpesvirus disease (including those with bone marrow failure as a result of underlying leukaemias, lymphomas or primary anaemias, and/or with immunosuppression as a result of intensive radiotherapy or cytotoxic chemotherapy), have demonstrated virtually complete suppression of latent clinical HSV and VZV infections during intravenous or oral aciclovir prophylaxis. In addition, up to 50% of the HSV infections which did recur manifested as asymptomatic viral shedding (see review by O'Brien & Campoli-Richards 1989).

Protection was confined to the period of drug administration in most patients. Long term (6-month) aciclovir prophylaxis in patients undergoing bone marrow transplant suppressed varicella zoster infection completely, but localised VZV infection developed in about 20 to 30% of patients

on drug withdrawal (Ljungman et al. 1986; Perren et al. 1988; Sempere et al. 1992). These results were substantiated in a double-blind study of 52 patients with a pre-bone marrow transplant history of varicella given oral aciclovir (800mg twice daily) or placebo for a year after transplantation (Bowden et al. 1989). Six patients administered placebo and none administered aciclovir developed VZV infection during the year of treatment ($p = 0.02$). However, 2 aciclovir-treated patients developed VZV infections within 2 months of drug withdrawal.

However, extension of the period of prophylaxis may offer protection against HSV infections until relative immunocompetence is achieved in patients completing chemo- or radiotherapy. Ljungman et al. (1986) reported a significantly decreased incidence of HSV episodes in the follow-up period after aciclovir treatment compared with placebo. In one recent placebo-controlled trial involving 82 patients undergoing bone marrow transplant (Selby et al. 1989), treatment with intravenous aciclovir for 23 days followed by oral aciclovir to a total of 6 months profoundly reduced the number of HSV and VZV infections, and the reduction in HSV infections remained statistically significantly different between the groups throughout the 1-year follow-up. However, contrasting results were presented in another study employing extended aciclovir prophylaxis: the incidence of HSV reactivation after aciclovir prophylaxis was greater than that seen in placebo recipients (Shepp et al. 1987).

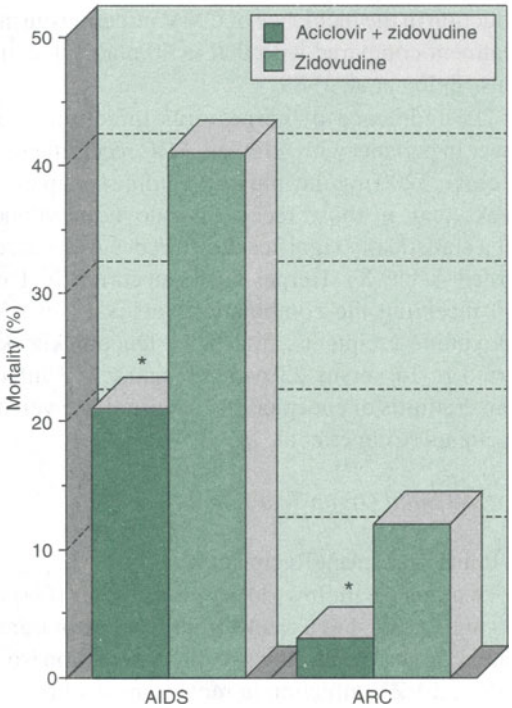

Fig. 3. Comparative mortality associated with oral aciclovir (800mg every 6 hours) plus zidovudine (250mg every 6 hours) versus zidovudine monotherapy in 131 patients with acquired immunodeficiency syndrome (AIDS) and 134 patients with AIDS-related complex (ARC) receiving therapy for 1 year (from Cooper et al. 1993). * $p < 0.05$ between treatment groups.

Aciclovir is ineffective in treating established CMV disease, and appears to have reduced activity in preventing reactivation of CMV infection in immunocompromised patients compared with its effect on HSV and VZV. Nonetheless, a randomised placebo-controlled trial of 39 bone marrow transplant recipients (Gluckman et al. 1983) demonstrated significantly decreased viral shedding during oral aciclovir prophylaxis (800 mg/day for 4 weeks) and fewer CMV infections in the follow-up period after treatment. The incidences of CMV infection, CMV viraemia and HSV disease were reduced during the double-blind evaluation of intravenous (1500 mg/m^2/day for 1 month) followed by oral (3200 mg/day for 8 months) aciclovir in 105 patients undergoing bone marrow transplant, compared with 103 patients who received oral aciclovir (1600 mg/m^2/day for 1 month) and then placebo for 8 months (Ljungman et al. 1993). Mortality from all causes was also lower in the group receiving intravenous plus oral aciclovir prophylaxis (25%) than in patients receiving oral aciclovir plus placebo (41%). Similarly, a nonrandomised study found that intravenous aciclovir prophylaxis (500 mg/m^2 every 8 hours for 6 weeks from 5 days before allogeneic bone marrow transplantation) reduced the incidence of invasive CMV disease (pneumonia and gastrointestinal infection; 22 *vs* 38%; $p = 0.008$) and mortality (29 *vs* 59%; $p <$

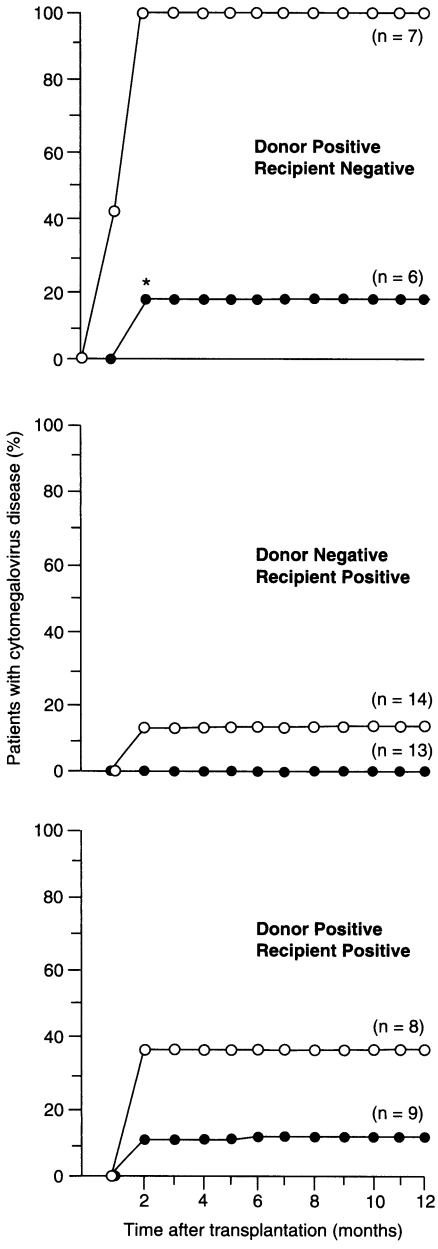

Fig. 4. Outcome for 73 renal allograft recipients after receiving aciclovir 800 to 3200 mg/day for 12 weeks as prophylaxis for cytomegalovirus (CMV) disease, according to initial CMV serological status of recipient and donor. In 16 seronegative patients (8 aciclovir, 8 placebo) who received seronegative donor organs no disease developed (from Balfour et al. 1989). *Symbols:* • = aciclovir recipients; o = placebo recipients; * p = 0.005 *vs* placebo.

0.01) in 86 patients seropositive for CMV compared with 65 untreated seropositive controls (Meyers et al. 1988). Further, 10 patients with AIDS and CMV retinitis stabilised by ganciclovir induction experienced a median delay in progression of retinitis of 32 days, and the prevention of progression of retinitis to all previously uninvolved eyes, in a recent investigation of intravenous aciclovir (10 mg/kg every 8 hours for 14 days) plus oral zidovudine (Sha et al. 1991).

However, in most well designed trials reviewed in O'Brien and Campoli-Richards (1989), CMV infections of varying severity occurred in several patients receiving prophylactic aciclovir. Similarly, intravenous (5 mg/kg [250 mg/m^2 in children] every 8 hours for 23 days) followed by oral (800mg [400mg in children] every 6 hours for 6 months) prophylaxis starting the day before bone marrow transplantation in 42 patients caused no reduction in the incidence of CMV infection during treatment compared with that in 40 placebo recipients (Selby et al. 1989).

The incidence of herpesvirus infections was lower in patients with AIDS or ARC receiving oral aciclovir 3200 mg/day plus zidovudine for up to 48 weeks than in those receiving zidovudine alone, but a statistically significant difference was not recorded (table X). Herpes zoster occurred in 1 of 129 receiving the combination versus 12 of 136 zidovudine recipients, oral hairy leucoplakia occurred in 14 versus 23 patients, and CMV infections (retinitis or encephalitis) occurred in 5 versus 8 patients (Cooper et al. 1993).

4.2.2 Solid Organ Transplant Recipients

Renal Transplant Recipients

Treatment with low-dose oral aciclovir (600 to 800 mg/day for 4 to 6 weeks from the time of transplantation) has been shown to offer protection from HSV and VZV infection in renal transplant recipients in several comparative studies (see review by O'Brien & Campoli-Richards 1989). Clinical symptoms were completely suppressed but virological breakthrough did occur. During follow-up, significantly fewer patients who had received pla-

cebo during the active treatment phase remained free of an infectious episode. These results were substantiated in a nonrandomised nonblinded study of low-dose oral aciclovir (400 to 600 mg/day) in renal allograft recipients during muromonab-CD3 (OKT3) administration (9 to 10 days) for treatment of acute rejection (Tang et al. 1989). Significantly fewer aciclovir recipients developed HSV infection during treatment plus the 60-day follow-up period than did untreated controls.

High dose oral aciclovir (800mg 4 times daily for 12 weeks) prophylaxis completely suppressed HSV shedding in 23 of 25 renal allograft recipients compared with 11 of 25 patients receiving placebo in a double-blind randomised trial (Schlech et al. 1993). Clinically evident HSV disease developed in 3 placebo recipients and 1 noncompliant aciclovir recipient. VZV, EBV and CMV infection had previously occurred in 8, 46 and 25 of the 50 enrolled patients, but no recurrences were seen in either group during the trial. Grafts tended to survive longer in aciclovir recipients (mean 215 weeks) than in the placebo group (150 weeks), and the difference became statistically significant when the 42 patients seropositive for HSV before the trial were analysed separately (237 *vs* 153 weeks, $p = 0.03$).

CMV is reported to be the main cause of infection after solid organ transplant (Balfour 1991; Stratta et al. 1992). Among renal allograft recipients not receiving CMV prophylaxis, 51 to 61% will become infected with CMV, and 20 to 29% will develop clinically apparent disease (Balfour et al. 1991). Several studies have addressed the efficacy of high-dose aciclovir in preventing infections caused by this organism. Balfour et al. (1989) performed a placebo-controlled double-blind trial of high-dose oral aciclovir (800 to 3200 mg/day for 12 weeks) in 104 patients receiving cadaveric renal allograft transplants. The rates of CMV infection and clinically evident disease were reduced with aciclovir prophylaxis from 61 to 36% and 29 to 8%, respectively, during 1 year of observation. Aciclovir prophylaxis appeared most effective in seronegative patients receiving a graft from seropositive donors ($p = 0.005$; fig. 4). The emergence of CMV disease in aciclovir-treated seropositive recipients of transplants from seropositive or seronegative donors was also decreased, but this difference was not significant (fig. 4).

These results were supported by a noncomparative trial of high-dose oral aciclovir (800 to 3200 mg/day for 12 weeks) in 14 CMV-seronegative recipients of renal allografts from seropositive donors, of whom only one patient, who admitted noncompliance with aciclovir, developed CMV infection (Vasquez et al. 1993). Wong et al. (1991) reported a CMV disease rate of 38% in 21 seropositive patients treated with high-dose oral aciclovir in a nonblind study. However, CMV infection and disease occurred significantly less often in 32 CMV-seropositive patients treated with oral aciclovir (800 to 3200 mg/day depending on serum creatinine clearance) for 3 months from renal transplant than in 32 historical controls in a study by Legendre et al. (1993). The difference was not significant for the 10 seronegative patients in this study when compared with 20 similar controls.

Prophylaxis of CMV infections in renal transplant patients has also been investigated using low-dose oral aciclovir (200 to 1000 mg/day). However, investigations are limited to 2 noncomparative trials in seronegative recipients of grafts from seropositive donors which reported conflicting results. Among 56 patients treated with aciclovir 600 mg/day for 6 months, the CMV disease rate was 3.6% (MacDonald et al. 1991), while Barton and Nicholson (1991) reported a disease rate of 41.6% and an infection rate of 83% among 12 patients treated with a single perioperative dose of intravenous pooled immunoglobulin plus oral aciclovir 200 to 1000 mg/day (depending on renal function) for 6 weeks.

Liver Transplant Recipients

In a nonblinded randomised comparative study, 50 patients undergoing liver transplantation received prophylactic oral aciclovir (600 to 2000 mg/day depending on bodyweight and renal function) for 12 weeks, plus intravenous immunoglob-

ulin and muromonab CD3 (OKT3) therapy, while 50 patients received muromonab CD3 alone (Stratta et al. 1992). The percentage of patients experiencing any viral infection was less in the combination therapy group (66 *vs* 44%; $p < 0.05$), as were the incidences of CMV infection (42 *vs* 36%; $p > 0.05$), HSV infections (32 *vs* 12%; $p < 0.05$), and EBV infections (10 *vs* 0%; $p < 0.05$).

Reduced infection rates were also seen in another nonblinded randomised trial of intravenous aciclovir (500 mg/m^2 every 8 hours) for 10 days, followed by oral aciclovir (3200 mg/day adjusted for renal function) for a total of 12 weeks in 60 CMV-seropositive liver transplant recipients (Saliba et al. 1993). There was a significantly lower incidence of CMV infection (18.3 *vs* 38.3%, $p = 0.01$), disease (6.6 *vs* 23.3%, $p = 0.01$) and interstitial pneumonia (5 *vs* 16.6%, $p = 0.04$) in the aciclovir recipients than in 60 untreated control patients.

These results are substantiated in 2 nonblinded nonrandomised comparative trials investigating the effects of prophylaxis with oral aciclovir (2000 to 3200 mg/day, adjusted for renal function, for 12 weeks) in patients undergoing liver transplantation (Mollison et al. 1991; Stratta et al. 1991). Mollison et al. (1991) reported a decrease in the rate of infection from 100% in 12 untreated controls to 30.8% in 13 patients receiving prophylaxis ($p = 0.0014$); CMV disease involving body organs occurred in 3 versus 1 patient(s). In the second trial, the rate of development of primary CMV disease was reduced from 71.4% in 21 untreated controls to 23.8% in 21 patients receiving prophylaxis with aciclovir plus intravenous immunoglobulin ($p < 0.01$; Stratta et al. 1991).

The efficacy of intravenous aciclovir (5 mg/kg/day) plus intravenous gamma globulin (200 mg/kg twice weekly; $n = 52$) was compared with that of intravenous ganciclovir (5 mg/kg/day) plus gamma globulin ($n = 52$) as prophylaxis during hospitalisation in patients receiving hepatic transplants (Nakazato et al. 1993). All patients received oral aciclovir (5 mg/kg/day) as outpatients (duration of therapy not given). There were no significant differences in patient or graft survival between the groups at 3 months (aciclovir 86 and 83% *vs* ganciclovir 88 and 86%) and 6 months (86 and 83% *vs* 86 and 85%). CMV disease occurred in 8 aciclovir recipients and 2 ganciclovir recipients ($p < 0.05$).

