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Muromonab CD3

A Reappraisal of its Pharmacology and Use as Prophylaxis of Solid Organ Transplant Rejection

Michelle I. Wilde and *Karen L. Goa*

Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by:

D. Abramowicz, Department of Nephrology, Hôpital Erasme, Brussels, Belgium; ***P.N. Bennett***, University of Bath, School of Postgraduate Medicine, Bath, England; ***H.A. Bock***, Division of Nephrology, Kantonsspital, Basel, Switzerland; ***L. Chatenoud***, Inserm U 25, Hôpital Necker, Paris, France; ***J.M. Grinyó***, Institut Català de la Salut, Ciutat Sanitària i Universitària de Bellvitge, Barcelona, Spain; ***K. Fukao***, Department of Surgery, University of Tsukuba, Tsukuba City, Japan; ***G. Ippoliti***, Clinica Medica II, IRCCS S Matteo, Pavia, Italy; ***L.J. Swinnen***, Division of Hematology/Oncology, Stritch School of Medicine, Loyola University of Chicago, Illinois, USA; ***E.M. Vasquez***, Department of Pharmacy Practice, University of Illinois at Chicago, Chicago, USA.

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Synopsis

The murine monoclonal antibody muromonab CD3 (OKT3) is directed against the CD3 antigen on peripheral human T cells and effectively blocks all T cell function.

Prophylaxis with muromonab CD3 (5mg intravenously once daily for 10 to 14 days) as induction therapy together with corticosteroids, azathioprine and delayed cyclosporin (sequential therapy) optimises early graft function by delaying the potentially nephrotoxic and hepatotoxic effects of cyclosporin until graft function is established.

Although clinical data are limited (by inconsistencies in trial design and trial size), prophylactic muromonab CD3–based sequential therapy is significantly more effective than standard triple therapy in the prophylaxis of allograft rejection in renal and hepatic, but not cardiac, transplant recipients. Benefits are particularly notable in patients with delayed graft function. No significant between-treatment differences in patient survival have been observed.

The overall efficacy of muromonab CD3– and polyclonal–based prophylactic regimens appears to be similar, although results vary between investigators and confirmation is needed. An anti–interleukin-2 monoclonal antibody–based prophylactic regimen improved graft and patient survival compared with muromonab CD3–based prophylaxis in hepatic transplant recipients.

Antimuromonab CD3 antibodies may develop; however, muromonab CD3 may be successfully reused in patients with low titres.

Preliminary pharmacoeconomic data suggest that mean drug costs are greater with quadruple immunosuppressive regimens containing muromonab CD3, antithymocyte globulin (ATG) or antilymphocyte globulin (ALG) than with triple therapy. Drug costs with prophylactic muromonab CD3–based regimens were similar or greater than those with polyclonal–based protocols.

The first doses of muromonab CD3 are associated with the 'cytokine-release syndrome'. More severe first-dose events include aseptic meningitis, intragraft thromboses, seizures and potentially fatal pulmonary oedema. The incidence and/or severity of cytomegalovirus infection with prophylactic muromonab CD3–based immunosuppression is similar to or greater than that with triple therapy and ATG- or ALG–based regimens. However, the risk of infection and also the observed increase in lymphoproliferative disorders appears to be related to the degree of immunosuppression rather than to the drug itself.

Thus, sequential muromonab CD3–based therapy is more effective than standard triple therapy (in renal and hepatic transplant recipients) and appears to be similar to that of polyclonal–based regimens in the prophylaxis of transplant rejection. Although the routine use of prophylactic muromonab CD3 in low-risk patients with primary graft function does not appear to be justified, prophylactic muromonab CD3–based therapy has a role in patients at high risk of rejection.

Pharmacodynamic Properties

Muromonab CD3 (OKT3), a murine monoclonal antibody directed against the CD3 antigen (linked to the T cell antigen receptor; TCR) on mature peripheral human T cells, effectively blocks all T cell function. The mechanism of action includes antigenic modulation of the CD3/TCR complex with subsequent opsonisation and removal of circulating T cells; other mechanisms are proposed.

Cytokine release associated with an acute phase reaction occurs after the first doses of muromonab CD3. This is manifest as first-dose adverse events (see 'Tolerability' summary).

A biphasic reversible haemodynamic response and biphasic activation of coagulation and fibrinolysis, both of which coincide with cytokine release and/or complement activation, occur after initiation of muromonab CD3. Evidence suggests that intraoperative administration of the first muromonab CD3 dose is associated with fewer cardiovascular and pulmonary disturbances than administration in the immediate postoperative period.

High antimuromonab CD3 antibody titres (≥1:1000) were detected in 5.8% of >12 000 serum samples from patients who received muromonab CD3 for the treatment or prevention of transplant rejection. IgG but not IgM antibodies are able to reduce the activity of muromonab CD3. Administration of concomitant immunosuppressants such as corticosteroids and azathioprine reduces the likelihood of antimuromonab CD3 antibody formation.

Pharmacokinetic Properties

Muromonab CD3 is a pure standardised product for which pharmacokinetic data are limited.

Plasma muromonab CD3 concentrations vary according to the muromonab CD3 'antibody status', transplanted organ and age. Muromonab CD3 plasma concentrations were 996 μg/L after 1 hour and 104 μg/L at 24 hours in renal transplant recipients receiving 5mg once daily for 10 to 14 days. Mean trough steady-state serum concentrations range from 500 to 1000 μg/L after 2 to 4 days; approximately 1000 μg/L is required to block cytotoxic T cell function *in vitro*. Steady-state serum muromonab CD3 concentrations are achieved earlier with prophylactic administration than administration for the treatment of rejection. There is evidence of drug accumulation after repeated doses. Muromonab CD3 plasma elimination half-lives of approximately 18 hours (following administration for treatment of rejection) and 36 hours (prophylactic administration) have been reported.

Therapeutic Use

There are 2 main reasons for using muromonab CD3 as induction therapy in sequential immunosuppressive regimens (including azathioprine, methylprednisolone/prednisone and delayed cyclosporin): to optimise early graft function by delaying the administration of potentially nephrotoxic and hepatotoxic cyclosporin until graft function is established; and to reduce and delay the occurrence of rejection episodes.

Data from clinical trials of muromonab CD3–based prophylaxis are limited by trial size and inconsistencies in design. However, compared with triple therapy, prophylactic muromonab CD3–based sequential therapy was significantly more effective as assessed by severity and/or incidence of rejection episodes and time to first rejection episode in renal transplant recipients and by incidence and/or severity of early acute rejection episodes and time to first rejection in hepatic transplant recipients. Benefits appeared to be maintained for up to 3 years in renal transplant recipients and were particularly marked in patients with delayed graft function. In those with delayed renal graft function, overall graft survival was significantly greater with muromonab CD3–based induction therapy than with triple therapy. Three-year graft survival in renal transplant recipients was significantly greater with sequential muromonab CD3–based therapy (delayed cyclosporin) than with cyclosporin–based therapy not containing muromonab CD3; in high-risk patients, sequential therapy was also associated with significantly greater 3-year graft survival rates than simultaneous muromonab CD3 and cyclosporin administration. Muromonab CD3–based prophylaxis appeared to be similar to triple therapy in terms of rejection incidence, time to first rejection episode

and graft survival in cardiac transplant recipients. There were no significant between-treatment differences in patient survival for any type of transplant.

In renal transplant recipients, significantly more of those receiving muromonab CD3–based prophylaxis required postoperative dialysis than those receiving triple therapy; in hepatic transplant recipients, muromonab CD3 improved or maintained renal function in the early postoperative period.

Data on the relative effects of muromonab CD3–based and polyclonal–based prophylactic regimens are conflicting. In renal transplant recipients, some investigators show muromonab CD3– and antilymphocyte globulin (ALG)– or antithymocyte globulin (ATG)–based prophylaxis to be similar in terms of rejection incidence and/or time to first rejection, while others show ALG or ATG to be superior. The incidence of rejection episodes with muromonab CD3–based induction therapy in dual renal-pancreas transplant recipients is either similar to or lower than that with ALG- or ATG–based induction. Similarly, in cardiac transplant recipients, some studies show a longer time to first rejection episode and/or a lower incidence of rejection with muromonab CD3–based prophylaxis; others show no differences or a lower incidence of rejection or a longer time to first rejection episode with ATG–based therapy. Rejection episodes were fewer with ATG than with muromonab CD3 in the 1 available study in hepatic transplant recipients. Generally, no between-treatment differences were apparent in patient and graft survival or the incidence of delayed graft function. However, an anti–interleukin-2 monoclonal antibody–based prophylactic regimen improved graft and patient survival compared with muromonab CD3–based prophylaxis in hepatic transplant recipients.

Several noncomparative trials have shown early rejection in children and adolescents undergoing renal, hepatic or cardiac transplantation to be effectively reduced by prophylactic muromonab CD3 administered as part of a sequential immunosuppressive protocol. Although rejection incidence during the first 14 days was lower with muromonab CD3–based prophylaxis than with standard triple therapy in hepatic transplant recipients, no overall reduction was observed. Further comparative trials are needed to determine the relative benefits of prophylactic muromonab CD3 in this patient group.

Although muromonab CD3 reuse following prophylactic use is not recommended in patients with anti-idiotypic antibody titres ≥1:1000, successful retreatment may occur in patients with lower titres.

Pharmacoeconomic Considerations

In theory, potential cost savings with prophylactic muromonab CD3 because of reduced rejection incidence compared with triple therapy may be offset by the increased incidence of infections and adverse events, but this has not been addressed in formal pharmacoeconomic assessments.

Preliminary data from cost-minimisation studies suggest that mean first-year drug costs are greater with quadruple immunosuppressive regimens containing muromonab CD3, ATG or ALG than with triple therapy, and hospital costs with prophylactic muromonab CD3–based regimens were similar to or greater than those with polyclonal–based protocols.