Heart or Lung Transplant Recipients

Some success in preventing CMV infection has been achieved with the combination of aciclovir plus CMV-specific immunoglobulin for 12 weeks in a noncomparative trial involving 10 children (500 mg/m^2/day; route of administration not reported) [Zandotti et al. 1992] and in 12 CMV-seropositive patients (2400 mg/day orally) in a nonblinded sequential trial (Maurer et al. 1993) after lung transplantation. Of the 4 CMV-seronegative children who received seropositive donor lungs, 2 developed CMV infection, 1 without clinical symptoms (Zandotti et al. 1992). CMV pneumonitis developed in 8 of the 12 patients receiving high-dose oral aciclovir versus 5 of 28 receiving immunoglobulin alone, and 7 of 22 receiving immunoglobulin plus intravenous ganciclovir prophylaxis (Maurer et al. 1993).

There is similar evidence of some efficacy for this combination in patients with heart transplants. Of 23 patients receiving oral aciclovir (1600 mg/day for 6 weeks) plus CMV-specific immunoglobulin in a noncomparative trial, all 5 CMV-seronegative recipients of seropositive donor hearts developed CMV infection, but not clinical disease (Eisenmann et al. 1990). CMV infection was reactivated in five of 13 seropositive recipients of seropositive donor hearts but only 2 of these developed manifest disease. Similarly, Jazzar et al. (1992) mention a complete lack of symptomatic CMV disease in a series of 53 heart transplant patients receiving prophylactic aciclovir 3200 mg/day for 12 weeks, irrespective of CMV serology, in a retrospective study.

The possible benefits of aciclovir as prophylaxis against HSV infection in heart or lung transplant recipients is less well-examined. In a retrospective study of 82 patients (Carrier et al. 1992), significant reductions in the percentage of patients

developing HSV infection after heart transplant and in the duration of hospital stay, and significant increases in the percentage of patients free of HSV infection 1, 6 and 12 months after the operation, were associated with oral aciclovir 600 mg/day treatment for a mean of 22 days versus untreated controls.

5. Tolerability

5.1 General Effects

As discussed in previous reviews in the Journal (Richards et al. 1983; O'Brien & Campoli-Richards 1989), aciclovir therapy by ocular, topical, oral or intravenous routes is generally very well tolerated. Ocular administration of the ophthalmic ointment is rarely associated with adverse events, and although local burning or stinging may occur after topical application of the cream, only a small proportion of patients have reported mild erythema or drying. Allergic contact dermatitis has been documented occasionally in patients using topical aciclovir cream (Baes & van Hecke 1990; Goday et al. 1991; Goh 1990; Gola et al. 1989; Valsecchi et al. 1990) but recent noncomparative studies of the ointment in healthy volunteers confirm the general low level of adverse effects with this preparation (Niimura et al. 1990a, b).

Oral aciclovir has been associated with nausea, vomiting, diarrhoea, stomach pain, rash and headache in fewer than 5% of patients, with similar incidences reported for placebo (Mertz et al. 1988b). Exogenous lactase has been successfully used to prevent gastrointestinal intolerance believed to be related to the lactose base in aciclovir tablets rather than to the active compound (Manka 1989). A postmarketing surveillance report has suggested that users (n = 1165) of oral aciclovir are no more likely to be hospitalised or develop illnesses (with the possible exception of carpal tunnel syndrome) than nonusers (Johnson et al. 1991).

Reports of acute reversible renal failure (Eck et al. 1991; Hernandez et al. 1991) and of neurotoxicity (Davenport et al. 1992; Eck et al. 1991; Ferré et al. 1992; MacDiarmaid-Gordon et al. 1992; Swan & Bennett 1989) occurring in patients receiving oral therapy are rare, but emphasise the necessity for evaluation of renal function and state of hydration, especially in elderly patients, before initiating aciclovir therapy. A double-blind placebo-controlled study of oral aciclovir in patients with recurrent genital herpes found no significant clastogenic effect in peripheral lymphocytes, despite previous reports of such effects at very high doses *in vitro* and in animal models (Clive et al. 1991).

Inflammation and phlebitis at the injection site are the most frequently reported reactions with intravenous aciclovir. Reports continue to appear of neurological and/or psychiatric effects (lethargy, tremors, confusion, hallucinations, seizures) [Davenport et al. 1992; Fischer et al. 1990; Haefeli et al. 1993; Krieble et al. 1993] and of renal precipitation of the drug resulting in reversible renal insufficiency (Bennasr et al. 1992; Bianchetti et al. 1991; Bömers & Gedebjerg 1991; Firat et al. 1992; Fischer et al. 1990; Gill & Burgess 1990; Haefeli et al. 1993; Krieble et al. 1993; Rashed et al. 1990). Both these effects have usually been reported in patients with high peak plasma aciclovir concentrations.

The administration of oral aciclovir (3200 mg/day for 3 months) to renal transplant recipients in a retrospective study did not affect trough serum cyclosporin concentrations or cause changes in serum creatinine concentrations (Dugandzic et al. 1991). However, a decline in renal function was demonstrated in all dogs administered intravenous aciclovir, with short high-dose regimens more detrimental than longer treatment periods at lower doses (Kimes et al. 1989), and short term coadministration of aciclovir plus cisplatin in rats caused a slight (nonsignificant) increase in nephrotoxicity over that caused by cisplatin alone (Hannemann et al. 1992). The use of slow aciclovir infusion rates, adequate hydration and, in patients with renal dysfunction, lower aciclovir doses are recommended to minimise renal complications.

Aciclovir does not significantly alter the pharmacokinetics of zidovudine and the tolerability of the combination appears to be similar to that of

zidovudine alone (Hollander et al. 1989; Tartaglione et al. 1991).

Inadvertent intravenous aciclovir overdose in 2 neonates (100 mg/kg for 3 doses in a 5-day-old infant and 65 mg/kg for 1 dose in a 13-day-old infant) caused no toxicity (McDonald et al. 1989). One infant was treated with an exchange transfusion and the other with oral activated charcoal. However, a retrospective review of 94 children (mean age 5.9 years) receiving intravenous aciclovir (41 to 1191 mg/m^2 for 7 to 9 days) demonstrated an overall rate of toxicity associated with treatment of 30.2% (Kowalczyk et al. 1991). Transient renal toxicity unrelated to aciclovir dosage developed in 13.3% of 75 patients with evaluable renal function, hepatotoxicity developed in 10.2% of 59 patients and neurotoxicity developed in 2.1%. Many of these children had restricted fluid intake. Bianchetti et al. (1991) reported a similar rate of paediatric renal insufficiency (15.8% of 19 children) as a consequence of intravenous aciclovir therapy in children with restricted fluid intake.

After 6 years of monitoring the use of aciclovir in pregnant women, the Aciclovir in Pregnancy Registry has prospectively followed 312 pregnancies (Andrews et al. 1992). Healthy infants were born to 67% of 239 women exposed during the first trimester, 100% of 31 exposed during the second trimester and 98% of 42 exposed during the third trimester. No increase has been seen in the number of birth defects among aciclovir recipients compared with the general population, and there appears to be no consistent pattern of abnormalities. However, because the sample size is small, the Advisory Committee recommend the use of systemic aciclovir only in life-threatening infections.

5.2 Effects on Immune Function

The effects of nucleoside antiviral drugs on host immune response to the infecting virus have not been well defined. Since recovery from viral disease is linked to immune function, any potential toxicity to this function is of importance. The role of cellular immunity in the prevention of HSV recurrence is exemplified by the increased incidence and virulence of herpesvirus infections in immunocompromised patients. Cell-mediated immunity, as assayed *in vitro* using several methods, appears to be minimally affected by aciclovir (reviewed in Richards et al. 1983; see also Heagy et al. 1991), but Stahlmann et al. (1992) have demonstrated impaired function of the immune system in rats after prenatal exposure to aciclovir, with decreased resistance to *Trichinella spiralis* infection. Therapeutic concentrations of aciclovir appear to have only minor effects on macrophage functions *in vitro* (Stenseth et al. 1993). Phagocytosis and production of interferon and tumour necrosis factor were slightly increased, and production of lysozyme reduced.

Clinically, aciclovir appears to interfere with the development of an immune response to herpesvirus antigens, but this could reflect reduced antigen exposure resulting from drug-associated viral inhibition rather than a direct immunosuppressant effect. Thus, antibody titres to certain HSV proteins were depressed by intravenous and oral aciclovir treatment (Ashley & Corey 1984; Ashley et al. 1982; Bernstein et al. 1984). Similarly, early relapses, all associated with lack of detectable antibodies to VZV, occurred in 8 of 98 immunocompromised children who had received intravenous aciclovir 1500 mg/m^2/day for 5 days, extended to 7 to 10 days with oral aciclovir 2000 to 4000 mg/day if clinically required, as treatment for varicella or herpes zoster in a retrospective study (Mészner et al. 1990). In a further 7 patients, oral aciclovir treatment was extended until the production of antibodies, and no early relapse occurred.

In contrast, oral aciclovir treatment of children with primary herpetic gingivostomatitis did not significantly affect the production of antibodies (Cizman et al. 1991). Further, oral aciclovir for 5 to 7 days for VZV infections in children did not influence the immune response to VZV antigen for 1 to 3 years post treatment (Englund et al. 1990a; Rotbart et al. 1993).

Significant reductions (versus placebo) in lymphocyte proliferation response to HSV and VZV

antigens have been noted in aciclovir recipients in some trials of aciclovir prophylaxis (Ljungman et al. 1986; Wade et al. 1984). Seroconversion to VZV was seen in only 21 of 25 (84%) previously unexposed immunocompetent children receiving oral aciclovir 40 or 80 mg/kg/day for 7 days beginning 7 to 9 days after first exposure to the index case of varicella in the family (Asano et al. 1993). The authors suggested that either the remaining 4 children were not infected despite familial contact, or that aciclovir may have completely inhibited the virus in these children, increasing susceptibility to reinfection later, perhaps with more serious consequences.

Recurrent herpesvirus lesions develop in humans despite immunity and often without a detectable rise in circulating neutralising antibodies (Douglas & Couch 1970). Ragab et al. (1989) observed a direct relationship between the extent of the immune response to the initial genital HSV infection and the subsequent frequency of recrudescent symptoms. Oral aciclovir treatment (200mg 5 times daily for 10 days) reduced the antibody titres compared with untreated controls and significantly decreased the number of recurrences. However, this has not been corroborated by other well controlled studies.

Although prophylactic treatment with aciclovir has been shown to prevent outbreaks of genital HSV infection in those suffering frequent recurrences (section 3.1.1), herpesvirus infections of increased severity have recurred immediately after withdrawal of aciclovir treatment in some trials (Ashley & Corey 1984; Wade et al. 1982a). Mean levels of antibodies have been reported to fall significantly during long term aciclovir therapy in patients with frequently occurring genital HSV infection (Gold et al. 1988; Molin et al. 1991). However, the cell-mediated immune response (assessed by *in vitro* lymphocyte proliferation to HSV antigens), decreased in patients with frequently versus infrequently recurring genital HSV infections, was reported to be increased in patients treated with daily suppressive oral aciclovir by Frenkel et al. (1989), falling to prestudy levels on withdrawal of the drug.

6. Dosage and Administration

The recommended dosages of various aciclovir formulations for use as treatment and prophylaxis of a variety of viral infections are presented in table XI. Therapy should be initiated as early as possible following onset of signs and symptoms. For recurrent episodes of mucocutaneous HSV infection, treatment should preferably commence during the prodromal period or when lesions first appear.

Rapid or bolus intravenous injection of parenteral aciclovir should be avoided, as should intramuscular or subcutaneous administration. Intravenous aciclovir should be administered by slow infusion over 1 hour, with sufficient hydration to provide adequate urine flow to prevent aciclovir precipitation in renal tubules. This formulation may be administered via a controlled-rate infusion pump or otherwise should be diluted to less than 5 mg/ml for infusion, since higher concentrations may produce phlebitis or inflammation at the injection site upon inadvertent extravasation. Administration by infusion is also recommended to avoid rapid increases in blood urea and creatinine levels occasionally seen with bolus injection. Continuous infusion of high dose (1.2 to 6.2 mg/kg/hour) aciclovir for up to 6 weeks has been used in immunocompromised patients with HSV infections resistant to usual doses of aciclovir because of altered thymidine kinase activity (Engel et al. 1990; Fletcher et al. 1989), but alternative drugs may also be effective in this situation.

Although the recommended dosage of intravenous aciclovir for prophylaxis of HSV infections in immunocompromised patients is 5 mg/kg every 8 hours (table XI), the minimal effective dose may be lower than this. Peitier and Weisdorf (1991) reported effective prophylaxis with 5 mg/kg every 12 hours in a retrospective study of 42 bone marrow transplant patients (none with HSV disease during therapy) and 32 historical controls receiving aciclovir every 8 hours (3% with HSV disease).

Recommended dosages are available for the treatment and/or prophylaxis of HSV, VZV and CMV infections. Clinical trials of aciclovir treatment of EBV infections have used intravenous and oral doses similar to those used in VZV infections. Oral dosages of 600 to 1600 mg/day, 600 to 2000 mg/day and 600 to 3200 mg/day have been used as prophylaxis against VZV, EBV and CMV in immunocompromised patients in clinical trials to date. A nonblinded comparative trial of two 400mg tablets versus one 800mg tablet given 5 times daily for 7 days to patients with VZV infections found no difference in outcome between the 2 formulations (Palmieri et al. 1993). The few clinical trials

Table XI. Recommended dosages of aciclovir in patients with normal renal function (data on file, Wellcome Foundation Ltd)

Formulation	Indication	Patient group	Dose	Dosage interval	Treatment duration
Ophthalmic ointment (3%)	HSV keratitis	Adults and children	10mm inside lower conjunctival sac	5xd	≥ 3 days after healing
Topical cream (5%)	Treatment of HSV infections of the skin	Adults and children	As required	5xd	5-10 days
Oral tablets, capsules and suspension[a]	Treatment of mucocutaneous HSV infections	Adults and children (>2y)	200mg (400mg[b])	5xd	≥ 5 days
		Children (≤2y)	100mg	5xd	≥ 5 days
	Suppression of recurrent HSV infections[c]	Adults	200mg	2-4xd	As appropriate[d]
			400mg	2xd	As appropriate[d]
	Prophylaxis of HSV infections[e]	Adults and children (>2y)	200mg (400mg[b])	4xd	As appropriate
		Children (≤2y)	100mg	4xd	As appropriate
	Treatment of varicella (chickenpox)	Adults	800mg	5xd	7 days
		Children	20 mg/kg (≤800mg)	4xd	5 days
	Treatment of herpes zoster (shingles)	Adults	800mg	5xd	7 days
	Management of severely immunocompromised patients[f]	Adults and children (>2y)	800mg	4xd	≥ 6 months
Intravenous solution for infusion[g]	Treatment of HSV infections	Adults	5 (10[h]) mg/kg	q8h	≥ 5 days
		Children (3mo-12y)	250 (500[h]) mg/m^2	q8h	≥ 5 days
		Neonates	10 mg/kg	q8h	≥ 10 days
	Prophylaxis of HSV infections[e]	Adults	5 mg/kg	q8h	As appropriate
	Treatment of VZV infections	Adults	5 (10[e]) mg/kg	q8h	≥ 5 days
		Children (3mo-12y)	250 (500[e]) mg/m^2	q8h	≥ 5 days
	Prophylaxis of CMV infections[i]	Adults and children (>2y)	500 mg/m^2	q8h	5 days before transplant to a month after

a Available as 200mg, 400mg and 800mg tablets, 200mg capsules and a suspension containing 200 or 400 mg/5ml.

b In severely immunocompromised patients or those with impaired absorption from the gut.

c In immunocompetent patients.

d Therapy should be interrupted every 6 to 12 months for observation of the natural history of the disease.

e In immunocompromised patients.

f Patients with advanced HIV disease or bone marrow transplant recipients.

g Available as 125mg, 250mg and 500mg vials.

h In patients with herpes encephalitis.

i In bone marrow transplant recipients.

Abbreviations: CMV = cytomegalovirus; HIV = human immunodeficiency virus; HSV = herpes simplex virus; mo = months; q8h = every 8 hours; VZV = varicella zoster virus; xd = times daily; y = years.

that have been performed using oral aciclovir in patients positive for HIV have employed dosages of 600 to 3200 mg/day in combination with zidovudine.

Dosage recommendations for an eyedrops formulation are not currently available, although 2 drops of a 3% solution have been administered 5 times daily (duration not given) in a clinical trial (Cabezas 1991).

Aciclovir dosage should be reduced in patients with renal dysfunction. Recommendations for adult patients are detailed in table XII, but elderly patients and children with renal impairment also require appropriate dosage adjustments.

Washing of hands before and after application of topical aciclovir is recommended to prevent autoinoculation of other body sites and transmission of infection to other persons.

Table XII. Recommended dosages of intravenous and oral aciclovir in adults with acute or chronic renal impairment (data on file, Wellcome Foundation Ltd)

Creatinine clearance in L/h (ml/min)	Route	Dose	Dosage interval
1.5-3.0 (25-50)	Oral	NA	NA
	IV	NA	12-hourly
0.6-1.5 (10-25)	Oral	HSV NA	HSV NA
		VZV 800mg	VZV 8-hourly
		IC 800mg	IC 8-hourly
	IV	NA	24-hourly
0-0.6 (0-10)	Oral	HSV 200mg	HSV 12-hourly
		VZV 800mg	VZV 12-hourly
		IC 800mg	IC 12-hourly
	IV	2.5-5 mg/kg[a]	24-hourly[b] (and after haemodialysis)

a Half the recommended dose for patients with normal renal function (see table XI).

b In patients receiving continuous ambulatory peritoneal dialysis or haemodialysis.

Abbreviations: HSV = herpes simplex virus; IC = severely immunocompromised patients; IV = intravenous; NA = no adjustment required; VZV = varicella zoster virus.

7. Place of Aciclovir in Therapy

Over the past decade, a secure position has been established for aciclovir in the treatment of infections caused by herpes viruses responsible for a wide range of potentially serious diseases. Treatment of patients with herpesvirus infections has become increasingly important as the immunocompromised population grows with the rapid and global spread of AIDS, and the more frequent use of bone marrow and organ transplantation procedures.

Aciclovir is generally well tolerated. Topical formulations are associated with low levels of irritancy, and most adverse events associated with the oral formulation occur with similar frequencies in placebo recipients. Nephrotoxicity and neurotoxicity are rarely reported with oral aciclovir therapy, but can occur more frequently with intravenous administration, especially with high plasma aciclovir concentrations and in patients with renal dysfunction. Slow aciclovir infusion rates, adequate hydration and lower aciclovir dosages in patients with renal impairment are recommended to minimise renal complications.

The recommended indications for aciclovir include:

- treatment of HSV keratitis (ophthalmic ointment)
- treatment of initial and recurrent HSV infections (cream, oral and intravenous formulations)
- treatment of other HSV infections, including those in the neonate (intravenous formulations)
- suppression of recurrent HSV infections in immunocompetent patients (oral formulations)
- prophylaxis of HSV infections in immunocompromised patients (oral and intravenous formulations)
- treatment of VZV infection and complications in immunocompetent and immunocompromised patients (oral and intravenous formulations)
- prophylaxis of CMV infections in bone marrow transplant recipients (intravenous and oral formulations)
- management of severely immunocompromised patients (oral formulations).

7.1 Immunologically Competent Patients

Placebo-controlled investigations of oral or intravenous aciclovir initiated within 4 days of the appearance of symptoms have demonstrated a significant decrease in the duration of viral shedding and general symptoms in immunocompetent patients with HSV infections, especially in primary episodes. The rate of recurrence of infection after treatment withdrawal is not affected. Topical aciclovir has also significantly attenuated the progression of mucocutaneous HSV infections in some trials, but less reliably than with systemic administration, even when therapy was initiated early. Intravenous aciclovir appears to be equally as effective as intravenous vidarabine in neonates with HSV infections, and has been established as the treatment of choice for HSV encephalitis in comparative trials with vidarabine. Aciclovir ophthalmic ointment is at least as effective as idoxuridine, trifluridine and vidarabine ointments in treating herpetic ocular infections.

Administration of oral aciclovir for up to 2 years has suppressed recurrence of HSV infections in > 70% of patients in most trials, with reversion to pretreatment frequencies after discontinuation of the drug. Comparisons of oral aciclovir with oral inosine pranobex have demonstrated a clear advantage for aciclovir in the suppression of recurrent genital HSV infection.

Several well-designed studies have established the efficacy of oral aciclovir in the treatment of VZV infections in otherwise healthy individuals. There is some controversy over the role of aciclovir in treating varicella (chickenpox), since the disease is usually self-limiting, and there is concern over the possibility of decreased immunological protection against herpes zoster (Lassiter 1992) and the possible development of resistant strains of VZV (although this seems unlikely considering the short duration of therapy in immunocompetent children). Serious complications of the disease (such as secondary bacterial infection, Reye's syndrome, acute cerebellar ataxia and meningoencephalitis, and varicella pneumonia) occur only rarely and a reduction in their development with oral aciclovir treatment has not been unequivocally demonstrated. However, the Committee on Infectious Diseases (Hall et al. 1993) recommend consideration of its use, within the first 24 hours of onset of rash, for those at increased risk of severe varicella or its complications. This group includes otherwise healthy nonpregnant patients aged 13 or more, and children older than 1 year with a chronic cutaneous or pulmonary disorder, receiving long term salicylate therapy or corticosteroids. The inclusion of siblings of index cases in this group at increased risk has been suggested by some experts but remains controversial.

Intravenous or oral aciclovir, begun within 72 hours of exanthem onset, attenuates the development of rash and pain associated with herpes zoster (shingles). The incidence and duration of post-herpetic neuralgia was decreased after aciclovir treatment in some trials. Topical idoxuridine and oral brivudine offered some advantages over aciclovir in isolated studies, but there were no differences between these antivirals and aciclovir in time to disappearance of vesicles and time to full crusting. Ocular complications and pain are significantly reduced in patients with zoster ophthalmicus when oral aciclovir is begun within 72 hours of skin eruption. Complications of herpes zoster infections (such as encephalitis and zoster oticus) have been successfully treated with intravenous aciclovir, but comparative trials are few in these patients.

The use of aciclovir in EBV and hepatitis B virus infections in immunocompetent patients has resulted in equivocal success. Trends toward faster improvement with aciclovir than with placebo have been demonstrated in patients with infectious mononucleosis, and addition of aciclovir to interferon-α therapy appears to offer some advantages in patients with chronic hepatitis B.

Combining interferon-α and aciclovir *in vitro* has resulted in synergistic antiviral activity against HSV, VZV and CMV, while interferon-β has shown synergistic activity with aciclovir against HSV. Clinical trials have shown some additional benefit over aciclovir monotherapy with aciclovir

plus interferon-α in the treatment of immunocompetent patients with ocular HSV infections, and with aciclovir plus interferon-β in treating HSV encephalitis (in one subset of patients).

7.2 Immunologically Compromised Patients

The use of intravenous and oral aciclovir is well established in the treatment of immunocompromised patients with HSV infections. The period of viral shedding and the time to healing are reduced and the resolution of pain is accelerated. High doses may be necessary for severe infections not responding to normal doses.

Aciclovir reduces the duration of viral shedding and scabbing time, with accompanying reductions in the progression of the disease, in immunocompromised patients with cutaneous dissemination of herpes zoster or children with varicella. A limited number of comparative trials suggest that intravenous aciclovir is at least as effective as oral brivudine or intravenous vidarabine. High dose oral aciclovir was reported to be as effective as intravenous therapy in a nonblinded randomised trial, but well-designed studies in severely immunocompromised patients would be required to substantiate this finding.

Little clinical improvement is seen in immunocompromised patients with CMV or EBV infections treated with aciclovir and reactivation occurs frequently on withdrawal of the drug. However, patients with infections unresponsive to intermittent therapy with intravenous aciclovir may respond to continuous aciclovir infusion.

Although earlier trials showed no additional effect on p24 antigen levels or CD4+ cell counts when aciclovir was combined with zidovudine therapy in patients with AIDS or ARC, recent studies suggest that the combination may result in improved survival and decreased incidence of opportunistic infections compared with zidovudine alone. However, patient numbers were limited in these trials, the mechanism of the effect is unclear, and further investigation is required to confirm any effect on survival.

With the spread of AIDS and the increased worldwide frequency of bone marrow and organ transplantation, the population of immunosuppressed patients is growing, with a subsequent increase in the necessity for prophylactic suppression of potentially fatal herpesvirus infections in these patients.

Intravenous or oral aciclovir causes virtually complete suppression of latent clinical HSV and VZV infections during prophylactic treatment (associated with decreased severity or incidence of infection on drug withdrawal in some trials) in most patients considered at increased risk of reactivation (patients with haematological disorders who received a bone marrow transplantation, radiotherapy or cytotoxic chemotherapy, and patient who received a solid organ transplant). The prevention of reactivation of CMV infection has been less successful. However, viral shedding and the incidence of invasive CMV disease have been substantially reduced with high dose oral aciclovir prophylaxis, and the addition of CMV-specific immunoglobulin to aciclovir therapy has been successful in some patients undergoing heart or lung transplants.

7.3 Conclusions

The place of aciclovir as an effective agent in the therapy of herpesvirus infections in both immunocompetent and immunocompromised patients remains firmly established. Aciclovir is a first-line option for treatment and prophylaxis of HSV and VZV infections, with no clear advantage shown for newer agents in the few comparisons performed to date. Although higher doses are required for infections caused by other herpes viruses, the prophylactic role of aciclovir in patients at increased risk of herpesvirus infections associated with immune deficiency is now accepted. However, these infections may still recur after completion of aciclovir treatment or prophylaxis, since the latent virus is not eradicated. Finally, further comparisons of aciclovir with alternative antiviral agents, investigations into the clinical effects of the drug in combination with other drugs in herpesvirus and hepa-

titis B infections, particularly in immunocompromised patients, and examination of the effects on survival of combining aciclovir with zidovudine in HIV-positive patients, may well broaden the scope of aciclovir use in the future.

References

Agut H, Aubin J-T, Huraux J-M. Homogeneous susceptibility of distinct human herpesvirus 6 strains to antivirals in vitro. Journal of Infectious Diseases 163: 1382-1383, 1991

Agut H, Huraux J-M, Collandre H, Montagnier L. Susceptibility of human herpesvirus 6 to acyclovir and ganciclovir. Lancet 2: 626, 1989

Albeck H, Ninn-Pedersen K. Aciclovir in the treatment of facial palsy due to the zoster virus. In Danish. Ugeskrift for Laeger 151: 90-92, 1989

Åkesson-Johansson A, Harmenberg J, Wahren B, Linde A. Inhibition of human herpesvirus 6 replication by 9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine (2HM-HBG) and other antiviral compounds. Antimicrobial Agents and Chemotherapy 34: 2417-2419, 1990

Alexander GJM, Fagan EA, Hegarty JE, Yeo J, Eddleston ALWF, et al. Controlled clinical trial of acyclovir in chronic hepatitis B virus infection. Journal of Medical Virology 21: 81-87, 1987

Aliaga A, Armijo M, Camacho F, Castro A, Cruces M, et al. Topical 40% idoxuridine in dimethylsulfoxide versus oral acyclovir in the treatment of herpes zoster. A multicenter double blind clinical study. In Spanish. Medicina Clinica 98: 245-249, 1992

Andersson J, Britton S, Ernberg I, Andersson U, Henle W, et al. Effect of acyclovir on infectious mononucleosis: a double-blind placebo-controlled study. Journal of Infectious Diseases 153: 283-290, 1986

Andrei G, Snoeck R, Schols D, Goubau P, Desmyter J, et al. Comparative activity of selected antiviral compounds against clinical isolates of human cytomegalovirus. European Journal of Clinical Microbiology and Infectious Diseases 10: 1026-1033, 1991

Andreoni M, Canfarini M, Grint PCA, Martorelli M, di Luzio Paparatti U, et al. A double blind, placebo controlled trial of efficacy and safety of oral acyclovir (Zovirax®) in the treatment of chickenpox in adults. European Review for Medical and Pharmacological Sciences 14: 1-8, 1992

Andrews EB, Yankaskas BC, Cordero JF, Schoeffler K, Hampp S, et al. Acyclovir in pregnancy registry: six years' experience. Obstetrics and Gynecology 79: 7-13, 1992

Asano Y, Yoshikawa T, Suga S, Kobayashi I, Nakashima T, Yazaki T, et al. Postexposure prophylaxis of varicella in family contact by oral acyclovir. Pediatrics 92: 219-222, 1993

Ashley RL, Corey L. Effect of acyclovir treatment of primary genital herpes on the antibody response to herpes simplex virus. Journal of Clinical Investigation 73: 681-688, 1984

Ashley RL, Fife K, Corey L. Specific humoral immunity in patients receiving acyclovir treatment for primary genital herpes simplex virus (HSV) infections. Abstract. Clinical Research 30: 361A, 1982

Baba M, Ito M, Shigeta S, de Clercq E. Synergistic antiviral effects of antiherpes compounds and human leukocyte interferon on varicella-zoster virus in vitro. Antimicrobial Agents and Chemotherapy 25: 515-517, 1984

Baes H, van Hecke E. Contact dermatitis from Zovirax cream. Contact Dermatitis 23: 200-201, 1990

Baildam EM, Ewing CI, D'Souza SW, Stevens RF. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): response to acyclovir. Journal of the Royal Society of Medicine 85: 179-180, 1992

Baker DA, Blythe JG, Kaufman R, Hale R, Portnoy J. One-year suppression of frequent recurrences of genital herpes with oral acyclovir. Obstetrics and Gynecology 73: 84-87, 1989