Tolerability

The first doses of muromonab CD3 are associated with flu-like 'cytokine-release syndrome' symptoms (e.g. fever, chills, gastrointestinal disturbance), which occur within 45 to 60 minutes and last for 2 to 48 hours. More severe but rare first-dose effects include aseptic meningitis, intragraft thromboses, seizures and potentially fatal pulmonary oedema. The incidence and severity of initial adverse

events with muromonab CD3–based prophylaxis are similar to or greater than those associated with polyclonal antilymphocyte–based regimens.

Cytomegalovirus (CMV), herpes simplex virus and bacterial infections are the primary cause of morbidity and mortality in muromonab CD3 recipients. However, the risk of infection appears to be related to the degree of immunosuppression rather than to the drug itself. The risk of CMV infection is increased by high doses (total doses >75mg) and repeated exposure to muromonab CD3. The incidence and/or severity of CMV infection with prophylactic muromonab CD3–based immunosuppression is similar to or greater than that with triple therapy and ATG- or ALG–based regimens. The overall incidence of bacterial and fungal infections with these treatment options is largely similar.

Muromonab CD3–based immunosuppression has been associated with an increased risk of neoplasia, mainly lymphoproliferative disorders. However, this is most probably a direct result of the degree of immunosuppression; Epstein-Barr virus infection has also been implicated. The risk of lymphoproliferative disease may be increased by the use of high muromonab CD3 doses (total dose >75mg), long durations of administration, multiple courses and early retreatment. While some investigators report the incidence of neoplasia to be similar with muromonab CD3 and polyclonal preparations, others report a trend towards a greater incidence with muromonab CD3.

Other clinically significant pulmonary, cardiovascular or neurological events are uncommon.

Adverse events with muromonab CD3 may be prevented or minimised by the intraoperative administration of the first dose of muromonab CD3, pretreatment with a corticosteroid, administration of an antipyretic and antihistamine, prophylactic use of an antimicrobial(s) and correction of increased temperature and fluid overload before prophylaxis initiation.

Dosage and Administration

Induction therapy with muromonab CD3 together with azathioprine, methylprednisolone/prednisone and delayed cyclosporin therapy is the most accepted muromonab CD3–based regimen for allograft rejection prophylaxis.

Although the optimal dosage of muromonab CD3 has not been established, the currently recommended adult dosage is 5mg administered intravenously once daily for 10 to 14 days, irrespective of the organ transplanted. A dosage of 2.5 mg/day has usually been used in children although higher doses may be needed. The dosage should be adjusted according to the presence of clinical signs of rejection in addition to antimuromonab CD3 antibodies, plasma muromonab CD3 concentrations and CD3+ cell levels.

Patients should be closely monitored during administration of the first few doses. Intraoperative administration of the first dose and the use of preventative measures improve the tolerability of muromonab CD3.

Evidence suggests that procoagulant activity is increased with the concomitant administration of muromonab CD3 and high-dose corticosteroids, and indomethacin may increase the risk of encephalopathy and volatile anaesthetic agents or drugs that decrease cardiac contractility increase the risk of developing cardiovascular problems when administered with muromonab CD3.

Muromonab CD3 (murine monoclonal antibody towards the Cluster of Differentiation 3 antigen; OKT3), an IgG_{2a} immunoglobulin, is a purified murine monoclonal antibody directed specifically against the CD3 antigen. This monoclonal antibody is one of a series of monoclonal antibodies (OKT series) directed towards human T cell surface antigens and is the only commercially available anti-CD3 monoclonal antibody.

While muromonab CD3–based immunosuppression is widely accepted as a treatment for acute allograft rejection episodes and as 'rescue' therapy for steroid-resistant allograft rejection,[1] the prophylactic use of muromonab CD3 is less well established. Issues central to the prophylactic use of this agent are whether muromonab CD3 is more effective than standard 'triple therapy' (prednisone, azathioprine plus cyclosporin) and whether muromonab CD3 should be used to prevent rejection or be reserved for the treatment of rejection episodes.

The rationale for using muromonab CD3–based therapy (section 3) in the prevention of rejection is to optimise early graft function by delaying administration of potentially toxic cyclosporin until organ function is established and to improve graft and patient survival by reducing the incidence of early rejection episodes.

The therapeutic potential of muromonab CD3 in both the treatment and prevention of rejection episodes has been previously reviewed.[1] This review provides a reappraisal of muromonab CD3 in the prevention of renal, hepatic and cardiac transplant rejection as well as in dual (renal/pancreas) solid organ transplant rejection. The efficacy of prophylactic muromonab CD3–based immunosuppression in patients undergoing cardiac/lung transplantation or nonsolid organ transplantation (e.g. bone marrow transplantation) is not addressed in this review.

1. Pharmacodynamic Properties

1.1 Mechanism of Action

Muromonab CD3 is directed specifically against the CD3 antigen which is found on mature peripheral human T cells (and medullary thymocytes) and is linked to the T cell antigen receptor (TCR) [fig. 1][1-5] In contrast, polyclonal antilymphocyte antibody preparations are directed against more than one T cell epitope.[3] In effect, muromonab CD3 blocks all T cell function and is, there-

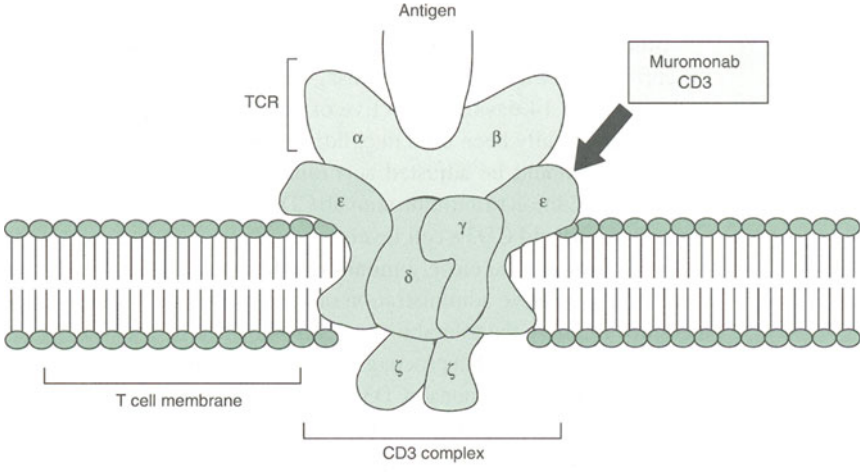

Fig. 1. Diagrammatic representation of the CD3 complex, T cell antigen receptor (TCR) and site of muromonab CD3 binding (epsilon chain of the CD3 complex).

Table I. Known and proposed mechanisms of action of muromonab CD3

Known mechanisms	Proposed mechanisms
• Antigenic modulation of the CD3/T cell receptor complex on peripheral T cells resulting in failure of antigen recognition[1-3,5] • Mediates the opsonisation of circulating T cells and subsequent removal by the reticuloendothelial system[1-3,5]	• Immunomodulation of graft-infiltrating lymphocytes[6,7] • Elimination of activated CD3+ cells by induction of apoptosis (programmed cell death)[3,8] • Modulation of CD3 complex density by shedding CD3 antigens or the whole CD3 complex[9] • Increasing lymphocyte adhesion molecule expression on peripheral blood lymphocytes resulting in increased adhesion of lymphocytes to vascular endothelium[10,11] • Induction of cell-mediated cytolysis[12]

fore, classified as a pan-T cell suppressive monoclonal antibody.

The immunological mechanisms by which muromonab CD3 produces its effects are not completely understood. Known and proposed mechanisms of action are summarised in table I.

Although CD3+ cells are cleared from the circulation within minutes of the first dose of muromonab CD3 (CD2+, CD4+ and CD8+ are also depleted),[1,5] CD3+ cells may reappear during continued once-daily administration (usually as a result of antimuromonab CD3 antibody formation; section 1.3). Furthermore, rejection has been observed despite low circulating CD3+ cell levels.[13] These findings support the notion that mechanisms other than CD3+ cell depletion and CD3/T cell antigen receptor modulation are involved in the immunological activity of muromonab CD3.

Modulated cells rapidly re-express the CD3+ marker after withdrawal of muromonab CD3 with CD3+ cell levels returning to baseline within 1 week.[1,5]

No studies have directly compared the degree of immunosuppression with muromonab CD3 and other agents.

1.2 T Cell–Activating Properties

Cytokines including tumour necrosis factor (TNF) alpha, interleukins (IL) 2, 3, 6 and 10 and interferon gamma are released after administration of muromonab CD3. This is associated with an acute phase reaction involving C-reactive protein, neopterin, endothelin-1, complement, transferrin, alpha-1 proteinase inhibitor and neutrophilic granulocytes.[1,14-20] Although this response usually occurs after the first and possibly second and third dose(s), a similar response (particularly IL-6 release[21]) may also occur later in the course of treatment if CD3+ cell levels substantially increase (sections 1.3 and 2); this may account for some of the late adverse events observed with muromonab CD3 (section 5.1.1). The T cell–activating properties of muromonab CD3 manifest clinically as first-dose adverse events ('cytokine-release syndrome') [section 5.1].