Balfour Jr HH. Options for prevention of cytomegalovirus disease. Annals of Internal Medicine 114: 598-599, 1991

Balfour Jr HH, Bean B, Laskin OL, Ambinder RF, Meyers JD, et al. Acyclovir halts progression of herpes zoster in immuno-compromised patients. New England Journal of Medicine 308: 1448-1453, 1983

Balfour Jr HH, Chace BA, Stapleton JT, Simmons RL, Fryd DS. A randomized, placebo-controlled trial of oral acyclovir for the prevention of cytomegalovirus disease in recipients of renal allografts. New England Journal of Medicine 320: 1381-1387, 1989

Balfour Jr HH, Kelly JM, Suarez CS, Heussner RC, Englund JA, et al. Acyclovir treatment of varicella in otherwise healthy children. Journal of Pediatrics 116: 633-639, 1990

Balfour Jr HH, Fletcher CV, Dunn D. Prevention of cytomegalovirus disease with oral acyclovir. Transplantation Proceedings 23 (Suppl. 1): 17-19, 1991

Balfour Jr HH, Rotbart HA, Feldman S, Dunkle LM, Feder Jr HM, et al. Acyclovir treatment of varicella in otherwise healthy adolescents. Journal of Pediatrics 120: 627-633, 1992

Barnass S, O'Toole C, Colvin B. Cytomegalovirus infection and progression to AIDS. Lancet 2: 336, 1989

Barton IK, Nicholson F. Use of pooled immunoglobulin and acyclovir as prophylaxis against cytomegalovirus disease in recipients of renal allografts. Nephrology Dialysis Transplantation 6: 525-526, 1991

Barton IG, Kinghorn GR, Rowland M, Jeavons M, Al-Omer LS, et al. Recurrences after first episodes of genital herpes in patients treated with topical acyclovir cream. Antiviral Research 4: 293-300, 1984

Bennasr S, Brun P, Loirat C, Jacqz-Aigrain E. Aciclovir et insuffisance renale: deux cas pediatriques. Abstract no.21. Therapie 47: 223, 1992

Benninger MS. Acyclovir for the treatment of idiopathic vocal fold paralysis. Ear Nose and Throat Journal 71: 207-208, 1992

Berger SA, Weinberg M, Treves T, Sorkin P, Geller E, et al. Herpes encephalitis during pregnancy: failure of acyclovir and adenine arabinoside to prevent neonatal herpes. Israel Journal of Medical Sciences 22: 41-44, 1986

Bergström T, Alestig K. Treatment of primary and recurrent herpes simplex virus type 2 induced meningitis with acyclovir. Scandinavian Journal of Infectious Diseases 22: 239-240, 1990

Bergström T, Trollfors B. Recurrent herpes simplex virus type 2 encephalitis in a preterm neonate. Favourable outcome after prolonged acyclovir treatment. Acta Paediatrica Scandinavica 80: 878-881, 1991

Berk L, Schalm SW, de Man RA, Heytink RA, Berthelot P, et al. Failure of acyclovir to enhance the antiviral effect of α lymphoblastoid interferon on HBe-seroconversion in chronic hepatitis B. A multi-centre randomized controlled trial. Journal of Hepatology 14: 305-309, 1992

Bernstein DI, Lovett MA, Bryson YJ. The effects of acyclovir on antibody response to herpes simplex virus in primary genital herpetic infections. Journal of Infectious Diseases 150: 7-13, 1984

Bevilacqua F, Marcello A, Toni M, Zavattoni M, Cusini M, et al. Acyclovir resistance/susceptibility in herpes simplex virus type 2 sequential isolates from an AIDS patient. Journal of Acquired Immune Deficiency Syndromes 4: 967-969, 1991

Beyer CF, Arens MQ, Hill GA, Rose BT, Beyer LR, et al. Oral acyclovir reduces the incidence of recurrent herpes simplex keratitis in rabbits after penetrating keratoplasty. Archives of Ophthalmology 107: 1200-1205, 1989

Bianchetti MG, Roduit C, Oetliker OH. Acyclovir-induced renal failure: course and risk factors. Pediatric Nephrology 5: 238-239, 1991

Birch CJ, Tachedjian G, Doherty RR, Hayes K, Gust ID. Altered sensitivity to antiviral drugs of herpes simplex virus isolates from a patient with the acquired immunodeficiency syndrome. Journal of Infectious Diseases 162: 731-734, 1990

Biron KK, Elion GB. Effect of acyclovir combined with other antiherpetic agents on varicella zoster virus in vitro. Acyclovir Symposium. American Journal of Medicine 73: 54-57, 1982

Blum MR, Liao SHT, de Miranda P. Overview of acyclovir pharmacokinetic disposition in adults and children. Acyclovir Symposium. American Journal of Medicine 73: 186-192, 1982

Boivin G, Erice A, Crane DD, Dunn DL, Balfour Jr HH. Acyclovir susceptibilities of herpes simplex virus strains isolated from solid organ transplant recipients after acyclovir or ganciclovir prophylaxis. Antimicrobial Agents and Chemotherapy 37: 357-359, 1993

Bömers K, Gedebjerg K. Renal involvement during intravenous treatment with acyclovir. In Danish. Ugeskrift for Laeger 153: 288, 1991

Bowden RA, Rogers KS, Meyers JD. Oral acyclovir (ACV) for the long-term suppression of varicella zoster virus (VZV) infection after marrow transplant. Program and Abstracts of the 29th Interscience Conference on Antimicrobial Agents and Chemotherapy, Texas, September 17-20, 1989. Abstract no.62, p.111, 1989

Bowman CA, Woolley PD, Herman S, Clarke J, Kinghorn GR. Asymptomatic herpes simplex virus shedding from the genital tract whilst on suppressive doses of oral acyclovir. International Journal of STD and AIDS 1: 174-177, 1990

Brigden D, Fowle A, Rosling A. Acyclovir, a new antiherpetic drug: early experience in man with systemically administered drug. In Collier LH & Oxford J (Eds) Developments in antiviral therapy, pp. 53-62, Academic Press, London, 1980

Brisebois JJ, Dumas VM, Joncas JH. Comparison of two methods in the determination of the sensitivity of 84 herpes simplex virus (HSV) type 1 and 2 clinical isolates to acyclovir and alpha-interferon. Antiviral Research 11: 67-76,1989

Brockmeyer NH, Kreuzfelder E, Mertins L, Daecke C, Goos M. Zidovudine therapy of asymptomatic HIV1-infected patients and combined zidovudine-acyclovir therapy of HIV1-infected patients with oral hairy leukoplakia. Journal of Investigative Dermatology 92: 647, 1989

Broussard RC, Payne DK, George RB. Treatment with acyclovir of varicella pneumonia in pregnancy. Chest 99: 1045-1047, 1991

Brown ZA, Baker DA. Acyclovir therapy during pregnancy. Obstetrics and Gynecology 73: 526-531, 1989

Burgess ED, Gill MJ. Intraperitoneal administration of acyclovir in patients receiving continuous ambulatory peritoneal dialysis. Journal of Clinical Pharmacology 30: 997-1000, 1990

Burns WH, Sandford GR. Susceptibility of human herpesvirus 6 to antivirals in vitro. Journal of Infectious Diseases 162: 634-637, 1990

Cabezas A. Treatment of mild keratitis with acyclovir 3% eye drops, a new pharmaceutical formulation. European Journal of Clinical Pharmacology 40: 533-534, 1991

Carmack MA, Twiss J, Enzmann DR, Amylon MD, Arvin AM. Multifocal leukoencephalitis caused by varicella-zoster virus in a child with leukemia: successful treatment with acyclovir. Pediatric Infectious Diseases Journal 12: 402-406, 1993

Carrier M, Pelletier GB, Cartier R, Leclerc Y, Pelletier LC. Prevention of herpes simplex virus infection by oral acyclovir after cardiac transplantation. Canadian Journal of Surgery 35: 513-516, 1992

Charles SJ, Gray JJ. Ocular herpes simplex virus infections: reduced sensitivity to acyclovir in primary disease. British Journal of Ophthalmology 74: 286-288, 1990

Chavanet P, Lokiec F, Portier H. Meningeal diffusion of high doses of acyclovir given with probenecid. Journal of Antimicrobial Chemotherapy 26: 294-295, 1990a

Chavanet P, Malet J, Waldner A, Aho S, Buisson M, et al. A double-blind randomized placebo trial on very high doses of acyclovir in weakly symptomatic HIV-patients. Cancer Detection and Prevention 14: 669-673, 1990b

Chazotte C, Anderson HF, Cohen WR. Disseminated herpes simplex infection in an immunocompromised pregnancy: treatment with intravenous acyclovir. American Journal of Perinatology 4: 363-364, 1987

Chotmongkol V, Phankingthongkum R. Herpes zoster myelitis treated with acyclovir. Case study. Southeast Asian Journal of Tropical Medicine and Public Health 23: 541-542, 1992

Cinatl Jr J, Cinatl J, Rabenau H, Mainke M, Kornhuber B, et al. Effect of aciclovir on the replication of herpes simplex virus type 1 in MA-104 cell line resistant to aciclovir. Arzneimittel-Forschung 42: 977-980, 1992

Cizman M, Mozetic M, Novakovic S, Zaletel-Kragelj L. Humoral immune response and prevention of herpes labialis after treatment of primary herpetic gingivostomatitis with acyclovir suspension. European Society for Paediatric Infectious Diseases 8th Annual Meeting, Göteborg, May 17-19, 1989. Abstract no.4. Pediatric Research 29: 116, 1991

Clive D, Corey L, Reichman RC, Davis LG, Hozier JC. A double-blind, placebo-controlled cytogenic study of oral acyclovir in patients with recurrent genital herpes. Journal of Infectious Diseases 164: 753-757, 1991

Cobo LM, Foulks GN, Liesegang T, Lass J, Sutphin J, et al. Oral acyclovir in the therapy of acute herpes zoster ophthalmicus. Ophthalmology 92: 1574-1583, 1985

Cobo LM, Foulks GN, Liesegang T, Lass J, Sutphin JE, et al. Oral acyclovir in the treatment of acute herpes zoster ophthalmicus. Ophthalmology 93: 763-770, 1986

Coen DM, Goldstein DJ, Weller SK. Herpes simplex virus ribonucleotide reductase mutants are hypersensitive to acyclovir. Antimicrobial Agents and Chemotherapy 33: 1395-1399, 1989

Colin J, Chastel C, Renard G, Cantell K. Combination therapy for dendritic keratitis with human leukocyte interferon and acyclovir. American Journal of Ophthalmology 95: 346-348, 1983

Colin J, Malet F, Chastel C. Acyclovir in herpetic anterior uveitis. Annals of Ophthalmology 23: 28-30, 1991

Collins P. The spectrum of antiviral activities of acyclovir *in vitro* and *in vivo*. Journal of Antimicrobial Chemotherapy 12 (Suppl.B): 19-27, 1983

Collins P, Ellis MN. Sensitivity monitoring of clinical isolates of herpes simplex virus to acyclovir. Journal of Medical Virology 1 (Suppl.): 58-66, 1993a

Collins P, Ellis MN. Virus sensitivity following the introduction of acyclovir. Poster presented at the 18th International Congress of Chemotherapy. Stockholm, Sweden, 1993b

Collier AC, Bozzette S, Coombs RW, Causey DM, Schoenfeld DA, et al. A pilot study of low-dose zidovudine in human immunodeficiency virus infection. New England Journal of Medicine 323: 1015-1021, 1990

Collum LMT, Akhtar J, McGettrick P. Oral acyclovir in herpetic keratitis. Transactions of the Ophthalmological Societies of the United Kingdom 104 (Pt 6): 629-631, 1985

Connell EV, Cerruti RL, Trowne PW. Synergistic activity of combinations of recombinant human alpha interferon and acyclovir, administered concomitantly and in sequence, against a lethal herpes simplex virus type 1 infection in mice. Antimicrobial Agents and Chemotherapy 28: 1-4, 1985

Cooper DA, Pedersen C, Aiuti F, Vilde JL, Ruhnke M, et al. The efficacy and safety of zidovudine with or without acyclovir in the treatment of patients with AIDS-related complex. AIDS 5: 933-943, 1991

Cooper DA, Pehrson PO, Pedersen C, Moroni M, Oksenhendler E, et al. The efficacy and safety of zidovudine alone or as cotherapy with acyclovir for the treatment of patients with AIDS and AIDS-related complex: a double-blind, randomized trial. AIDS 7: 197-207, 1993

Corey L, Adams HG, Brown ZA, Holmes KK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. Annals of Internal Medicine 98: 958-972, 1983

Corey L, Benedetti JK, Critchlow CW, Remington MR, Winter CA, et al. Double-blind controlled trial of topical acyclovir in genital herpes simplex virus infections. Acyclovir Symposium. American Journal of Medicine 73: 326-334, 1982

Cox SM, Phillips LE, DePaolo HD, Faro S. Treatment of disseminated herpes simplex virus in pregnancy with parenteral acyclovir. Journal of Reproductive Medicine 31: 1005-1007, 1986

Crane LE, Milne DA. Comparative activities of combinations of acyclovir, vidarabine or its 5'-monophosphate, and cloned human interferons against herpes simplex virus type 2 in human and mouse fibroblast cultures. Antiviral Research 5: 325-333, 1985

Crane LR, Milne DA, Sunstrum JC, Lerner AM. Comparative activities of selected combinations of vidarabine, arabinosyl hypoxanthine, interferon and polyriboinosinic acid-polyribo-cytidylic acid complex against herpes simplex virus type 2 in tissue culture and intravaginally inoculated mice. Antimicrobial Agents and Chemotherapy 26: 557-562, 1984

Crane LR, Sunstrum JC. Enhanced efficacy of nucleoside analogs and recombinant alpha interferon in weanling mice lethally infected with herpes simplex virus type 2. Antiviral Research 9: 1-10, 1988

Crooks RJ, Jones DA, Fiddian AP. Zoster-associated chronic pain: an overview of clinical trials with acyclovir. Scandinavian Journal of Infection 23 (Suppl.80): 62-68, 1991

Datta AK, Pagano JS. Phosphorylation of acyclovir in vitro in activated Burkitt somatic cell hybrids. Antimicrobial Agents and Chemotherapy 24: 10-14, 1983

Davenport A, Goel S, Mackenzie JC. Neurotoxicity of acyclovir in patients with end-stage renal failure treated with continuous ambulatory peritoneal dialysis. American Journal of Kidney Diseases 20: 647-649, 1992

de Koning EWJ, van Bijsteveld P, Cantell K. Combination therapy for dendritic keratitis with acyclovir and α-interferon. Archives of Ophthalmology 101: 1866-1869, 1983

de Miranda P, Blum MR. Pharmacokinetics of acyclovir after intravenous and oral administration. Journal of Antimicrobial Chemotherapy 12 (Suppl.B): 29-37, 1983

de Miranda P, Good SS, Krasny HC, Connor JD, Laskin OL, et al. Metabolic fate of radioactive acyclovir in humans. Acyclovir Symposium. American Journal of Medicine 73: 215-220, 1982a

de Miranda P, Whitley RJ, Barton N, Page D, Creagh-Kirk T, et al. Systemic absorption and pharmacokinetics of acyclovir (ACV) [Zovirax] capsules in immunocompromised patients with herpesvirus infections. Abstract. 22nd Interscience Conference on Antimicrobial Agents and Chemotherapy, Florida, 4-6 October, 1982b

de Miranda P, Whitley RJ, Blum MR, Keeney RE, Barton N, et al. Acyclovir kinetics after intravenous infusion. Clinical Pharmacology and Therapeutics 26: 718-728, 1979

Douglas JM, Critchlow C, Benedetti J, Mertz GJ, Connor JD, et al. A double-blind study of oral acyclovir for suppression of recurrences of genital herpes simplex virus infection. New England Journal of Medicine 310: 1551-1556, 1984

Douglas Jr RG, Couch RB. A prospective study of chronic herpes simplex virus infection and recurrent herpes labialis in humans. Journal of Immunology 104: 289-295, 1970

Dugandzic RM, Sketris IS, Belitsky P, Schlech III WF, Givner ML. Effect of coadministration of acyclovir and cyclosporine on kidney function and cyclosporine concentrations in renal transplant patients. DICP: Annals of Pharmacotherapy 25: 316-317, 1991

Dunkle LM, Arvin AM, Whitley RJ, Rotbart HA, Feder Jr HM, et al. A controlled trial of acyclovir for chickenpox in normal children. New England Journal of Medicine 325: 1539-1544, 1991

Eck P, Silver SM, Clark EC. Acute renal failure and coma after a high dose of oral acyclovir. New England Journal of Medicine 325: 1178, 1991

Eisenmann D, Knipp H, Laube H, Stegmann Th. Prevention of cytomegalovirus disease in heart transplant recipients by prophylaxis with cytomegalovirus hyperimmune globulin plus oral acyclovir. Transplantation Proceedings 22: 2322-2323, 1990

Ellis MN, Lobe DC, Spector T. Synergistic therapy by acyclovir and A1110U for mice orofacially infected with herpes simplex viruses. Antimicrobial Agents and Chemotherapy 33: 1691-1696, 1989

Engel JP, Englund JA, Fletcher CV, Hill EL. Treatment of resistant herpes simplex virus with continuous-infusion acyclovir. Journal of the American Medical Association 263: 1662-1664, 1990

Englund JA, Arvin AM, Balfour Jr HH. Acyclovir treatment for varicella does not lower gpI and IE-62 (p170) antibody responses to varicella-zoster virus in normal children. Journal of Clinical Microbiology 28: 2327-2330, 1990a

Englund JA, Fletcher CV, Balfour Jr HH. Acyclovir therapy in neonates. Journal of Pediatrics 119: 129-135, 1991

Englund JA, Zimmerman ME, Swierkosz EM, Goodman JL, Scholl DR, et al. Herpes simplex virus resistant to acyclovir. A study in a tertiary care center. Annals of Internal Medicine 112: 416-422, 1990b

Erlich KS, Mills J, Chatis P, Mertz GJ, Busch DF, et al. Acyclovir-resistant herpes simplex virus infections in patients with the acquired immunodeficiency syndrome. New England Journal of Medicine 320: 293-296, 1989

Feder Jr HM. Treatment of adult chickenpox with oral acyclovir. Archives of Internal Medicine 150: 2061-2065, 1990

Ferré C, Espino A, Cruzado JM, Carratalá J. Toxicidad neurológica grave por aciclovir oral. Medicina Clinica 98: 679, 1992

Firat H, Brun P, Loirat C, Jacqz-Aigrain E. Acyclovir-induced renal failure. In French. Archives Francaises de Pediatrie 49: 641-643, 1992

Fischer A, Fellay G, Ragamey C. Toxicité rénale et neurologique de l'acyclovir. A propos d'un cas. Schweizerische Medizinische Wochenschrift 120: 1200-1203, 1990

Fletcher CV, Englund JA, Bean B, Chinnock B, Brundage DM, et al. Continuous infusion of high-dose acyclovir for serious herpesvirus infections. Antimicrobial Agents and Chemotherapy 33: 1375-1378, 1989

Fletcher CV, Englund JA, Edelman CK, Gross CR, Dunn DL, et al. Pharmacologic basis for high-dose oral acyclovir prophylaxis of cytomegalovirus disease in renal allograft recipients. Antimicrobial Agents and Chemotherapy 35: 938-943, 1991

Foster CS, Barney NP. Systemic acyclovir and penetrating keratoplasty for herpes simplex keratitis. Documenta Ophthalmologica 80: 363-369, 1992

Frenkel L, Pineda E, Garratty E, Fall H, Dillon M, et al. A prospective study of the effects of acyclovir treatment on the HSV-2 lymphoproliferative response of persons with frequently recurring HSV-2 genital infections. Journal of Infectious Diseases 159: 845-850, 1989

Frenkel LM, Brown ZA, Bryson YJ, Corey L, Unadkat JD, et al. Pharmacokinetics of acyclovir in the term human pregnancy and neonate. American Journal of Obstetrics and Gynecology 164: 569-576, 1991

Frieden FJ, Ordorica SA, Goodgold AL, Hoskins IA, Silverman F, et al. Successful pregnancy with isolated herpes simplex virus encephalitis: case report and review of the literature. Obstetrics and Gynecology 75: 511-513, 1990

Galle PR, Theilmann L. Inhibition of hepatitis B virus polymerase-activity by various agents. Transient expression of hepatitis B virus DNA in hepatoma cells as novel system for evaluation of antiviral drugs. Arzneimittel-Forschung 40: 1380-1382, 1990

Garcia Quintana A, Alegre Martin J, Falcó V, Fernandez de Sevilla T, Martinez Vázquez JM. Pneumonia varicellosa in the adult. Study of thirteen cases. In Spanish. Revista Clinica Española 191: 314-316, 1992

Gateley A, Gander RM, Johnson PC, Kit S, Otsuka H, et al. Herpes simplex virus type 2 meningoencephalitis resistant to acyclovir in

a patient with AIDS. Journal of Infectious Diseases 161: 711-715, 1990
Ghirga G, Ghirga P, Pizzabiocca A, Maccarini I, Presti A. Treatment of varicella with low doses of acyclovir for two days. Journal of Pediatrics 120: 664, 1992
Gibson JR, Klaber MR, Harvey SG, Tosti A, Jones D, et al. Prophylaxis against herpes labialis with acyclovir cream - a placebo-controlled study. Dermatologica 172: 104-107, 1986
Gill MJ, Bryant HE. Oral acyclovir therapy of recurrent herpes simplex virus type 2 infection of the hand. Antimicrobial Agents and Chemotherapy 35: 382-383, 1991
Gill MJ, Burgess E. Neurotoxicity of acyclovir in end stage renal disease. Journal of Antimicrobial Chemotherapy 25: 300-301, 1990
Glick M, Pliskin ME. Regression of oral hairy leukoplakia after oral administration of acyclovir. General Dentistry 38: 374-375, 1990
Gluckman E, Lotsberg J, Devergie A, Zhao XM, Melo R, et al. Prophylaxis of herpes infections after bone-marrow transplantation by oral acyclovir. Lancet 2: 706-708, 1983
Gnann JW, Whitley RJ. Natural history and treatment of varicella-zoster in high-risk populations. Journal of Hospital Infection 18 (Suppl.A): 317-329, 1991
Goday J, Aguirre A, Gil Ibarra N, Eizaguirre X. Allergic contact dermatitis from acyclovir. Contact Dermatitis 24: 380-381, 1991
Goh CL. Compound allergy to Spectraban® 15 lotion and Zovirax® cream. Contact Dermatitis 22: 61-62, 1990
Gola M, Francalanci S, Brusi C, Lombardi P, Sertoli A. Contact sensitization to acyclovir. Contact Dermatitis 20: 394-395, 1989
Gold D, Ashley R, Solberg G, Abbo H, Corey L. Chronic-dose acyclovir to suppress frequently recurring genital herpes simplex virus infection: effect on antibody response to herpes simplex virus type 2 proteins. Journal of Infectious Diseases 158: 1227-1234, 1988
Goldberg LH, Kaufman R, Batenhorst RL, Acyclovir Study Group. Safety and efficacy of long-term suppressive oral acyclovir (ACV) for the treatment of frequently recurring genital herpes: 4th year results. Program and Abstracts of the 29th Interscience Conference on Antimicrobial Agents and Chemotherapy, Texas, September 17-20, 1989. Abstract no.66, p 112, 1989
Goldberg LH, Kaufman RK, Kurtz TO, Conant MA, Eron LJ, et al. Long-term suppression of recurrent genital herpes with acyclovir. Archives of Dermatology 129: 582-587, 1993
Gonsho A, Imanidis G, Vogt P, Kern ER, Tsuge H, et al. Controlled (trans)dermal delivery of an antiviral agent (acyclovir). I: An in vivo animal model for efficacy evaluation in cutaneous HSV-1 infections. International Journal of Pharmaceutics 65: 183-194, 1990
Gray JJ, Wreghitt TG, Baglin TP. Susceptibility to acyclovir of herpes simplex virus: emergence of resistance in patients with lymphoid and myeloid neoplasia. Journal of Infection 19: 31-40, 1989
Grover L, Kane J, Kravitz J, Cruz A. Systemic acyclovir in pregnancy: a case report. Obstetrics and Gynecology 65: 284-287, 1985
Guarascio P, De Felici AP, Migliorini D, Alexander GJM, Fagan EA, et al. Treatment of chronic HBeAg-positive hepatitis with acyclovir: a controlled trial. Journal of Hepatology 3 (Suppl. 2): 143-147, 1986a
Guarascio P, De Felici AP, Migliorini D, Alexander GJM, Fagan EA, et al. An open study of human lymphoblastoid interferon and oral acyclovir in chronic hepatitis B virus infection. Journal of Hepatology 3 (Suppl. 2): 149-153, 1986b
Guarascio P, Farinelli G, Girardi E, Antonelli L, Tossini G, et al. Treatment of chronic hepatitis B based on interferon, acyclovir and prednisolone. Abstract. Italian Journal of Gastroenterology 22: 172, 1990
Haake DA, Zakowski PC, Haake DL, Bryson YJ. Early treatment with acyclovir for varicella pneumonia in otherwise healthy adults: retrospective controlled study and review. Reviews of Infectious Diseases 12: 788-798, 1990
Haddad J, Langer B, Astruc D, Messer J, Lokiec F. Oral acyclovir and recurrent genital herpes during late pregnancy. Obstetrics and Gynecology 82: 102-104, 1993
Haefeli W, Schoenenberger RAZ, Weiss P. Acyclovir-induced neurotoxicity: concentration-side effect relationship in acyclovir overdose. American Journal of Medicine 94: 212-215, 1993
Hall CB, Granoff DM, Gromisch DS, Halsey NA, Kohl S, et al. The use of oral acyclovir in otherwise healthy children with varicella. Pediatrics 91: 674-676, 1993
Halsos AM, Salo AP, Lassus A, Tjøtta EAL, Hovi T, et al. Oral acyclovir suppression of recurrent genital herpes: a double-blind, placebo-controlled, crossover study. Acta Dermato-Venereologica 65: 59-63, 1985
Hammer SM, Kaplan JC, Lowe BR, Hirsch MS. Alpha interferon and acyclovir treatment of herpes simplex virus in lymphoid cell cultures. Antimicrobial Agents and Chemotherapy 21: 634-640, 1982
Hanada N, Kido S, Kuzushima K, Goto Y, Rahman M, et al. Combined effects of acyclovir and human interferon-α on herpes simplex virus replication in cultured neural cells. Journal of Medical Virology 29: 7-12, 1989
Hannemann J, Wunderle W, Baumann K. Nephrotoxicity of acyclovir and *cis*-diamminedichloroplatinum(II) - effect of co-administration in rats. Journal of Cancer Research and Clinical Oncology 118: 181-186, 1992
Harding SP, Porter SM. Oral acyclovir in herpes zoster ophthalmicus. Current Eye Research 10 (Suppl.): 177-182, 1991
Hayashi M, Takeyama K, Takayama J, Ohira M, Tobinai K, et al. Severe herpes simplex virus hepatitis following autologous bone marrow transplantation: successful treatment with high dose intravenous acyclovir. Japanese Journal of Clinical Oncology 21: 372-376, 1991
Heagy W, Crumpacker C, Lopez PA, Finberg RW. Inhibition of immune functions by antiviral drugs. Journal of Clinical Investigation 87: 1916-1924, 1991
Heidl M, Scholz H, Dörffel W, Hermann J, Wutzler P. Vergleichende Prüfung der Wirksamkeit von Bromvinyldesoxyuridin und Aciclovir bei Varicella-Zoster-Virus-Infektionen immunsupprimierter Kinder - eine prospektive randomisierte Studie. Zeitschrift fur Klinische Medizin 45: 1259-1262, 1990
Heidl M, Scholz H, Dörffel W, Hermann J. Antiviral therapy of varicella-zoster virus infection in immunocompromised children - a prospective randomized study of aciclovir versus brivudin. Infection 19: 401-405, 1991
Henderson GI, Hu Z-Q, Johnson RF, Perez AB, Yang Y, et al. Acyclovir transport by the human placenta. Journal of Laboratory and Clinical Medicine 120: 885-892, 1992
Herbort CP. Acyclovir in herpes zoster ophthalmicus. British Journal of Ophthalmology 76: 639, 1992
Herbst JS, Morgan J, Raab-Traub N, Resnick L. Comparison of the efficacy of surgery and acyclovir therapy in oral hairy leukoplakia. Journal of the American Academy of Dermatology 21: 753-756, 1989
Hernandez E, Praga M, Moreno F, Montoyo C. Acute renal failure induced by oral acyclovir. Clinical Nephrology 36: 155-156, 1991
Hilfenhaus J, De Clercq E, Köhler R, Guersen R, Seiler F. Combined antiviral effects of acyclovir or bromovinyldeoxyuridine and human immunoglobulin in herpes simplex virus-infected mice. Antiviral Research 7: 227-235, 1987
Hill EL, Rogers JT, Ellis MN. In vitro acyclovir susceptibility monitoring of HSV clinical isolates. Abstract no.134. Antiviral Research 20 (suppl.1): 116, 1993
Hintz M, Connor JD, Spector SA, Blum MR, Keeney RE, et al. Neonatal acyclovir pharmacokinetics in patients with herpes virus infections. Acyclovir Symposium. American Journal of Medicine 73: 210-214, 1982

Hoang-Xuan T, Büchi ER, Herbort CP, Denis J, Frot P, et al. Oral acyclovir for herpes zoster ophthalmicus. Ophthalmology 99: 1062-1071, 1992

Hollander H, Lifson AR, Maha M, Blum R, Rutherford GW, et al. Phase I study of low-dose zidovudine and acyclovir in asymptomatic human immunodeficiency virus seropositive individuals. American Journal of Medicine 87: 628-632, 1989

Holmberg SD, Gerber AR, Stewart JA, Lee FK, O'Malley PM, et al. Herpesviruses as co-factors in AIDS. Lancet 2: 746-747, 1988