Monocyte-dependent Fc receptor–mediated cell activation appears to be the main mechanism underlying these events.[15,16,22-24]

The release of IL-6 and IL-10 may be involved in the pathogenesis of Epstein-Barr virus (EBV)-associated lymphoproliferative disorders in transplant recipients receiving muromonab CD3 (section 5.3).[25,26] Anti-CD3 monoclonal antibodies have been shown to trigger T cell mitogenesis *in vitro*.[18]

Several agents including corticosteroids, pentoxiphylline and IL-10 can reduce muromonab CD3–induced cytokine release.[27-32] However, although corticosteroids can reduce first-dose cytokine-related adverse events (see table V), pretreatment with pentoxifylline does not appear to reduce the cytokine-release syndrome associated with prophylactic muromonab CD3.[33,34]

1.3 Immunogenicity

Despite improvements in muromonab CD3 dosage regimens, antibodies to this agent may develop. High antibody titres (≥1:1000) were de-

tected in 5.8% of 12 133 serum samples from patients who received muromonab CD3 for the treatment or prevention of transplant rejection.[35] These antibodies may result in decreased muromonab CD3 plasma concentrations (section 2.2) and increased circulating CD3+ cell levels (section 1.1) and may preclude reuse of the agent in some patients (section 3.6).[36]

The 2 types of anti–muromonab CD3 antibodies that may be induced are anti-idiotypic and anti-isotypic antibodies.[1,18,36] Anti-idiotypic antibodies compete with muromonab CD3 for binding to the CD3 complex and can neutralise the activity of muromonab CD3; IgG but not IgM anti-muromonab CD3 antibodies are able to reduce the activity of this agent. Although anti-isotypic antibodies bind to the constant portion of the muromonab CD3 antibody molecule, they do not block the effects of the drug. Anti-idiotypic antibodies to muromonab CD3 do not cross-react with murine antibodies of similar or different isotypes and cross-react with only 10% of other anti-CD3 monoclonal antibodies.[37]

Although variation in antibody test results between centres is significant, the incidence of anti-muromonab CD3 antibodies and the percentage of high antibody titres (≥1:1000) appears to be greatest in liver or kidney transplant recipients and least in cardiac transplant recipients.[35,38-40] The risk of high antimuromonab CD3 antibody titres also appears to be greatest in patients aged <30 years, in those who have undergone previous transplantation or muromonab CD3 courses, and in those receiving muromonab CD3 for rescue treatment (versus prophylaxis or first-line treatment of rejection).[35]

Administration of concomitant immunosuppressants reduces the likelihood of antimuromonab CD3 antibody formation.[18,19,36,41-43]

1.4 Effects on Rejection Histopathology

Although the microscopic appearance of lymphocytic infiltrates in hepatic transplant recipients experiencing acute allograft rejection was similar with prophylactic muromonab CD3 and conventional prophylaxis with triple therapy,[44] infiltrate cellularity was reduced with prophylactic muromonab CD3 in cardiac transplant recipients.[45] The latter may partly explain the discrepant results reported by different research groups (section 3).

Prophylactic antithymocyte globulin (ATG) has been associated with less cellular infiltration of allograft biopsies, lymphocyte growth and donor-specific cytolytic activity than prophylactic muromonab CD3 in cardiac transplant recipients.[46] However, these findings do not appear to have translated into a consistently demonstrable clinical advantage (section 3). Increased adhesion of peripheral blood mononuclear cells to human arterial endothelial cells with muromonab CD3 but not ATG may partly explain why vascular rejection may occur with muromonab CD3 but not ATG.[47]

1.5 Cardiovascular, Pulmonary and Haematological Parameters

Following muromonab CD3 administration, a biphasic reversible haemodynamic response has been observed (involving increases in ventricular ejection fractions and cardiac index and decreases in systemic vascular resistance index within the first 2 hours, then reductions in ejection fractions, cardiac index and right atrial and pulmonary capillary wedge pressures after 5 to 6 hours).[48] These changes coincide with increases in TNF levels (section 1.2) and are suggestive of a capillary leak syndrome.

Evidence suggests that the intraoperative administration of muromonab CD3 is associated with fewer cardiovascular and pulmonary disturbances (changes in heart rate, blood pressure, mean pulmonary artery pressure, central venous pressure, pulmonary capillary wedge pressure, pulmonary and systemic vascular resistance, cardiac index and blood gases) than administration in the immediate postoperative period.[49-51]

Biphasic activation of coagulation and fibrinolysis also occurs after the first dose of muromonab CD3 and other antilymphocyte antibodies. The initial phase appears to be associated with complement activation and the latter with cytokine release

(section 1.2).[52-55] This dual activation may explain the general lack of thromboembolic events with recommended muromonab CD3 dosages (although intragraft thromboses may develop; section 5.1). Pentoxifylline inhibits the *in vitro* procoagulant activity of muromonab CD3.[56]

2. Pharmacokinetic Properties

Muromonab CD3 is a pure standardised product (in contrast to polyclonal antilymphocyte antibody preparations) and is administered via the intravenous route.[3]

No studies have specifically compared the pharmacokinetics of muromonab CD3 when administered intraoperatively or in the immediate postoperative period.

2.1 Pharmacokinetic Parameters

As plasma muromonab CD3 concentrations are dependent on the presence and degree of sensitisation (section 1.3) and the number of available CD3 molecules, significant interindividual variation exists.[57,58] Following a single dose of muromonab CD3 2.5mg (lower than the recommended dosage; section 7) administered 12 to 24 hours before renal transplantation in 7 patients, a maximum serum concentration (C_{max}) of 185 μg/L was reached at 1 hour; serum concentrations decreased rapidly thereafter and were undetectable by 12 hours.[59] In 66 renal transplant recipients receiving intravenous muromonab CD3 5mg once daily for 10 to 14 days for the prevention of transplant rejection, mean serum muromonab CD3 concentrations were 996 μg/L after 1 hour and decreased to 104 μg/L at 24 hours.[60] Plasma muromonab CD3 concentrations increase gradually over the treatment period and decrease sharply after discontinuation.[61-63] Mean trough steady-state serum concentrations range from 500 to 1000 μg/L after 2 to 4 days; approximately 1000 μg/L is required to block cytotoxic T cell function *in vitro*.[60,64]

Mean serum muromonab CD3 concentrations were significantly higher on days 1 to 6 in patients receiving the drug as prophylaxis than in those being treated for rejection (greatest difference was on day 1; 678 *vs* 333 μg/L) but significantly lower on days 7 to 14 (greatest difference on day 11; 555 *vs* 784 μg/L; $p < 0.05$); steady-state serum muromonab CD3 concentrations were achieved earlier (approximately 1 *vs* 5 days) with prophylactic administration.[40] Most patients in each group received a conventional muromonab CD3 dosage of 5 mg/day, while the remainder received increased dosages (dosage not stated). These findings may be explained by muromonab CD3 binding to CD3+ cells associated with rejection. Mean serum muromonab CD3 concentrations were also higher in women than in men, in hepatic transplant recipients compared with renal or cardiac transplant recipients during the first 7 to 10 days of administration and in renal compared with cardiac transplant recipients during the latter part of treatment.[40] They were also higher in those aged <10 years compared with older patients, in those who were antimuromonab CD3 antibody-negative before treatment compared with those who had low titres, and in patients who remained antimuromonab CD3 antibody-negative compared with those who seroconverted.[40]

The apparent volume of distribution of muromonab CD3 is approximately 6.5L.[64] The route of elimination of muromonab CD3 is via binding to lymphocytes and subsequent removal by the reticuloendothelial system.[40] There is an initial rapid clearance of the drug (serum concentrations decreased by approximately 60% over the first 4 hours) and unmeasurably low concentrations are reached by 12 hours.[59,64] Muromonab CD3 plasma elimination half-lives ($t_{1/2}$) of approximately 18 hours (following administration for the treatment of rejection)[64] and 36 hours (with prophylactic administration)[65] have been reported; elimination is more rapid in the presence of antimuromonab CD3 antibodies.

2.2 Correlation Between Plasma Concentrations and Efficacy

Low plasma muromonab CD3 concentrations have been associated with failure of muromonab CD3 prophylaxis.[66-68] The CD3+ cell level alone

is not a reliable indicator of plasma muromonab CD3 concentrations or early sensitisation;[69-72] therefore, achieving optimal dosage adjustments and efficacy requires continued surveillance for clinical signs of rejection during muromonab CD3 prophylaxis in addition to monitoring serum muromonab CD3 concentrations, CD3+ cell levels and antimuromonab CD3 antibody titres, as appropriate.[58,67,68,70,73-78]

3. Therapeutic Use

The end-points of immunosuppressive trials, particularly those involving prophylactic regimens, should include rejection incidence and severity, time to first rejection episode and effects on organ function as well as graft and patient survival. Randomised, double-blind trials are necessary to determine significant between-treatment differences. In this section, the efficacy of prophylactic muromonab CD3–based regimens in terms of these end-points has been investigated in renal, hepatic and cardiac transplant recipients.

Two types of 'induction' therapy for the prevention of rejection are used in transplantation: administration of an antilymphocyte preparation, azathioprine and corticosteroids from the time of transplantation with cyclosporin withheld until renal function is established (sequential therapy); and administration of an antilymphocyte preparation, azathioprine, corticosteroids and low-dose cyclosporin from the time of transplantation. Most trials in this review involved muromonab CD3 administered as part of a sequential regimen followed by maintenance therapy. Muromonab CD3 was usually administered during the immediate postoperative period although some patients received the drug intraoperatively.

Prophylactic muromonab CD3–based immunosuppression has been compared with standard triple therapy (prednisone, azathioprine plus cyclosporin) and with quadruple regimens containing other antilymphocyte preparations (polyclonal preparations) or anti–IL-2 receptor antibodies. The most commonly used polyclonal preparations were antilymphocyte globulin (ALG) and ATG.

Most assessed trials were randomised, but the majority were not double-blind (the first-dose reaction to muromonab CD3 and the different modes of administration of antilymphocyte antibodies precluded double-blinding) and involved small numbers of patients. Furthermore, dosage regimens of concomitant immunosuppressants were varied and complex and administration of muromonab CD3 was preceded by a variety of prophylactic agents (for the prevention of first-dose effects and infections), making between-study comparisons difficult. Most recipients were undergoing cadaveric transplantation for the first time and some underwent dual transplantation. Rejection episodes were documented histologically or with appropriate laboratory tests of organ function.

Factors which may influence the outcome of rejection prophylaxis and should be controlled for in clinical trials include:

- primary disease and severity including baseline organ function;
- age and sex of donor and recipient[79];
- pre-existing antimuromonab CD3 antibody titres (section 1.3);
- delayed graft function[80,81];
- ABO blood group compatibility;
- previous transplantation or blood transfusions;
- donor/recipient cytomegalovirus (CMV) status;
- histocompatibility antigen matching and preformed reactive anti-HLA antibodies, although the potential beneficial effects of HLA matching, especially in those receiving antilymphocyte agents, are controversial[82,83];
- duration of organ cold ischaemia time;
- surgical technique;
- postoperative patient management including treatment of rejection.

Most muromonab CD3 trials selected patients according to primary disease and severity, controlled for ABO blood group compatibility, duration of organ cold ischaemia time, age and sex of donor/recipient, histocompatibility antigen matching and previous transplantation, and used standardised surgical techniques and postoperative patient management. Fewer controlled for donor/recipient

CMV status, delayed graft function or pre-existing antimuromonab CD3 antibody titres. However, clinical judgement should be exercised, as optimal matches are not always possible with the shortage of suitable organs and the usual urgency of transplantation.

3.1 Optimal Dosage

The currently recommended dosage of muromonab CD3 for the prevention of rejection is discussed in section 7.

Lower initial dosages (<5 mg/day) may be effective and are better tolerated and less costly than higher dosages of muromonab CD3.[84,85] Rejection incidences with low dosage muromonab CD3–based induction therapy in renal transplant recipients were similar to or lower than those with higher dosages.[84,85] In cardiac transplant recipients who received muromonab CD3 2.5 or 5mg for 7 days, no significant between-treatment differences were observed; however, rejection incidence tended to be lower and the incidence of adverse events and the number of infectious complications tended to be greater in the 5mg group.[86] Whether a low dosage regimen results in a reduction in the incidence of post-transplant lymphoproliferative disease remains to be determined.

High muromonab CD3 dosages (10 mg/day) have been associated with intragraft thromboses (section 5.1). Single high doses (30, 40 or 50mg) provided no efficacy advantages over 5 mg/day and were associated with a high incidence of adverse events.[87]

A 14-day course of prophylactic muromonab CD3 in cardiac transplant recipients was associated with a lower incidence of rejection episodes and was more likely to be associated with withdrawal of maintenance corticosteroids than a 10-day course.[88] No advantages with shorter-duration (4 to 6 days) muromonab CD3–based quadruple therapy have been reported.[89]

According to an abstract report, administration of prophylactic muromonab CD3 via a 2-hour continuous infusion reduced complement activation (section 1.2) and the incidence of adverse events compared with bolus administration in renal transplant recipients.[90] However, administration of muromonab CD3 via continuous infusion is not recommended by the manufacturer.[91]

3.2 Renal Transplant Recipients

Studies comparing prophylactic muromonab CD3–based sequential immunosuppression with triple therapy or regimens containing other antilymphocyte preparations, published since the previous review,[1] are summarised in table II.

3.2.1 Comparisons with Triple Therapy

Prophylactic muromonab CD3–based quadruple therapy (with delayed cyclosporin) was significantly more effective than standard triple therapy in terms of severity and/or incidence of rejection episodes (rejection incidence approximately 44 to 68% *vs* 66 to 78%)[13,93,94] and time to first rejection episode.[13,94] These benefits appeared to be maintained in the long term (for up to 3 years) and were noted irrespective of antiglobulin crossmatch (AGXM) status.[93] In patients with delayed graft function, overall graft survival was significantly increased by muromonab CD3–based therapy compared with triple therapy (the duration of graft nonfunction was decreased with muromonab CD3–based therapy).[92] Three-year graft survival rates in renal transplant recipients of first transplants and in those receiving retransplants were significantly greater with sequential muromonab CD3–based induction therapy (with delayed cyclosporin) than with cyclosporin–based prophylactic regimens not containing muromonab CD3 (75 *vs* 71% and 68 *vs* 62%, respectively; $p < 0.001$); corresponding survival rates were not greater with simultaneous muromonab CD3 and cyclosporin administration.[100] There were no significant between-treatment differences in patient survival (table II).

Compared with triple therapy, the muromonab CD3–containing regimen was associated with greater graft survival rates in patients with 2 mismatches at the HLA DR loci (86 *vs* 61% at 2 years; total $n = 51$; $p = 0.04$) and in those whose graft had

Table II. Efficacy of muromonab CD3 (MCD3)–based immunosuppression (delayed cyclosporin) as prophylaxis of renal allograft rejection versus standard triple therapy (Tr) [immediate cyclosporin] or other antilymphocyte-based regimens

Reference	Study design	No. of evaluable patients (characteristics)	Treatment	Time to initial rejection (days)	Actuarial graft survival (%)	Rejection incidence (%)	Actuarial patient survival (%)	Overall efficacy	Comments
Muromonab CD3–based immunosuppression versus triple therapy									
Abramowicz et al.[13]	r	56	MCD3[a,b]	23 (during first 3mo)*	83 (overall; 3y)[c] (92*[d])	4[e]; 32 (3y)*[f]	94.5 (3y)	MCD3 ≥ Tr	Fewer rejections with MCD3 were corticosteroid-resistant (15 *vs* 30%*)
		52	Tr[g]	11 (during first 3mo)	75 (overall; 3y)[c] (79[d])	6[e]; 22 (3y)[f]	93 (3y)		
Benvenisty et al.[92]	nb	34 (delayed graft function)	MCD3[a]		80 (1y)*, 74 (2y)*	44*	89	MCD3 ≥ Tr	MCD3 decreased the duration of graft nonfunction (9.4 *vs* 14.9 days)
		40 (delayed graft function)	Tr[g]		55 (1y), 47 (2y)	82	89		
Dafoe et al.[93]	nb	38 (positive AGXM)	MCD3[a]	35	88*	44[h]	100	MCD3 ≥ Tr	AGXM-positive patients: incidence of delayed graft function greater with MCD3 (75 *vs* 40%*)
		10 (positive AGXM)	Tr[g]	13	50	70	100		
		32 (negative AGXM)	MCD3[a]	22	72	44	97		
		32 (negative AGXM)	Tr[g]	13	92*	73*	100		
Norman et al.[94]	r, mc	105	MCD3[a]	45*	84 (2y); 73 (5y)	51*[h]	95 (2y); 90 (5y)	MCD3 ≥ Tr	
		102	Tr[g]	8	75 (2y); 64 (5y)	66[h]	94 (2y); 88 (5y)		
Muromonab CD3-based immunosuppression versus other antilymphocyte-based regimens									
Bock et al.[66]	r, nb	51	MCD3[a]		78 (1y)	45*	92 (1y)	ATG > MCD3	
		53	ATG[i]		91 (1y)*	26	96 (1y)		
Broyer et al. [95]	r	77	MCD3[a,b]		79 (1y), 71 (2y), 68 (3y)	11	96	MCD3 ≡ ALG	
		71	ALG[b,j]		80 (1y), 77 (2y), 73 (3y)	11	99		
Cole et al. [96]	r	83	MCD3[a]	ATG > MCD3 (1y)*	81 (1y)	31[k]	95 (1y)	ATG ≥ MCD3	More steroid-resistant rejections with MCD3 (25 *vs* 12*)
		83	ATG[i]		78 (1y)	57[k]*	89.5 (1y)		
Frey et al. [97]	r	67	MCD3[a,b]	MCD3 ≡ ALG	87 (1y), 83 (2y)[l]	36	96 (1y), 96 (2y)[l]	MCD3 ≡ ALG	
		71	ALG[j]		84 (1y), 80 (2y)[l]	45	93 (1y), 91 (2y)[l]		
Hanto et al. [98]	r	59	MCD3[a,b]	35	84 (1y), 79 (2y), 79 (3y)	33 (37)	98 (1, 2 and 3y)	MCD3 ≡ ALG	
		58	ALG[j]	29	81 (1y), 78 (2y), 78 (3y)	27 (31)	96 (1, 2 and 3y)		

Steinmuller et al.[99]	r	25	MCD3[a]	67.5	84 (<6mo)	64	99 (<6mo)	MCD3 ≡ ALG
		26	ALG[j]	95	85 (<6mo)	35	99 (<6mo)	

a MCD3-based regimen: MCD3 5 -10 mg/day or 0.05 or 0.1 mg/kg/day IV (7-21 PODs) + Az 1-10 mg/kg/day IV (POD 0-10) + MPr 1-8 mg/kg (250mg -2g) IV (preoperatively) + Pr 0.15-1.5 mg/kg/day, 30-60 mg/m^2 or 30 mg/day + Cs 4-14 mg/kg/day or 400 or 600 mg/day or 150 mg/ml/day PO (starting on POD 4-11).
b First antilymphocyte antibody dose administered intraoperatively.
c Total graft survival.
d Immunological graft survival rate (only losses from rejection were considered).
e Number of rejections per patient-month.
f Percentage of patients free from rejection.
g Triple therapy: Cs 6-14 mg/kg/day PO from POD 1 + Az 1-10 mg/kg/day IV + MPr 1-1.5 mg/kg (375mg-2g) + Pr 0.17-1.5 mg/kg/day (30 mg/day).
h The incidence of rejection after the first 2wk was equivalent.
i ATG-based regimen: ATG 0.15 ml/kg/day or 4 mg/kg/day (7-14 days) + MPr 1 mg/kg or 1g then 0.25 mg/kg 6-hourly (48h) then Pr 0.25-0.5 mg/kg/day + Az 1 mg/kg IV (preoperatively) then 1 or 2 mg/kg/day + Cs 4 mg/kg/day or 400-600 mg/day (from POD 4 to 7).
j ALG-based regimen: ALG 1-20 mg/kg/day IV (7-21 days) + MPr 7 mg/kg then Pr 30 mg/day or 0.3 to 1 mg/kg/day + Az 1-5 mg/kg/day + Cs 5-8 mg/kg/day (started when renal function normal).
k Patients with no rejection episodes. The rate of first rejection with MCD3 was 1.8 times higher than with ALG; overall 50 rejection episodes occurred with ALG and 83 with MCD3.
l Graft and patients survival rates included data from 35 patients who received kidney-pancreas transplant.