Horowitz GM, Hankins GDV. Early-second-trimester use of acyclovir in treating herpes zoster in a bone marrow transplant patient. A case report. Journal of Reproductive Medicine 37: 280-282, 1992

Høvding G. A comparison between acyclovir and trifluorothymidine ophthalmic ointment in the treatment of epithelial dendritic keratitis. A double-blind, randomized parallel group trial. Acta Ophthalmologica 67: 51-54, 1989

Huff JC, Bean B, Balfour HH Jr, Laskin OL, Connor JD, et al. Therapy of herpes zoster with oral acyclovir. Antiviral Symposium. Amerian Journal of Medicine 85 (Suppl.2A): 84-89, 1988

Hugo H, Linde A, Åbom P-E. Epstein-Barr virus induced thrombocytopenia treated with intravenous acyclovir and immunoglobulin. Scandinavian Journal of Infectious Diseases 21: 103-105, 1989

Hung SO, Patterson A, Rees PJ. Pharmacokinetics of oral acyclovir (Zovirax) in the eye. British Journal of Ophthalmology 68: 192-195, 1984

Jacobson MA, Berger TG, Fikrig S, Becherer P, Moohr JW, et al. Acyclovir-resistant varicella zoster virus infection after chronic oral acyclovir therapy in patients with the acquired immunodeficiency syndrome (AIDS). Annals of Internal Medicine 112: 187-191, 1990

Jazzar A, Cooper DKC, Zuhdi N. Cytomegalovirus disease in heart transplant patients. Transplantation 53: 1167-1168, 1992

Johnson RE, Mullooly JP, Valanis BG, McFarland BH, Andrews EB, Tilson HH. Method of examining oral acyclovir use for adverse events. Journal of Clinical Research and Pharmacoepidemiology 5: 331-345, 1991

Jones T, Alderman C. Acyclovir clearance by CAVHD. Intensive Care Medicine 17: 125-126, 1991

Kahlon JB, Kemp MC, Yawei N, Carpenter RH, Shannon WM, et al. In vitro evaluation of the synergistic antiviral effects of acemannan in combination with azidothymidine and acyclovir. Molecular Biotherapy 3: 214-223, 1991

Kaplowitz LG, Baker D, Gelb L, Blythe J, Hale R, et al. Prolonged continuous acyclovir treatment of normal adults with frequently recurring genital herpes simplex virus infection. Journal of the American Medical Association 265: 747-751, 1991

Karlsson A, Harmenberg J. Effects of ribonucleotide reductase inhibition on pyrimidine deoxynucleotide metabolism in acyclovir-treated cells infected with herpes simplex type 1. Antimicrobial Agents and Chemotherapy 32: 1100-1102, 1988

Kavaliotis J. Acyclovir therapy in neonates. Journal of Pediatrics 120: 665, 1992

Kawaguchi H, Baba M, Shigeta S. Synergistic inhibitory effect of acyclovir and human native beta-interferon on the growth of herpes simplex virus type 2 in human embryo fibroblast cell cultures. Microbiology and Immunology 30: 593-597, 1986

Kelly SP, Rosenthal AR. Chickenpox chorioretinitis. British Journal of Ophthalmology 74: 698-699, 1990

Ketchum DG, Gohd RS, Starszak ED, Van Dyke RB. Rapid screening of clinical herpes simplex virus isolates for resistance to acyclovir. Abstract no. 127. Antiviral Research 15 (Suppl.1): 111, 1991

Kimes AS, Kumor K, McCullough K, Holtzclaw D, Teller D, et al. Effects of acute and chronic acyclovir on canine renal function. Journal of Pharmacology and Experimental Therapeutics 249: 483-491, 1989

King SM, Gorensek M, Ford-Jones EL, Read SE. Fatal varicella-zoster infection in a newborn treated with varicella-zoster immunoglobulin. Pediatric Infectious Disease 5: 588-589, 1986

Kinghorn GR, Abeywickreme I, Jeavons M, Rowland M, Barton I, et al. Efficacy of oral treatment with acyclovir and co-trimoxazole in first episode genital herpes. Genitourinary Medicine 62: 33-37, 1986

Kinghorn GR, Woolley PD, Thin RNT, De Maubeuge J, Foidart JM, et al. Acyclovir vs isoprinosine (immunovir) for suppression of recurrent genital herpes simplex infection. Genitourinary Medicine 68: 312-316, 1992

Kingsley S. Fetal and neonatal exposure to acyclovir. Abstract. Second World Congress on Sexually Transmitted Diseases, Paris, June 1986

Klein NA, Mabie WC, Shaver DC, Latham PS, Adamec TA, et al. Herpes simplex virus hepatitis in pregnancy. Two patients successfully treated with acyclovir. Gastroenterology 100: 239-244, 1991

Kowalczyk AL, Dupuis LL, Domaratzki J. Acyclovir toxicity in pediatric patients: incidence and risk factors. Abstract no.90. Pharmacotherapy 11: 43, 1991

Kreiss J, Caraël M, Meheus A. Role of sexually transmitted diseases in transmitting human immunodeficiency virus. Genitourinary Medicine 64: 1-2, 1988

Krieble BF, Rudy DW, Glick MR, Clayman MD. Case report: acyclovir neurotoxicity and nephrotoxicity - the role for hemodialysis. American Journal of the Medical Sciences 305: 36-39, 1993

Kroon S, Petersen CS, Andersen LP, Rasmussen JR, Vestergaard BF. Long-term suppression of severe recurrent genital herpes simplex infections with oral acyclovir: a dose-titration study. Genitourinary Medicine 66: 101-104, 1990

Kroon S, Petersen CS, Andersen LP, Rasmussen JR, Vestergaard BF. Oral acyclovir suppressive therapy in severe recurrent genital herpes. A double-blind, placebo-controlled cross-over study. Danish Medical Bulletin 36: 298-300, 1989

Kunitomi T, Akazai A, Ikeda M, Oda M, Kodani N. Comparison of acyclovir and vidarabine in immunocompromised children with varicella-zoster virus infection. Acta Paediatrica Japonica 31: 702-705, 1989

Kuzushima K, Kudo T, Kimura H, Kido S, Hanada N, et al. Prophylactic oral acyclovir in outbreaks of primary herpes simplex virus type 1 infection in a closed community. Pediatrics 89: 379-383, 1992

Lagrew Jr DC, Furlow TG, Hager D, Yarrish RL. Disseminated herpes simplex virus infection in pregnancy: successful treatment with acyclovir. Journal of the American Medical Association 252: 2058-2059, 1984

Laskin OL. Clinical pharmacokinetics of acyclovir. Clinical Pharmacokinetics 8: 187-201, 1983

Laskin OL, de Miranda P, King DH, Page DA, Longstreth JA, et al. Effects of probenecid on the pharmacokinetics and elimination of acyclovir in humans. Antimicrobial Agents and Chemotherapy 21: 804-807, 1982a

Laskin OL, Longstreth JA, Saral R, de Miranda P, Keeney R, et al. Pharmacokinetics and tolerance of acyclovir, a new anti-herpesvirus agent, in humans. Antimicrobial Agents and Chemotherapy 21: 393-398, 1982b

Laskin OL, Longstreth JA, Whelton A, Rocco L, Lietman PS, et al. Acyclovir kinetics in end-stage renal disease. Clinical Pharmacology and Therapeutics 31: 594-601, 1982c

Lassiter HA. Use of acyclovir in the treatment of chickenpox. Pediatrics 89: 1, 1992

Lau RJ, Emery MG, Galinsky RE. Unexpected accumulation of acyclovir in breast milk with estimation of infant exposure. Obstetrics and Gynecology 69: 468-471, 1987

Legendre C, Ducloux D, Ferroni A, Chkoff N, Valette C, et al. Acyclovir in preventing cytomegalovirus infection in kidney transplant recipients: a case-controlled study. Transplantation Proceedings 25: 1431-1433, 1993

Levin MJ, Judson FN, Eron L, Bryson YJ, Corey L, et al. Comparison of intramuscular recombinant alpha interferon (rIFN-2A) with topical acyclovir for the treatment of first-episode herpes genitalis and prevention of recurrences. Antimicrobial Agents and Chemotherapy 33: 649-652, 1989

Levin MJ, Leary PL. Inhibition of human herpesviruses by combinations of acyclovir and human leukocyte interferon. Infection and Immunity 32: 995-999, 1981

Levin MJ, Zaia JA, Hershey BJ, Davis LG, Robinson GV, et al. Topical acyclovir treatment of herpes zoster in immunocompromised patients. Journal of the American Academy of Dermatology 13: 590-596, 1985

Levy DM, Sagar HJ. Herpes simplex type 2 meningitis treated with acyclovir. Postgraduate Medical Journal 60: 282-283, 1984

Linnemann Jr CC, Biron KK, Hoppenjans WG, Solinger AM. Emergence of acyclovir-resistant varicella zoster virus in an AIDS patient on prolonged acyclovir therapy. AIDS 4: 577-579, 1990

Littler E, Ertl P, Snowden W, Collins P. Comparative antiviral effects of acyclovir and penciclovir. Poster presented at the 18th International Congress of Chemotherapy. Stockholm, Sweden, 1993

Ljungman P, Ellis MN, Hackman RC, Shepp DH, Meyers JD. Acyclovir-resistant herpes simplex virus causing pneumonia after marrow transplantation. Journal of Infectious Diseases 162: 244-248, 1990

Ljungman P, Lönnqvist B, Ringdén O, Skinhöj P, Gahrton G. A randomized trial of oral versus intravenous acyclovir for treatment of herpes zoster in bone marrow transplant recipients. Bone Marrow Transplantation 4: 613-615, 1989

Ljungman P, Prentice HG, Powles R, Burnett A, Gluckman E, et al. Effects of high dose acyclovir on CMV infections and survival following bone marrow transplantation. Poster presented at the 4th International CMV Conference, Paris, France, 1993

Ljungman P, Wilczek H, Gahrton G, Gustavsson A, Lundgren G, et al. Long-term acyclovir prophylaxis in bone marrow transplant recipients and lymphocyte proliferation responses to herpes virus antigens in vitro. Bone Marrow Transplantation 1: 185-192, 1986

Lobato-Mendizábal E, Ruiz-Argüelles GJ. Low doses of zidovudine in the treatment of patients infected with virus HIV-1. In Spanish. Revista de Investigacion Clinica 44: 161-168, 1992

Lobe DC, Spector T, Ellis MN. Synergistic topical therapy by acyclovir and A1110U for herpes simplex virus induced zosteriform rash in mice. Antiviral Research 15: 87-100, 1991

Loftsson T, Somogyi G, Bodor N. Effect of choline esters and oleic acid on the penetration of acyclovir, estradiol, hydrocortisone, nitroglycerin, retinoic acid and trifluorothymidine across hairless mouse skin in vitro. Acta Pharmaceutica Nordica 1: 279-286, 1989

Lopez Aguado D, Perez Piñero B, Betancor L, Mendez A, Campos Bañales E. Acyclovir in the treatment of laryngeal papillomatosis. International Journal of Pediatric Otorhinolaryngology 21: 269-274, 1991

Lotshaw RR, Keegan JM, Gordon HR. Parenteral and oral acyclovir for management of varicella pneumonia in pregnancy: a case report with review of literature. West Virginia Medical Journal 87: 204-206, 1991

Lusso P, Malnati MS, Garzino-Demo A, Crowley RW, Long EO, et al. Infection of natural killer cells by human herpesvirus 6. Nature 362: 458-462, 1993

Lycke J, Andersen O, Svennerholm B, Appelgren L, Dahlöf C. Acyclovir concentrations in serum and cerebrospinal fluid at steady state. Journal of Antimicrobial Chemotherapy 24: 947-954, 1989

MacDiarmaid-Gordon AR, O'Connor M, Beaman M, Ackrill P. Neurotoxicity associated with oral acyclovir in patients undergoing dialysis. Nephron 62: 280-283, 1992

MacDonald AS, Belitsky P, Cohen A, Lee S. Cytomegalovirus disease prophylaxis in seronegative recipients of kidneys from seropositive donors by combination of cytomegalovirus-hyperimmune globulin and low-dose acyclovir. Transplantation Proceedings 23: 1355-1356, 1991

Main J. Therapy of chronic viral hepatitis. Journal of Hospital Infection 18 (Suppl.A): 335-340, 1991

Manka RL. Exogenous lactase in the treatment of oral acyclovir intolerance. American Journal of Ophthalmology 108: 733, 1989

Margolis TP, Ostler HB. Treatment of ocular disease in eczema herpeticum. American Journal of Ophthalmology 110: 274-279, 1990

Marino C, McDonald E. Oral acyclovir for chickenpox. Cutis 48: 36, 1991

Marrero M, Alvarez M, Millan JC, Mas Lago P, Soler M, et al. Acyclovir resistant genital herpes virus infection in a patient with AIDS. Acta Virologica 35: 86-89, 1991

Marsh RJ, Cooper M. Double-masked trial of topical acyclovir and steroids in the treatment of herpes zoster ocular inflammation. British Journal of Ophthalmology 75: 542-546, 1991

Maurer JR, Snell G, deHoyos A, Kesten S, Winton T. Outcomes of lung transplantation using three different cytomegalovirus prophylactic regimens. Transplantation Proceedings 25: 1434-1435, 1993

McDonald LK, Tartaglione TA, Mendelman PM, Opheim KE, Corey L. Lack of toxicity in two cases of neonatal acyclovir overdose. Pediatric Infectious Disease Journal 8: 529-532, 1989

McGill J, Chapman C. A comparison of topical acyclovir with steroids in the treatment of herpes zoster keratouveitis. British Journal of Ophthalmology 67: 746-750, 1983

McKendrick MW, Care C, Burke C, Hickmott E, McKendrick GDW. Oral acyclovir in herpes zoster. Journal of Antimicrobial Chemotherapy 14: 661-665, 1984

McKendrick MW, McGill JI, Wood MJ. Lack of effect of acyclovir on postherpetic neuralgia. British Medical Journal 298: 431, 1989

Menage MJ, de Clercq E, van Lierde A, Easty VS, Darville JM, et al. Antiviral drug sensitivity in ocular herpes simplex virus infection. British Journal of Ophthalmology 74: 532-535, 1990

Mertz GJ, Critchlow CJ, Benedetti J, Reichman RC, Dolin R, et al. Double-blind placebo-controlled trial of oral acyclovir in first-episode genital herpes simplex virus infection. Journal of the American Medical Association 252: 1147-1151, 1984

Mertz GJ, Eron L, Kaufman R, Goldberg L, Raab B, et al. Prolonged continuous versus intermittant oral acyclovir treatment in normal adults with frequently recurring genital herpes simplex virus infection. American Journal of Medicine 85 (Suppl.2A): 14-19, 1988a

Mertz GJ, Jones CC, Mills J, Fife KH, Lemon SM, et al. Long-term acyclovir suppression of frequently recurring genital herpes simplex virus infection. A multicenter double-blind trial. Journal of the American Medical Association 260: 201-206, 1988b