Abbreviations and symbols: AGXM = antiglobulin crossmatch; ALG = antilymphocyte globulin (Minnesota; horse antibody); ATG = antithymocyte globulin; Az = azathioprine; Cs = cyclosporin; IV = intravenous; mc = multicentre; MPr = methylprednisolone; nb = nonblind; PO = orally; POD = postoperative day; Pr = prednisone; r = randomised; ≡ indicates equivalence; > indicates significantly ($p < 0.05$) more effective than comparator; ≥ indicates significantly ($p < 0.05$) greater efficacy than comparator in terms of at least 1 efficacy parameter; * $p < 0.05$ compared with comparator.

a cold ischaemia time of >24 hours (84 *vs* 62% at 2 years; n = 98; p = 0.01).[94]

Despite delayed cyclosporin administration, significantly more patients receiving muromonab CD3–based therapy required postoperative dialysis than triple therapy recipients;[13,93] this was possibly a result of muromonab CD3–induced lymphokine release (section 1.2). Mean serum creatinine levels were similar in the 2 groups.

No studies directly compared the efficacy of intraoperative administration of the first dose of muromonab CD3 with administration in the immediate postoperative period.

3.2.2 Comparisons with Other Antilymphocyte–based Regimens

Muromonab CD3 and ALG or ATG were similar in terms of rejection incidence and/or time to first rejection (for up to 3 years' follow-up) in some studies;[95,97-99] others show ALG or ATG to be superior (1 year's follow-up) [table II].[65,96]

Although most studies showed no significant between-treatment differences in graft and patient survival, the 1-year graft survival rate was significantly greater with ATG than with muromonab CD3 in 1 study.[65] The incidence of delayed graft function was similar.[65,97]

One-year graft survival in highly sensitised (panel reactive antibodies > 50%) renal transplant recipients was similar with prophylactic muromonab CD3- and ALG–based regimens.[101]

In combined renal-pancreas transplant recipients (total of 220 patients) who received muromonab CD3- or ALG/ATG–based quadruple induction therapy, 12- or 15-month actuarial graft survival rates were similar (80 to 91 *vs* 88 to 96% for renal grafts and 60 to 88.5 *vs* 73 to 96% for pancreas grafts) as were patient survival rates (80 to 96 *vs* 89 to 100%).[102-104] The incidence of rejection was either similar (40 to 50 for both treatment groups;[102,104] mean number of rejection episodes per patient 1.4 *vs* 0.9[103]) or less (mean number of rejection episodes per patient 1.5 *vs* 2.7; p value not given) with muromonab CD3.[105] No studies comparing muromonab CD3–based induc-

Table III. Efficacy of muromonab CD3 (MCD3)–based immunosuppression (delayed cyclosporin) as prophylaxis of hepatic allograft rejection versus standard triple therapy (Tr) [immediate cyclosporin], other antilymphocyte-based regimens or anti–interleukin-2 monoclonal antibody–based immunosuppression

Reference	Study design	No. of evaluable patients	Treatment	Time to initial rejection (days)	Actuarial graft survival (%)	Rejection incidence (%)	Actuarial patient survival (%)	Overall efficacy	Comments
Muromonab CD3–based immunosuppression versus triple therapy									
Cosimi et al.[106]	r	38	MCD3[a]			13* (1wk), 39* (2wk), 68 (1y)	84	MCD3 ≥ Tr	Duration of the initial rejection-free period was longer with MCD3
		41	Tr[b]			46(1wk), 71 (2wk), 78 (1y)	73		
Farges et al.[107]	r, mc	44	MCD3[a]	38*	61 (4y)	34* (2wk); 67 (1y)	82 (1y); 69 (4y)	MCD3 ≥ Tr	
		50	Tr[b]	9	54 (4y)	61 (2wk); 75 (1y)	78 (1y); 62 (4y)		
McDiarmid et al.[108,109]	r	46	MCD3[a,c]	12[d]	63 (>3mo)	28 (POD 0-14)*[d] 46 (<1mo)[e] 91 (>3mo)[e]	67 (>3mo)	MCD3 ≥ Tr	Mean duration of follow-up was 648 days for MCD3 and 682 days for Tr
		39	Tr[b]	9.5[c]	73 (>3mo)	67 (POD 0-14)[d] 31 (rejection free; <1mo) 99 (rejection free; >3mo)	84 (>3mo)		
Mühlbacher et al.[110]		30	MCD3[a]			56*	57 (1y)	MCD3 > Tr	
		58	Tr[b]			79.5	45 (1y)		
Pons et al.[111][d]		25	MCD3[a]			25*	3.5 (2mo)*[f]		
		19	Tr[b]			69	26 (2mo)[f]		
Muromonab CD3–based immunosuppression versus other antilymphocyte-based regimens									
Steininger et al.[112]	rt	63	Cs + Pr[b]			67 (during first 3wk)		ATG > Cs + Pr and MCD3 (acute rejection)	Not standard regimens. Rejection advantage of ATG appeared to be abolished when severe rejection was considered
		32	MCD3[a]			44			
		49	ATG[g]			24*			
Muromonab CD3–based immunosuppression versus anti–interleukin-2 receptor monoclonal antibody–based regimen									
Reding et al.[113]	r	37 (adults and children)	MCD3[a]		86 (1y)	81 (first 3mo)	86 (1y)		
		35	AIL[h]		97 (1y)*	91 (first 3mo)	100 (1y)*		
		28	Tr[b]		75 (1y)	96 (first 3mo)	79 (1y)		

a MCD3-based regimen: MCD3 2.5-20 mg/day IV (10-14 days) + Az 1-5 mg/kg/day or 100 mg/day IV + MPr 0.3-5 mg/kg IV then Pr 0.3-2.5 mg/kg/day or 30-200 mg/day + Cs 3-15 mg/kg/day IV (starting on POD 7-11).

b Triple/double therapy: Cs 1-4 mg/kg/day IV ± Cs 8-14 mg/kg/day PO ± Az 1-5 mg/kg/day or 100 mg/day IV + MPr 0.3-5 mg/kg (200mg) then Pr 0.3-2.5 mg/kg/day (20-200mg).

c First antilymphocyte antibody dose administered intraoperatively.

d Based on the results of an initial study involving 25 muromonab CD3 and 27 triple therapy recipients.[114]

e Patients who were rejection free.

f Mortality rate.

g ATG-based regimen: ATG 2.5 mg/kg/day IV (10 days) + Pr (dosage not given) + Cs (dosage not given) PO (from POD 8).

h AIL-based regimen: AIL 10 or 20 mg/day IV (intraoperatively and for 9 PODs) + Cs 3-5 mg/kg/day IV + MPr 1 g/1.73m^2 (children) or 1 g/70kg (adults) IV (starting intraoperatively) then Pr 1 mg/kg/day (children) or 25 mg/day (adults) then 0.5 mg/kg/day (children) or 15 mg/kg (adults) + Az 1.5 mg/kg/day (children) or 1 mg/kg/day (adults).

Abbreviations and symbols: AIL = anti-interleukin-2 receptor monoclonal antibody; ATG = antithymocyte globulin; Az = azathioprine; Cs = cyclosporin; IV = intravenous; mc = multicentre; MPr = methylprednisolone; PO = oral; POD = postoperative day; Pr = prednisone; r = randomised; rt = retrospective study; > significantly ($p < 0.05$) greater efficacy than comparator; ≥ significantly ($p < 0.05$) greater efficacy in terms of at least one efficacy parameter; * $p < 0.05$ *vs* comparator.

tion therapy with triple therapy in this patient group are available.

3.3 Hepatic Transplant Recipients

In addition to the toxic effects of early cyclosporin use, hepatic transplant recipients are at an increased risk of renal impairment in the early postoperative period because of intraoperative haemodynamic instability, hepatorenal syndrome and pre-existing renal or hepatic dysfunction. Studies comparing prophylactic muromonab CD3–based sequential immunosuppression with triple therapy or regimens containing other antilymphocyte preparations or an anti–IL-2 antibody are summarised in table III.

Muromonab CD3–based sequential therapy reduced the incidence and/or severity of early (but not long term) acute rejection,[106-111] delayed the time to first rejection[107] and improved/maintained renal function or reduced renal dysfunction in the early postoperative period[106-108,111] compared with triple therapy. Plasma bilirubin levels were either similar or lower with muromonab CD3–based therapy.[110,111] Most studies reported no between-treatment differences in graft or patient survival.

In the one available study, ATG–based prophylaxis achieved a lower incidence of rejection episodes than muromonab CD3–based therapy (table III).[112] An anti–IL-2–based prophylactic regimen improved graft and patient survival compared with muromonab CD3–based prophylaxis;[113] these data need to be confirmed.

There have been reports of accelerated rejection leading to graft loss[115] in hepatic transplant recipients receiving muromonab CD3–based immunoprophylaxis with no evidence of antimuromonab CD3 antibodies in the majority of patients. Prior sensitisation to HLA or other cell surface antigens has been proposed as an explanation.[115]

Some investigators have shown that transplantation with ABO-incompatible hepatic grafts can be successful with the administration of prophylactic muromonab CD3 as part of triple or quadruple immunosuppressive regimens and lowering of preformed antibody titres by plasmapheresis or exchange transfusion.[116,117]

A prophylactic muromonab CD3–based regimen including alprostadil (prostaglandin E_1) [10 to 60 μg/h] has shown promise in hepatic transplant recipients.[118] No studies to date have compared this regimen with muromonab CD3–based regimens not containing alprostadil.

3.4 Cardiac Transplant Recipients

Prophylaxis of rejection is particularly important for cardiac transplant recipients because, unlike renal transplant failure, cardiac graft failure is usually fatal. Studies comparing prophylactic muromonab CD3–based sequential immunosuppression with triple therapy or regimens containing other antilymphocyte preparations are summarised in table IV.

Although direct comparisons are few, on available evidence muromonab CD3–based prophylaxis appears to be similar to cyclosporin plus prednisone[119] or triple therapy[121] as assessed by rejection incidence, time to first rejection episode and graft and patient survival. Time to rejection was significantly longer with muromonab CD3–based induction therapy than triple therapy in 1 study; however, there was no significant between-treatment difference in rejection incidence.[120]

Data on muromonab CD3–based therapy compared with other antilymphocyte–based regimens are conflicting; some investigators report a longer time to first rejection and/or a lower incidence of rejection with muromonab CD3;[122,129] others observe no differences[125,127,128,130] or a lower incidence of rejection[123,126] and/or a longer time to first rejection episode[123,124] with ATG–based therapy. No between-treatment differences in graft or patient survival have been reported.

Histological evidence of rejection in heart transplant recipients was observed in more BT563 (an anti–IL-2 receptor monoclonal antibody; n = 22) than muromonab CD3 recipients (n = 11) after 1 week of prophylactic therapy (50 *vs* 9%); however, the incidence of adverse events related to cytokine release was lower with BT563.[131]

Table IV. Efficacy of muromonab CD3 (MCD3)–based immunosuppression (delayed cyclosporin) as prophylaxis of cardiac allograft rejection versus standard triple therapy (Tr) [immediate cyclosporin] or other antilymphocyte-based regimens

Reference	Study design	No. of evaluable patients	Treatment	Time to initial rejection (days)	Actuarial graft survival (%)	Rejection incidence (%)	Actuarial patient survival (%)	Overall efficacy
Muromonab CD3–based immunosuppression versus triple therapy								
Balk et al.[119]	r	33	MCD3[a]		91	1.33 (1y)[b] 80 (1mo)[c] 31 (3mo)[c] 28 (6mo)[c]	91 (2y)	MCD3 ≡ Cs + Pr
		33	Cs + Pr[d]		94	1.36 (1y)[b] 66 (1mo)[c] 33 (3mo)[c] 27 (6mo)[c]	94	
Barr et al. [120]	rt	26	MCD3[a]	42*		0.003[e]	88 (6mo) 81 (18mo)	MCD3 ≡ Tr
		26	Tr[f]	21		0.003[e]	92 (6mo) 87 (18mo)	
Stapleton et al.[121]	rt, nb[g]	8	MCD3[a]	66		66 (6mo)[c]	100 (1y)	MCD3 ≡ Tr
		33	Tr[f]	57		75 (6mo)	91 (1y)	
Muromonab CD3–based immunosuppression versus other antilymphocyte-based regimens								
Costanzo-Nordin et al.[122]	r	12	MCD3[a]	32*		3.4		MCD3 ≥ ATG
		11	ATG[h]	15		5		
Griffith et al.[123]	r	43	MCD3[a]	33*		0.58/pt* (1mo); 0.43 (2mo); 0.2 (>2mo)	98 (1y)	MCD3 ≤ ATG
		39	ATG[h]	67		0.08/pt (1mo); 0.24 (2mo); 0.2 (>2mo)	95 (1y)	
Ippoliti et al.[124]	r	15	MCD3[a]	24*			80 (6mo)	ATG ≥ MCD3
		15	ATG[h]	28			93 (6mo)	
Kirklin et al. [125]	nb	15	MCD3[a]	21		1.3/pt (2mo)	100 (2y)	MCD3 ≡ ATG
		32	ATG[h]	16		1.5/pt (2mo)	100 (2y)	
Ladowski et al.[126]	r	30	MCD3[a]			0.8/pt (3mo); 1.03/pt (1y)	83 (1y)	ATG ≥ ALG and MCD3
		34	ATG[h]			0.24/pt (3mo)*; 0.26/pt (1y)*	82 (1y)	
		15	ALG[i]			1.14/pt (3mo); 1.27/pt (1y)	80 (1y)	
MacDonald et al.[127]	r	20	MCD3[a]	33		90	83 (1y)	MCD3 ≡ ATG
		21	ATG[h]	27		100	81 (1y)	
Menkis et al.[128]	r	20	MCD3[a]	5.6wk		2.1/pt (6mo)	92 (2y)	MCD3 ≡ ALG
		19	ALG[i]	5.3wk		1.4/pt (6mo)	84 (2y)	

Renlund et al.[129]	r[j]	26	MCD3[a]	76*	1.5/pt (6mo)*	96 (1y)	MCD3 ≥ ATG
					0.2 (1y)*		
		25	ATG[h]	36	2.2/pt (6mo)	96 (1y)	
					0.8 (1y)		
Wollenek et al.[130]	r		MCD3[a]		0.5 (1mo); 0.97 (3mo)[k]	82	MCD3 ≡ ATG
			ATG[h]		0.32 (1mo); 0.53 (3mo)[k]	83	

a MCD3-based regimen: MCD3 5-10 mg/day (7-14 days) IV + Az 2-4 mg/kg/day or 50 mg/day IV or PO + MPr 0.2-5 mg/kg IV (375-500mg) then Pr 0.1-1.5 mg/kg/day or 10-60 mg/day + Cs 4-10 mg/kg/day IV (starting on POD 4-11).
b Mean number of acute rejections per patient.
c Freedom from rejection.
d Cs 1-3 mg/kg/day IV (initiated 2-4h preoperatively) then PO + Pr 20mg IV then 10-60 mg/day.
e Rejection episodes per patient per month.
f Triple therapy: Cs 4-10 mg/kg/day IV + Cs 8-14 mg/kg/day PO + Az 2-4 mg/kg/day IV or PO + MPr 375-500mg then Pr 1 mg/kg/day (10-30mg).
g The decision to use muromonab CD3 was based on immediate postoperative renal insufficiency.
h ATG-based regimen: ATG 1.5-10 mg/kg/day IV or IM (4-10 days) + MPr 375-1000mg then Pr 0.2-1.5 mg/kg PO + Cs 2-10 mg/kg PO + Az 2-4 mg/kg PO or IV.
i ALG-based regimen: ALG 15-20 mg/kg/day IV (7-20 days) + MPr 0.375-1g (0.1-0.2 mg/kg/day) then Pr 30 mg/day or 0.1-0.5 mg/kg/day PO + Az 1-4 mg/kg/day PO or IV + Cs 5-7 mg/kg/day (from POD 4).
j According to availability of ATG.
k Cumulative incidence of rejection episodes per patient.

Abbreviations and symbols: ALG = antilymphocyte globulin; ATG = antithymocyte globulin; Az = azathioprine; Cs = cyclosporin; IM = intramuscular; IV = intravenous; MPr = methylprednisolone; nb = nonblind; PO = oral; POD = postoperative days; Pr = prednisone; pt = patient; r = randomised; rt = retrospective; ≥ significantly ($p < 0.05$) greater efficacy in terms of at least one parameter; ≤ significantly ($p < 0.05$) less efficacy in terms of at least one parameter; ≡ indicates equivalence; * $p < 0.05$ *vs* comparator.

According to a meta-analysis of 28 trials of prophylactic muromonab CD3–based therapy in renal, liver and cardiac transplant recipients, muromonab CD3 had no significant effect on patient survival.[132] However, the incidence of acute rejection with muromonab CD3 was lower than with triple therapy (11 studies), horse ATG (4 studies) and horse ALG (5 studies) but higher than with rabbit ATG (4 studies). The results of this meta-analysis are limited by the small number and methodological flaws of the available studies.

3.5 Special Patient Groups

3.5.1 High Risk Patients

Patients at high immunological risk of rejection and consequent reduced graft survival include those with delayed graft function, increased panel reactive antibody titres, previous but not current anti-donor lymphocytotoxic antibodies or a positive current crossmatch for donor B lymphocytes, those who rejected an earlier graft within the first 6 to 12 months, patients receiving multiple transplants or blood transfusions or who have had multiple pregnancies, patients receiving grafts with prolonged cold ischaemia times (>24 hours) and paediatric patients (section 3.5.2).[133-135]

The efficacy of prophylactic muromonab CD3–based therapy appears to be particularly marked in patients with delayed graft function (section 3.2.1). Patient survival was 100% (after a mean follow-up of 12 or 13 months)[134,136] and graft survival (at 1 year) was 70[134] or 78%[136] with muromonab CD3–based prophylaxis in high risk cadaver renal transplant recipients (previous transplant failure and/or panel reactive antibody titres >50%). These graft survival rates are superior to those reported for a historical group of similar patients who did not receive muromonab CD3 (50%) and are comparable to those of primary graft recipients (table II). Rejection incidence within 1 year (0.87 *vs* 1.35 mean episodes per patient) and 5 years (1.07 *vs* 1.49) was significantly lower and graft survival was significantly higher at 2 years (84 *vs* 64%) and 5 years (71 *vs* 56%) with prophylactic muromonab CD3–based immunosuppression (n = 78) than with triple

therapy (n = 81) in patients with renal graft cold ischaemia times >24 hours; no significant between-treatment differences were observed in patients with cold ischaemia times ≤24 hours.[135]

Three-year graft survival rates in high risk renal transplant recipients (whose highest preformed panel reactive lymphocytotoxic antibody level was >50%) were significantly greater with sequential muromonab CD3–based prophylaxis (delayed cyclosporin) than with simultaneous muromonab CD3 and cyclosporin administration and cyclosporin–based prophylaxis not containing muromonab CD3 (72 *vs* 53 *vs* 58%; $p < 0.01$).[100] However, an immunosuppressive regimen of simultaneous muromonab CD3 and cyclosporin (initiated from the time of transplantation regardless of graft function) plus azathioprine and prednisone was associated with a single rejection incidence of 50%, acute tubular necrosis in 58% of patients, and no graft losses or deaths in 12 immunological high risk renal transplant recipients followed for 3 to 28 months.[133]

3.5.2 Young or Elderly

The immune response and the propensity to develop acute rejection appear to be greater in children.[137] Furthermore, the incidence of high titre antimuromonab CD3 antibodies (section 1.3) is significantly greater in children (particularly those aged <10 years) than in adults (>30 years),[35] and increases in muromonab CD3 dosages are required more often in paediatric than adult patients (section 7).[40,137]

Several noncomparative trials involving a total of 118 patients show muromonab CD3 induction therapy prophylaxis, administered as part of a quadruple immunosuppressive protocol, to reduce early rejection in children and adolescents undergoing renal, hepatic or cardiac transplantation.[138-140] However, a rejection incidence of 75% during the first 2 months and a graft survival incidence of 50% at 1 and 5 years have been reported in 20 paediatric renal transplant recipients receiving muromonab CD3 induction therapy.[141] Furthermore, the rejection incidence with muromonab CD3–based prophylaxis was significantly lower than with standard triple therapy (25 *vs* 75%) during the first 14 days in 20 liver transplant recipients; however, there were no significant between-treatment differences in overall rejection incidence or graft or patient survival (mean duration of follow-up was 890 days for the muromonab CD3 group and 721 days for the triple therapy group).[142]

Quadruple therapy containing muromonab CD3, prednisone, azathioprine and cyclosporin was used successfully in 17 cadaveric renal transplant recipients aged ≥50 years; no grafts were lost.[143]

Further studies directly comparing the effects of muromonab CD3–based therapy with those of either no prophylaxis or prophylaxis with other agents are needed to determine whether these regimens are beneficial in these patient groups.