Mészner Z, Gyarmati É, Nyerges G, Simon M, Koller M. Early relapses of varicella-zoster virus infection in immunocompromised children treated with acyclovir. Acta Paediatrica Hungarica 30: 263-270, 1990

Mészner Z, Nyerges G, Bell AR. Oral acyclovir to prevent dissemination of varicella in immunocompromised children. Journal of Infection 26: 9-15, 1993

Meurs PF, van Bijsterveld OP. Combination therapy of recombinant human alpha 2 interferon and acyclovir in the treatment of herpes simplex keratitis. Antiviral Research (Suppl.1): 225-228, 1985

Meyer LJ, de Miranda P, Sheth N, Spruance S. Acyclovir in human breast milk. American Journal of Obstetrics and Gynecology 158: 586-588, 1988

Meyers JD. Treatment of herpesvirus infections in the immunocompromised host. Scandinavian Journal of Infectious Diseases 47 (Suppl.): 128-136, 1985

Meyers JD, Reed Ec, Shepp DH, Thornquist M, Dandliker PS, et al. Acyclovir for prevention of cytomegalovirus infection and disease after allogeneic marrow transplantation. New England Journal of Medicine 318: 70-75, 1988

Mindel A, Carney O, Sonnex C, Freris M, Patou G, et al. Suppression of frequently recurring genital herpes: acyclovir v inosine pranobex. Genitourinary Medicine 65: 103-105, 1989

Mindel A, Sutherland S. Genital herpes: the disease and its treatment including intravenous acyclovir. Journal of Antimicrobial Chemotherapy 12 (Suppl.B): 51-59, 1983

Mindel A, Weller IVD, Faherty A, Sutherland S, Hindley D, et al. Prophylactic oral acyclovir in recurrent genital herpes. Lancet 2: 56-59, 1984

Minuk GY, German GB, Bernstein C, Benarroch A, Gauthier T, et al. A pilot study of steroid withdrawal followed by oral acyclovir in the treatment of chronic type B hepatitis. Clinical and Investigative Medicine 15: 506-512, 1992

Molin L, Ruhnek-Forsbeck M, Svennerholm B. One year acyclovir suppression of frequently recurring genital herpes: a study of efficacy, safety, virus sensitivity and antibody response. Scandinavian Journal of Infectious Diseases 78 (Suppl.): 33-39, 1991

Mollison L, Richards M, Johnson P, Angus P, Hayes K, et al. Acyclovir reduces cytomegalovirus disease after liver transplantation. Abstract no.951. Hepatology 14: 285A, 1991

Morton P, Thomson AN. Oral acyclovir in the treatment of herpes zoster in general practice. New Zealand Medical Journal 102: 93-95, 1989

Myers MG, Stanberry LR. Drug testing for activity against varicella-zoster virus in hairless guinea pigs. Antiviral Research 15: 341-344, 1991

Nakazato PZ, Burns W, Moore P, Garcia-Kennedy R, Cox K, et al. Viral prophylaxis in hepatic transplantation: preliminary report of a randomized trial of acyclovir and gancyclovir. Transplantation Proceedings 25: 1935-1937, 1993

Näher H, Helfrich S, Hartmann M, Freese UK. EBV-Replikation und Therapie der oralen Haarleukoplakie mit Acyclovir. Hautarzt 41: 680-682, 1990

Niimura M, Honda M, Nishikawa T, Kawashima M, Yasuno H, et al. The optimal concentration of aciclovir ointment for the treatment of cutaneous herpes simplex virus infections. A controlled clinical trial. Rinsho Iyaku 8: 289-297, 1992

Niimura M, Yokoi K, Aoki I, Yamaguchi M. Single dose study and multiple dose study to evaluate safety and pharmacokinetics of aciclovir ointment in healthy volunteers. Rinsho Iyaku 6: 15-22, 1990a

Niimura M, Yokoi K, Yamaguchi M, Yasuda K, Onishi A. Patch test of aciclovir ointment in healthy volunteers. Rinsho Iyaku 6: 9-14, 1990b

Nugier F, Colin JN, Aymard M, Langlois M. Occurrence and characterization of acyclovir-resistant herpes simplex virus isolates: report on a two-year sensitivity screening survey. Journal of Medical Virology 36: 1-12, 1992

Nyerges G, Meszner Z, Gyarmati E, Kerpel-Fronius S. Acyclovir prevents dissemination of varicella in immunocompromised children. Journal of Infectious Diseases 157: 309-313, 1988

O'Brien JJ, Campoli-Richards DM. Acyclovir. An updated review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. Drugs 37: 233-309, 1989

O'Brien WJ, Coe EC, Taylor JL. Nucleoside metabolism in herpes simplex virus-infected cells following treatment with interferon and acyclovir, a possible mechanism of synergistic antiviral activity. Antimicrobial Agents and Chemotherapy 34: 1178-1182, 1990

Ong ELC, Mulvenna P, Webb KA. Varicella-zoster infection in adults with cystic fibrosis: role of acyclovir. Scandinavian Journal of Infectious Diseases 23: 283-285, 1991

Ostheimer KE, Busch Th, Görtelmeyer R, Hahn K-D. Randomized double-blind trial of tromantadine versus aciclovir in recurrent herpes orofacialis. Arzneimittel-Forschung 39: 1152-1155, 1989

Palmieri G, Bucci L, Contos S, Ferrante P. Comparison of two acyclovir tablet formulations for acute herpes zoster treatment. Abstract no.177. Antiviral Research 20 (Suppl.1): 138, 1993

Pancheva SN. Potentiating effect of ribavirin on the anti-herpes activity of acyclovir. Antiviral Research 16: 151-161, 1991

Park G-B, Shao Z, Mitra AK. Acyclovir permeation enhancement across intestinal and nasal mucosae by bile salt-acylcarnitine mixed micelles. Pharmaceutical Research 9: 1262-1267, 1992

Park N-H, Park JB, Min B-M, Cherrick HM. Combined synergistic antiherpetic effect of acyclovir and chlorhexidine in vitro. Oral Surgery Oral Medicine and Oral Pathology 71: 193-196, 1991

Parry GE, Dunn P, Shah VP, Pershing LK. Acyclovir bioavailability in human skin. Journal of Investigative Dermatology 98: 856-863, 1992

Pedersen A. Acyclovir in the prevention of severe aphthous ulcers. Archives of Dermatology 128: 119-120, 1992

Pedersen A. Varicella zoster virus and recurrent aphthous ulceration. Lancet 1: 1203, 1989

Pedersen C, Cooper DA, Brun-Vézinet F, Doherty R, Skinhøj P, et al. The effect of treatment with zidovudine with or without acyclovir on HIV p24 antigenaemia in patients with AIDS or AIDS-related complex. AIDS 6: 821-825, 1992

Peitier MKH, Weisdorf D. Efficacy of low-dose acyclovir for herpes simplex virus (HSV) prophylaxis in bone marrow transplant (BMT) patients. Abstract no.93. Pharmacotherapy 11: 278, 1991

Perren TJ, Powles RL, Easton D, Stolle K, Selby PJ. Prevention of herpes zoster in patients by long-term oral acyclovir after allogeneic bone marrow transplantation. Antiviral Symposium. American Journal of Medicine 85 (Suppl. 2A): 99-101, 1988

Poirier RH, Kingham JD, de Miranda P, Annel M. Intraocular antiviral penetration. Archives of Ophthalmology 100: 1964-1967, 1982

Porter SM, Patterson A, Kho P. A comparison of local and systemic acyclovir in the management of herpetic disciform keratitis. British Journal of Ophthalmology 74: 283-285, 1990

Power WJ, Hillery MP, Benedict-Smith A, Collum LMT. Acyclovir ointment plus topical betamethasone or placebo in first episode disciform keratitis. British Journal of Ophthalmology 76: 711-713, 1992

Prober CG, Kirk LE, Keeney RE. Acyclovir therapy of chickenpox in immunosuppressed children: a collaborative study. Journal of Pediatrics 101: 622-625, 1982

Pulliam L, Panitch HS, Baringer JR, Dix RD. Effect of antiviral agents on replication of herpes simplex virus type 1 in brain cultures. Antimicrobial Agents and Chemotherapy 30: 840-846, 1986

Rabalais GP, Nusinoff-Lehrman S, Arvin AM, Levin MJ. Antiviral susceptibilities of herpes simplex virus isolates from infants with recurrent mucocutaneous lesions after neonatal infection. Pediatric Infectious Disease Journal 8: 221-223, 1989

Raborn GW, Krueger GG, Hamill ML, Mills J, Martel A, et al. Topical acyclovir versus placebo creams in prevention of sun-induced herpes simplex labialis: a randomized blinded trial. Abstract no.462. Journal of Clinical Investigation 86: A75, 1990

Raborn GW, McGaw WT, Grace M, Percy J, Samuels S. Herpes labialis treatment with acyclovir 5% modified aqueous cream: a double-blind, randomized trial. Oral Surgery Oral Medicine and Oral Pathology 67: 676-679, 1989

Ragab NF, Habib MA, Ghozzi MY. Serological assessment of acyclovir treatment of herpes genitalis. Archives of Andrology 23: 147-153, 1989

Ragazzo PC, Zanini LA, Cendes F, deAzevedo L. Control of continuous partial motor seizures in Rasmussen encephalitis during therapy with acyclovir. Epilepsia 32: 91, 1991

Ramos Macias A, de Miguel Martinez I, Martin Sanchez AM, Gomez Gonzalez JL, Martin Galan A. Incorporación del aciclovir en el tratamiento de la parálisis periférica. Un estudio en 45 casos. Acta Otorrinolaringologica Española 43: 117-120, 1992

Rashed A, Azadeh B, Abu Romeh SH. Acyclovir-induced acute tubulo-interstitial nephritis. Nephron 56: 436-438, 1990

Reardon JE, Spector T. Acyclovir: mechanism of antiviral action and potentiation by ribonucleotide reductase inhibitors. Advances in Pharmacology 22: 1-27, 1991

Richards DM, Carmine AA, Brogden RN, Heel RC, Speight TM, et al. Acyclovir. A review of its pharmacodynamic properties and therapeutic efficacy. Drugs 26: 378-438, 1983

Rompalo AM, Bertz GJ, Davis LG, Benedetti J, Critchlow C, et al. Oral acyclovir for treatment of first-episode herpes simplex virus proctatitis. Journal of the American Medical Association 259: 2879-2881, 1988

Rooney JF, Straus SE, Mannix ML, Wohlenberg CR, Alling DW, et al. Oral acyclovir to suppress frequently recurrent herpes labialis. A double-blind, placebo-controlled trial. Annals of Internal Medicine 118: 268-272, 1993

Rooney JF, Straus SE, Mannix ML, Wohlenberg CR, Banks S, et al. UV light-induced reactivation of herpes simplex virus type 2 and prevention by acyclovir. Journal of Infectious Diseases 166: 500-506, 1992

Rotbart HA, Levin MJ, Hayward AR. Immune responses to varicella zoster virus infections in healthy children. Journal of Infectious Diseases 167: 195-199, 1993

Russler SK, Tapper MA, Carrigan DR. Susceptibility of human herpesvirus 6 to acyclovir and ganciclovir. Lancet 2, 382, 1989

Rüther U. Nunnensiek C, Müller HAG, Rupp W, Gförer S, et al. Herpes simplex-associated exacerbation of Crohn's disease successfully treated with aciclovir. In German. Deutsche Medizinische Wochenschrift 117: 46-50, 1992

Sacks SL. The role of acyclovir in the management of genital herpes simplex. Canadian Medical Association Journal 136: 701-707, 1987

Sacks SL, Wanklin RJ, Reece DE, Hicks KA, Tyler KL, et al. Progressive esophagitis from acyclovir-resistant herpes simplex. Annals of Internal Medicine 111: 893-899, 1989

Safrin S, Crumpacker C, Chatis P, Davis R, Hafner R, et al. A controlled trial comparing foscarnet with vidarabine for acyclovir-resistant mucocutaneous herpes simplex in the acquired immunodeficiency syndrome. New England Journal of Medicine 325: 551-555, 1991

Safrin S, Schacker T, Delehanty J, Hill E, Corey L. Topical treatment of infection with acyclovir-resistant mucocutaneous herpes simplex virus with the ribonucleotide reductase inhibitor 348U87 in combination with acyclovir. Antimicrobial Agents and Chemotherapy 37: 975-979, 1993

Saliba F, Eyraud D, Samuel D, David MF, Arulnaden JL, et al. Randomized controlled trial of acyclovir for the prevention of cytomegalovirus infection and disease in liver transplant recipients. Transplantation Proceedings 25: 1444-1445, 1993

Schalm SW, van Buuren HR, Heytink RA, de Man RA. Acyclovir enhances the antiviral effect of interferon in chronic hepatitis B. Lancet 2: 358-360, 1985

Schinazi RF, Chou T-C, Scott RT, Yao X, Nahmias AJ. Delayed treatment with combinations of antiviral drugs in mice infected with herpes simplex virus and application of the median effect method of analysis. Antimicrobial Agents and Chemotherapy 30: 491-498, 1986

Schinazi RF, Nahmias AJ. Different *in vitro* effects of dual combinations of anti-herpes simplex virus (HSV) compounds. American Journal of Medicine 73: 40-48, 1982

Schinazi RF, Peters J, Williams CC, Chance D, Nahmias AJ. Effect of combinations of acyclovir with vidarabine or its 5′-monophosphate on herpes simplex viruses in cell culture and in mice. Antimicrobial Agents and Chemotherapy 22: 499-507, 1982

Schlech III WF, Meagher N, Cohen AD, Belitsky P, MacDonald AS, et al. A randomized double-blind placebo controlled trial of oral acyclovir in renal allograft recipients. Canadian Journal of Infectious Diseases 4: 84-88, 1993

Schofield JK, Tatnall FM, Leigh IM. Recurrent erythema multiforme: clinical features and treatment in a large series of patients. British Journal of Dermatology 128: 542-545, 1993

Selby PJ, Powles RL, Easton D, Perren TJ, Stolle K, et al. The prophylactic role of intravenous and long-term oral acyclovir after allogeneic bone marrow transplantation. British Journal of Cancer 59: 434-438, 1989

Sempere A, Sanz GF, Senent L, de la Rubia J, Jarque I, et al. Long-term acyclovir prophylaxis for prevention of varicella zoster virus infection after autologous blood stem cell transplantation in patients with acute leukemia. Bone Marrow Transplantation 10: 495-498, 1992

Sha BE, Benson CA, Deutsch TA, Urbanski PA, Phair JP, et al. Suppression of cytomegalovirus retinitis in persons with AIDS with high-dose intravenous acyclovir. Journal of Infectious Diseases 164: 777-780, 1991

Shepp DH, Dandliker PS, Flournoy N, Meyers JD. Sequential intravenous and twice-daily oral acyclovir for extended prophylaxis of herpes simplex virus infection in marrow transplant patients. Transplantation 43: 654-657, 1987

Shepp DH, Dandliker PS, Meyers JD. Treatment of varicella-zoster virus infection in severely immunocompromised patients: a randomised comparison of acyclovir and vidarabine. New England Journal of Medicine 314: 208-212, 1986