3.6 Reuse of Muromonab CD3

The presence of antimuromonab CD3 antibodies (section 1.3) has the potential to decrease the efficacy of muromonab CD3 (section 2.2) and to hinder its subsequent use.[75]

All patients should be tested for the presence and type (section 1.3) of antimuromonab CD3 antibodies 3 to 4 weeks after initiation of the first dose, particularly if repeated or prolonged muromonab CD3 treatment is required. Muromonab CD3 reuse following prophylactic use is not recommended in patients with antimuromonab CD3 antibody titres ≥1:1000, but retreatment may be successful in those with lower titres.[39,63,144,145]

In addition to the type and titre of antimuromonab CD3 antibodies,[36] factors predictive of success with muromonab CD3 retreatment include longer elapsed time after initial treatment and effective T cell depletion/CD3 modulation (section 1.1).[146]

Anti-idiotypic antibodies to muromonab CD3 were detected in 70% of paediatric renal transplant recipients (n = 40) who received prophylactic muromonab CD3; antibody titres were not given.[147]

4. Pharmacoeconomic Considerations

The overall cost of immunosuppression in transplant recipients is substantial and is highly influenced by the use of biological agents.

No formal cost-effectiveness studies have been conducted to determine whether, and to what extent, potential cost savings from the lower incidence of rejection episodes with prophylactic muromonab CD3 than with triple therapy (section 3) are offset by the increased incidence of infections and other adverse events (section 5); adverse events complicate postoperative care and prolong hospitalisation of patients.[148,149] The relative pharmacoeconomic merits of prophylactic muromonab CD3 versus administration for the treatment of rejection have not been determined. Nor have the economic consequences of reduced acute rejection incidence on long term graft survival or subsequent requirement for dialysis, or the economic impact of muromonab CD3 reuse and adverse event preventative strategies (see table V) been determined.

Not unexpectedly, in an Australian cost minimisation study, mean first-year drug costs per renal transplant recipient were greater with a quadruple immunosuppressive regimen containing muromonab CD3, ATG or ALG than with triple therapy alone ($A10 194 *vs* $A7679; 1991 prices).[150]

According to another cost minimisation analysis, the total cost of 1 week's muromonab CD3 (as induction therapy) administered to a 70kg patient undergoing renal transplantation would be $US1500 (1992) more than for ALG.[97] However, this increased cost is likely to be balanced by savings resulting from the shorter time spent in hospital by patients receiving muromonab CD3 than those treated with ALG. Similarly, the cost of a 14-day prophylactic course of muromonab CD3 in cardiac transplant recipients was higher than the cost of a 10-day course of ALG or a 4-day course of ATG ($US6650 *vs* $US1914 *vs* $US2350); despite different administration durations, the overall efficacy of ALG and muromonab CD3 was similar and slightly inferior to that of ATG (table IV).[126] In an abstract report, the mean costs (definition and year of prices not given) of induction therapy based on muromonab CD3 (n = 102) or ALG (n = 511) were similar ($US63 416 *vs* $US62 176) but significantly greater than those with conventional immunotherapy ($US47 002; n = 970) in renal transplant recipients.[151]

Prospective studies assessing the comparative pharmacoeconomics of these agents in the long term are needed. No formal studies have directly assessed the effects of muromonab CD3 on quality of life in transplant recipients.

5. Tolerability

The general complications of immunosuppressants and the problems associated with the narrow therapeutic range of these agents (infection or malignancy because of over immunosuppression) plus the use of multiple agents complicate the determination of the cause of adverse events in transplant patients receiving muromonab CD3.

Although anaphylaxis has been reported (in 1 patient) following a second course of prophylactic muromonab CD3 (high antimuromonab CD3 titres were present before treatment),[152] the tolerability profile of muromonab CD3 during reuse (section 3.6) has not formally been determined. Long term tolerability data are also lacking.

Strategies for preventing drug-related toxicity are of critical importance in the management of transplant recipients. Adverse events with muromonab CD3 may be prevented or minimised by several strategies including the intraoperative administration of the first dose of muromonab CD3, pretreatment with a corticosteroid, administration of an antipyretic and antihistamine, prophylactic use of an antimicrobial(s) and correction of increased temperature and fluid overload before initiation of prophylaxis (table V).

5.1 First-Dose Effects

The first doses of muromonab CD3 are associated with a number of adverse events ('cytokine-release syndrome'; section 1.2) which, although usually mild, may be severe and life-threaten-

Table V. Approaches to prevent or decrease adverse events associated with muromonab CD3

Adverse event	Approach
First-dose effects	Intravenous methylprednisolone sodium succinate 8 mg/kg 1-4h before the first dose[150,154-158]
	Antipyretics, e.g. paracetamol (acetaminophen)[150]
	Antihistamines, e.g. diphenhydramine[150]
	Reduction of body temperature to <37.8°C before muromonab CD3 administration
	Intraoperative administration of first muromonab CD3 dose[19,43,159,160]
	Agents that neutralise cytokine effects, e.g. anti-tumour necrosis factor[43,157]
Pulmonary oedema	Correction of pre-existing fluid overload[43,158,161]
	Restriction of bodyweight gain to ≤3% in the 7 days before treatment
	Strict management of fluid, electrolyte and mineral balance especially in patients with diabetes and those with delayed graft function[43,150,161]
Infections	Cotrimoxazole (trimethoprim-sulfamethoxazole) [*Pneumocystis carinii* pneumonia][19,162,163]
	Ganciclovir, aciclovir and cytomegalovirus hyperimmune globulin (cytomegalovirus infection and other viral infections)[19,162,164,165]

ing.[1,19,154,156,165] The most frequent effect is a 'flu-like' complex consisting of fever and chills (incidence of >50%); other frequently reported effects include dyspnoea, tremor, chest pain/tightness, wheezing, diarrhoea, nausea and vomiting (approximately 10 to 20%). Most adverse events occur within 45 to 60 minutes of administration and last for 2 to 48 hours. More severe first-dose effects are aseptic meningitis (generally self-limiting without sequelae), seizures, intragraft thromboses and potentially fatal pulmonary oedema. Intragraft thromboses have also occurred later (within 2 weeks) during prophylaxis; 9 of 93 renal transplant recipients who received prophylactic muromonab CD3 (10 mg/day) developed a thrombosis with associated graft failure.[166] Significant increases in plasma prothrombin fragment 1 and 2 concentrations occurred 4 hours after the first dose. The first-dose response in children appears to be similar to that in adults.[19,167]

Risk factors for life- or allograft-threatening adverse events include diabetes mellitus, impaired renal allograft function, uraemia, fluid overload, high-dose muromonab CD3 (dosage not documented), a history of CNS disease, hyponatraemia and hypocalcaemia.[165,168,169]

The incidence of initial adverse events with muromonab CD3 (fever, headache, hypotension and/or signs and symptoms of fluid overload) is reported to be similar to or greater than that with polyclonal agents, and events tend to be more severe with muromonab CD3.[65,96,97,99,170,171] The most common adverse events with polyclonal preparations are fever, flushing and chills.

Some investigators report first-dose effects to be more frequent or severe when muromonab CD3 is administered as prophylaxis than when it is used as treatment[156] whereas others report the reverse.[172]

5.1.1 Late Reactions

Cytokine-related adverse events may also occur after more than 4 or 5 doses of muromonab CD3.[172] Reactions involving angioedema, hypotension or serum sickness-like syndrome (compatible with IgE-mediated anaphylaxis or serum sickness mediated by antibody formation) 9 to 13 days after the initial dose of prophylactic muromonab CD3 have also occasionally been reported.[173] Continued treatment with muromonab CD3 after such a reaction is not recommended.

5.2 Infections

In common with other immunosuppressants, muromonab CD3 is associated with an increased risk of infections (the most common pathogens being CMV, herpes simplex virus and bacteria); these infections are the primary cause of morbidity and mortality in muromonab CD3 recipients.[19] The risk of infection appears to be related to the overall

degree of immunosuppression rather than to intrinsic factors of the drug.

The risk of CMV infection which is greatest in CMV-positive donor/CMV-negative recipients and in patients seropositive before treatment, is increased by high doses of muromonab CD3 (total doses >75mg) and repeated exposure to the agent.[1,174,175] The risk of invasive CMV disease was greater (16 *vs* 1 patient) when muromonab CD3 was administered during the first 14 post-transplant days than when administered subsequently.[176]

The incidence of CMV infection with prophylactic muromonab CD3–based immunosuppression (approximately 30 to 50%) is greater than or similar to that of triple therapy, with the severity of CMV infection tending to be greater in muromonab CD3 recipients.[107,108,111,119,121,177,178] The overall incidence of bacterial and fungal infections with these treatment options appears to be similar.