Shiraki K, Miyaki C, Namazue J, Yamanishi K, Takahashi M. Enhancement of plaque formation of herpes simplex virus (HSV) and varicella-zoster virus (VZV) by subinhibitory dose of acyclovir (ACV). Acta Virologica 33: 565-568, 1989

Shishkov S, Pancheva S. Synergistic antiviral effect of acyclovir and ribavirin towards herpes simplex virus type 1 and the virus of pseudorabias in vitro. In Russian. Acta Microbiologica Bulgarica 25: 69-75, 1990

Smego Jr RA, Asperilla MO. Use of acyclovir for varicella pneumonia during pregnancy. Obstetrics and Gynecology 78: 1112-1116, 1991

Smith CA, Wigdahl B, Rapp F. Synergistic antiviral activity of acyclovir and interferon on human cytomegalovirus. Antimicrobial Agents and Chemotherapy 24: 325-332, 1983

Snoeck R, Andrei G, Schols D, Balzarini J, De Clercq E. Activity of different antiviral drug combinations against human cytomegalovirus replication in vitro. European Journal of Clinical Microbiology and Infectious Diseases 11: 1144-1155, 1992

Spector SA, Connor JD, Hintz M, Quinn RP, Blum MR, et al. Single dose pharmacokinetics of acyclovir. Antimicrobial Agents and Chemotherapy 19: 608-612, 1981

Spector SA, Hintz M, Wyborny C, Connor JD, Keeney RE, et al. Treatment of herpes virus infections in immunocompromised patients with acyclovir by continuous intravenous infusion. Acyclovir Symposium. American Journal of Medicine 73: 275-280, 1982a

Spector SA, Kelley E. Inhibition of human cytomegalovirus by combined acyclovir and vidarabine. Antimicrobial Agents and Chemotherapy 27: 600-604, 1985

Spector SA, Tyndall M, Kelley E. Effects of acyclovir combined with other antiviral agents on human cytomegalovirus. Acyclovir Symposium. American Journal of Medicine 73: 36-39, 1982b

Spector T. 348U87: an inactivator of herpes virus ribonucleotide reductase that potentiates the antiviral activity of acyclovir. Drugs of the Future 18: 25-28, 1993

Spector T, Lobe DC, Ellis MN, Blumenkopf TA, Szczech GM. Inactivators of herpes simplex virus ribonucleotide reductase: hematological profiles and in vivo potentiation of the antiviral activity of acyclovir. Antimicrobial Agents and Chemotherapy 36: 934-937, 1992

Spruance SL, Freeman DJ, Stewart JCB, McKeough MB, Wenerstrom LG, et al. The natural history of ultraviolet radiation-induced herpes simplex labialis and response to therapy with per-

oral and topical formulations of acyclovir. Journal of Infectious Diseases 163: 728-734, 1991

Spruance SL, Stewart JCB, Rowe NH, McKeough MB, Wenerstrom G, et al. Treatment of recurrent herpes simplex labialis with oral acyclovir. Journal of Infectious Diseases 161: 185-190, 1990

Stahlmann R, Korte M, Van Loveren H, Vos JG, Thiel R, et al. Abnormal thymus development and impaired function of the immune system in rats after prenatal exposure to aciclovir. Archives of Toxicology 66: 551-559, 1992

Stanwick TL, Schinazi RF, Campbell DE, Nahmias AJ. Combined antiviral effect of interferon and acyclovir on herpes simplex virus types 1 and 2. Antimicrobial Agents and Chemotherapy 19: 672-674, 1981

Stenseth AM, Rollag H, Degré M. Effect of in vitro acyclovir treatment on selected functions of blood-derived macrophages. Chemotherapy 39: 197-202, 1993

Stratta RJ, Shaefer MS, Cushing KA, Markin RS, Reed EC, et al. A randomized prospective trial of acyclovir and immune globulin prophylaxis in liver transplant recipients receiving OKT3 therapy. Archives of Surgery 127: 55-64, 1992

Stratta RJ, Shaefer MS, Cushing KA, Markin RS, Wood RP, et al. Successful prophylaxis of cytomegalovirus disease after primary CMV exposure in liver transplant recipients. Transplantation 51: 90-97, 1991

Straus SE, Seidlin M, Takiff HE, Rooney JF, Felser JM, et al. Effect of oral acyclovir treatment on symptomatic and asymptomatic virus shedding in recurrent genital herpes. Sexually Transmitted Diseases 16: 107-113, 1989

Straus SE, Smith HA, Brickman C, de Miranda P, McLaren C, et al. Acyclovir for chronic mucocutaneous herpes simplex virus infection in immunosuppressed patients. Annals of Internal Medicine 96: 270-277, 1982

Stray-Pedersen B. Acyclovir in late pregnancy to prevent neonatal herpes simplex. Lancet 336: 756, 1990

Sugiura H, Sawai T, Miyauchi H, Uehara M, Watanabe S, et al. Successful treatment of disseminated cutaneous cytomegalic inclusion disease associated with Hodgkin's disease. Journal of the American Academy of Dermatology 24: 346-352, 1991

Surman OS, Flynn T, Schooley RT, Baer L, Parker S, et al. A double-blind, placebo-controlled study of oral acyclovir in postherpetic neuralgia. Psychosomatics 31: 287-292, 1990

Sutton D, Boyd MR. Comparative activity of penciclovir and acyclovir in mice infected intraperitoneally with herpes simplex virus type 1 SC16. Antimicrobial Agents and Chemotherapy 37: 642-645, 1993

Sutton D, Taylor J, Bacon TH, Boyd MR. Activity of penciclovir in combination with azidothymidine, ganciclovir, acyclovir, foscarnet and human interferons against herpes simplex virus replication in cell culture. Antiviral Chemistry and Chemotherapy 3: 85-94, 1992

Swan SK, Bennett WM. Oral acyclovir and neurotoxicity. Annals of Internal Medicine 3: 188, 1989

Tang IYS, Maddux MS, Veremis SA, Bauma WD, Pollak R, et al. Low-dose oral acyclovir for prevention of herpes simplex virus infection during OKT3 therapy. Transplantation Proceedings 21: 1758-1760, 1989

Tanna S, Wood C, Lawrence MJ. Competition studies to elucidate the mechanisms of acyclovir uptake in the small intestine. Journal of Pharmacy and Pharmacology 44 (Suppl.): 1047, 1992

Tartaglione TA, Collier AC, Opheim K, Gianola FG, Benedetti J, et al. Pharmacokinetic evaluations of low- and high-dose zidovudine plus high-dose acyclovir in patients with symptomatic human immunodeficiency virus infection. Antimicrobial Agents and Chemotherapy 35: 2225-2231, 1991

Tatnall FM, Schofield J, Proby C, Leigh IM. A double blind placebo controlled trial of continuous acyclovir in recurrent erythema multiforme. Abstract. British Journal of Dermatology 125 (Suppl.38): 29, 1991

Taylor JL, Casey MS, O'Brien WJ. Synergistic antiherpes virus activity of acyclovir and interferon in human corneal stromal cells. Investigative Ophthalmology and Visual Science 30: 365-370, 1989

Thin RN. Management of genital herpes simplex infections. American Journal of Medicine 85 (Suppl.2A): 3-6, 1988

Thomas RHM, Dodd HJ, Yeo JM, Kirby JDT. Oral acyclovir in the suppression of recurrent non-genital herpes simplex virus infection. British Journal of Dermatology 113: 731-735, 1985

Trépo C, Ouzan D, Fontanges T, Chevallier M, Chossegros P, et al. Therapeutic potential of acyclovir and of the interferons in HBV-related chronic active hepatitis due to HBV with or without HDV superinfection. Journal of Hepatology 3 (Suppl.2): 129-135, 1986

Upadhyay JM, Hill JM, Jemison M, Helmy MF, Kaufman HE. The effect of HSV multiplication rate on antiviral drug efficacy in vitro. Antiviral Research 15: 67-76, 1991

Uri N, Greenberg E, Meyer W, Kitzes-Cohen R. Herpes zoster oticus: treatment with acyclovir. Annals of Otology, Rhinology and Laryngology 101: 161-162, 1992

Vajpayee RB, Gupta SK, Beraja U, Mohan M. Evaluation of acyclovir in the management of various types of herpetic corneal lesions: a prospective controlled clinical trial in 34 patients. Medical Science Research 17: 93-94, 1989

Valsecchi R, Imberti G, Cainelli T. Contact allergy to acyclovir. Contact Dermatitis 23: 372-373, 1990

van der Horst C, Joncas J, Ahronheim G, Gustafson N, Stein G, et al. Lack of effect of peroral acyclovir for the treatment of acute infectious mononucleosis. Journal of Infectious Diseases 164: 788-792, 1991

Van Dyke R, Straube R, Large K, Hintz M, Spector S, et al. Pharmacokinetics of increased dose oral acyclovir. Abstract. 22nd Interscience Conference on Antimicrobial Agents and Chemotherapy, Florida, 4-6 October 1982

Vasquez EM, Sanchez J, Pollak R, Vrahnos D, Fabrega AJ, et al. High-dose oral acyclovir prophylaxis for primary cytomegalovirus infection in seronegative renal allograft recipients. Transplantation 55: 448-450, 1993

Velasco M, Saavedra T, Sepulveda C, Suarez M. Prolonged treatment of recurrent genital herpes with oral acyclovir. In Spanish. Revista Medica de Chile 119: 876-880, 1991

Vere Hodge RA. Famciclovir and penciclovir. The mode of action of famciclovir including its conversion to penciclovir. Antiviral Chemistry and Chemotherapy 4: 67-84, 1993

Vildé JL, Bricaire F, Leport C, Renaudie M, Brun-Vézinet F. Comparative trial of acyclovir and vidarabine in disseminated varicella-zoster virus infections in immunocompromised patients. Journal of Medical Virology 20: 127-134, 1986

Wade JC, Hintz M, McGuffin RW, Springmeyer SC, Connor JD, et al. Treatment of cytomegalovirus pneumonia with high-dose acyclovir. Acyclovir Symposium. American Journal of Medicine 73: 249-255, 1982b

Wade JC, Newton B, Flournoy N, Meyers JD. Oral acyclovir for prevention of herpes simplex virus reactivation after marrow transplantation. Annals of Internal Medicine 100: 823-828, 1984

Wade JC, Newton B, McLaren C, Flournoy N, Keeney RE, et al. Intravenous acyclovir to treat mucocutaneous herpes simplex virus infection after marrow transplantation. A double-blind trial. Annals of Internal Medicine 96: 265-269, 1982a

Wallace MR, Bowler WA, Murray NB, Brodine SK, Oldfield III EC. Treatment of adult varicella with oral acyclovir. A randomized, placebo-controlled trial. Annals of Internal Medicine 117: 358-363, 1992

Weber R, Bonetti A, Jost J, Vogt MW, Spacey B, et al. Low-dose zidovudine in combination with either acyclovir or lymphoblastoid interferon-alpha in asymptomatic HIV-infected patients: a pilot study. Infection 19: 395-400, 1991

Webster A, Lee CA, Cook DG, Grundy JE, Emery VC, et al. Cytomegalovirus infection and progression towards AIDS in haemo-

philiacs with human immunodeficiency virus infection. Lancet 2: 63-65, 1989

Weinberg A, Bate BJ, Masters HB, Schneider SA, Clark JC, et al. In vitro activities of penciclovir and acyclovir against herpes simplex virus types 1 and 2. Antimicrobial Agents and Chemotherapy 36: 2037-2038, 1992

Whatley JD, Thin RN. Episodic acyclovir therapy to abort recurrent attacks of genital herpes simplex infection. Journal of Antimicrobial Chemotherapy 27: 677-681, 1991

Whitley R, Arvin A, Prober C, Burchett S, Corey L, et al. A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. New England Journal of Medicine 324: 444-449, 1991

Whitley RJ, Barton N, Collins E, Whelchel J, Diethelm AG. Mucocutaneous herpes simplex virus infections in immunocompromised patients. A model for evaluation of topical antiviral agents. Acyclovir Symposium. American Journal of Medicine 73: 236-240, 1982a

Whitley RJ, Blum MR, Barton N, de Miranda P. Pharmacokinetics of acyclovir in humans following intravenous administration. Acyclovir Symposium. American Journal of Medicine 73 (Suppl.): 165-170, 1982b

Whitley RJ, Gnann Jr JW, Hinthorn D, Liu C, Pollard RB, et al. Disseminated herpes zoster in the immunocompromised host: a comparative trial of acyclovir and vidarabine. Journal of Infectious Diseases 165: 450-455, 1992

Williams REA, Lever R. Very low dose acyclovir can be effective as prophylaxis for post-herpetic erythema multiforme. British Journal of Dermatology 124: 111, 1991

Wintergerst U, Belohradsky BH. Acyclovir monotherapy versus acyclovir plus beta-interferon in focal viral encephalitis in children. Infection 20: 207-212, 1992

Wirth S, Ehninger G, Baumann W. Zur Behandlung konnataler Varizelien mit Acyclovir. Monatsschrift fur Kinderheilkunde 135: 696-698, 1987

Wong T, Toupance O, Chanard J. Acyclovir to prevent cytomegalovirus infection after renal transplantation. Annals of Internal Medicine 115: 68, 1991

Wood MJ, Ogan PH, McKendrick MW, Care CD, McGill JI, et al. Efficacy of oral acyclovir treatment of acute herpes zoster. Antiviral Symposium. American Journal of Medicine 85 (Suppl.2A): 79-83, 1988

Wormser GP, Mack L, Lenox T, Hewlett D, Goldfarb J, et al. Lack of effect of oral acylovir on prevention of aphthous stomatitis. Otolaryngology - Head and Neck Surgery 98: 14-17, 1988

Wutke K, Wutzler P, Alken RG, Kowal K. BVDU (bromovinyldesoxyuridine) versus aciclovir: therapy of severe herpes zoster in cancer patients. Results of a double-blind trial. Abstract no. 58. Onkologie 14 (Suppl.3): 21, 1991

Yao QY, Ogan P, Rowe M, Wood M, Rickinson AB. Epstein-Barr virus-infected B cells persist in the circulation of acyclovir-treated virus carriers. International Journal of Cancer 43: 67-71, 1989

Youle MS, Gazzard BG, Johnson MA, Cooper DA, Hoy JF, et al. Effects of high dose oral acyclovir on cytomegalovirus (CMV) disease and survival in patients with advanced HIV disease. Poster presented at the 4th International CMV Conference, Paris, France, 1993

Zandotti C, de Lamballerie X, Viard L, Noirclerc M, de Micco P. Acyclovir and immune globulin prevention and ganciclovir treatment of cytomegalovirus infections in children after lung transplantation: analysis of 12 patients. Médecine et Maladies Infectieuses 22 (Suppl.): 606-609, 1992

Zwartouw HT, Humphreys CR, Collins P. Oral chemotherapy of fatal B virus (herpesvirus simiae) infection. Antiviral Research 11: 275-284, 1989

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Erratum

Vol. 46, Supplement 1, 1993, page 103: In the first sentence both of the Summary and of the Patients and Methods section, the dosage of naproxen should be 250mg twice daily, *not* 500mg twice daily, as shown.