This is also the case for comparisons with ALG- or ATG–based regimens although some investigators have reported more severe infections and/or a greater incidence with muromonab CD3, especially in patients at high risk.[65,95-99,122-124,126-128,170,171,179]

The incidence of nosocomial infections (staphylococci, *Candida* sp. and *Enterobacter* sp.) but not community-acquired infections was greater (52 *vs* 35%) with muromonab CD3–based than ATG–based prophylaxis in 100 cardiac transplant recipients.[180]

5.3 Neoplasia

Muromonab CD3–based immunosuppression (administered as prophylaxis or treatment of rejection) has been associated with an increased risk of malignancies, mainly lymphoproliferative disorders, compared with conventional triple therapy.[19,181-188] The incidence of post-transplantation lymphoproliferative disorder was 9-fold higher with muromonab CD3 plus standard triple therapy (n = 79) than with triple therapy alone (n = 75) [11.4 *vs* 1.3%] in retrospectively-assessed cardiac transplant recipients who received therapy mainly for the prevention of rejection. The risk of this disorder was dose-dependent; the incidence was significantly greater in patients who received a cumulative dose >75mg than in patients who received ≤75mg (35.7 *vs* 6.2%).[181] An increased risk of post-transplantation lymphoproliferative disorder in cardiac transplant recipients has also been reported by other research groups;[182,186,188] however, some investigators have reported a low incidence with prophylactic muromonab CD3.[189]

The factors responsible for the increased risk of lymphoproliferation with muromonab CD3 are unknown but are likely to be related to the overall degree of immunosuppression (including that conferred by concomitant immunosuppressants) rather than to mechanisms specific to muromonab CD3.[26,184,190,191] EBV infection and muromonab CD3–induced IL-6 and IL-10 release have been implicated in the development of this disorder.[26,184,190,192,193]

In addition to high muromonab CD3 dosages (total cumulative dose >75mg), the risk of lymphoproliferative disease may be increased by long durations of muromonab CD3 treatment,[187] multiple courses of the drug in close succession[194] and early retreatment.[195] No studies have specifically compared the risk of lymphoproliferative disorder with prophylactic muromonab CD3 versus administration for the treatment of rejection. Preliminary evidence suggests that screening for changes in peripheral CD19+ B lymphocytes may represent an effective strategy for identifying transplant recipients at risk of post-transplant lymphoproliferative disease.[196]

Some investigators report the incidence of neoplasia to be similar with muromonab CD3 and ALG;[170,171] others note a trend towards a greater incidence with muromonab CD3 prophylaxis than with ATG or ALG.[170,171,188,197]

5.4 Other Events

No clinically significant pulmonary or cardiovascular events have been noted in renal transplant recipients who received intraoperative muromonab CD3.[158,159] However, rare adverse events involving these and other systems during post-

operative administration include cardiopulmonary arrest[198] and hyperpyrexia-related ventricular tachycardia,[199] each in 1 patient, 1 report of reversible aseptic meningoencephalopathy following muromonab CD3 induction therapy[200] and 2 reports of aseptic encephalitis, with associated blindness due to bilateral optic nerve palsy in one patient after muromonab CD3 administration for delayed renal graft function.[201]

Seven per cent of renal transplant recipients (n = 247) who received muromonab CD3 induction therapy developed 'cytokine encephalopathy' (hallucinations, seizure, confusion, obtundation and coma) during the first 4 postoperative days; all but 1 patient (who died from a cardiac arrest) recovered fully with or without withdrawal of muromonab CD3.[202] The presence of delayed renal allograft function and/or insulin-dependent diabetes mellitus was significantly associated with the occurrence of this disorder. Early acute reversible nephrotoxicity associated with cytokine release occurs in some muromonab CD3 recipients,[157,203-205] as does *de novo* or recurrent haemolytic uraemic syndrome.[206,207]

Biphasic granulocytopenia has been observed after the first dose of muromonab CD3,[208] and reversible pancytopenia occurred in 2 renal transplant recipients receiving muromonab CD3 as prophylaxis or treatment of rejection.[209]

Prophylactic muromonab CD3 did not appear to adversely affect growth in children receiving a cardiac transplant.[139]

6. Drug Interactions

Although there is potential for a host of drug interactions between muromonab CD3 and concomitant immunosuppressants, anaesthetics and agents used to prevent or decrease adverse events, data are limited. There are no data on the potential for adverse interactions between muromonab CD3 and agents used to reduce the adverse events associated with this drug (table V).

Median trough blood concentrations of cyclosporin (administered preoperatively and in the immediate postoperative period) were significantly higher on day 5 in renal transplant recipients who received muromonab CD3 induction therapy than in patients who received ALG.[210] Although corticosteroid pretreatment reduces cytokine release and first-dose adverse events with muromonab CD3 (table V), evidence suggests that procoagulant activity (section 1.5) is increased.[53]

Coadministration of indomethacin may increase the risk of encephalopathy in muromonab CD3 recipients.[211]

Although anaesthetic agents themselves may at least partly account for the reduced incidence or severity of first-dose effects observed with the intraoperative administration of muromonab CD3 (adverse events may be prevented or compensated for during anaesthesia),[212] concomitant treatment with muromonab CD3 and volatile anaesthetic agents or drugs that decrease cardiac contractility increases the risk of developing cardiovascular problems.[19]

7. Dosage and Administration

Induction therapy with muromonab CD3 plus azathioprine, methylprednisolone/prednisone and delayed cyclosporin therapy (section 3) is the most accepted muromonab CD3–based regimen for allograft rejection prophylaxis.

The optimal dosage of muromonab CD3 has not been established (section 3.1). Nevertheless, the currently recommended adult dosage in renal, hepatic and cardiac transplant recipients is 5mg administered intravenously as a once-daily bolus for 10 to 14 days. Although there are no specific dosage recommendations in children, 2.5mg once daily has usually been used in clinical trials (section 3.5.2). Higher doses may, however, be needed; paediatric patients appear to require increased dosages more frequently than adults.[40] Surveillance for clinical signs of rejection in addition to anti-muromonab CD3 antibodies, plasma muromonab CD3 concentrations and CD3+ cell levels, as appropriate, is required for optimal muromonab CD3 dosage adjustments (section 2.2). Most patients receive muromonab CD3 from the first postoperative

Table VI. Factors to consider when assessing the risk-benefit profile of muromonab CD3 for the prevention of solid organ transplant rejection

Benefits	Limitations
• Efficacy (section 3) • Effect on graft dysfunction (section 3) • Minimisation of cyclosporin toxicity • Less batch variability, greater specificity, less cross-reactivity with blood components other than T cells and relative ease of administration (peripheral versus central line administration) compared with polyclonal antibodies (sections 1.1 and 2.1)	• Tolerability: first-dose cytokine-related adverse events (section 5.1), infections (section 5.2), neoplasia (section 5.3) • Immunogenicity (section 1.3) and potential to prevent reuse (section 3.6) • Cost: drug and hospital costs (section 4)

day; however, intraoperative administration appears to improve the tolerability of the drug.

The first few doses should be administered in a facility equipped for cardiopulmonary resuscitation; vital signs should be closely monitored. Subsequent doses may be administered on an outpatient basis with monitoring as appropriate.

The preventative measures outlined in table V should be observed with muromonab CD3 use, and only the lowest effective dosages of concomitant immunosuppressive agents should be administered (to minimise the potential for malignancies and infections; section 5).

Patients receiving muromonab CD3 should be monitored for signs of lymphoproliferative disorder, and antilymphocyte agents should be used with caution in those at risk of EBV infection and in those with pre-existing tumours.

8. Place of Muromonab CD3 in the Prevention of Transplant Rejection

Despite substantial improvements in the surgical and medical management of transplant recipients, acute rejection remains a significant problem.

Although the use of muromonab CD3–based immunosuppression as first-line and 'rescue' therapy of rejection is well established,[1] its use as prophylaxis of rejection, particularly as routine therapy, has been controversial. The 2 major immunosuppressive protocols currently in use for the prophylaxis of rejection episodes are standard triple therapy (corticosteroids, azathioprine and cyclosporin) and monoclonal (muromonab CD3) or polyclonal (ALG or ATG) antilymphocyte antibody–based sequential therapy. Cyclosporin-associated nephrotoxicity and hepatotoxicity in the early postoperative period prompted, in part, the development of the latter more specific regimens. Antilymphocyte–based sequential therapy consists of an induction phase with an antilymphocyte preparation plus azathioprine, corticosteroids and cyclosporin (delayed until graft function is established) and maintenance therapy.

The definitive answer to whether muromonab CD3 should be used routinely as prophylaxis or be reserved for the treatment of rejection episodes has yet to be determined. The risks and benefits that need to be considered when making such a decision are detailed in table VI.

The ideal immunosuppressant agent/regimen would:

- induce specific tolerance to donor antigens and obviate the need for long term immunosuppression;
- be associated with minimal adverse events and achieve a balance between the risks of over-immunosuppression (e.g. infections and malignancies) and underimmunosuppression (e.g. graft loss);
- optimise early graft function;
- reduce rejection incidence and improve graft and patient survival;
- have no sensitising or activating properties;
- minimise hospitalisation.

Muromonab CD3 induction therapy as part of sequential therapy is significantly more effective than standard triple therapy in the prophylaxis of allograft rejection in renal and hepatic, but not cardiac, transplant recipients. The overall efficacy of muromonab CD3- and polyclonal–based prophylactic regimens appears to be similar, although results vary between investigators. Muromonab CD3

also improves overall graft survival in renal transplant recipients with delayed graft function or other high-risk factors, optimises early graft function and may minimise hospitalisation. However, as with other currently available immunosuppressants, rejection may still occur, patient survival does not appear to be improved, adverse events (particularly infections) and immunogenicity limit its use, and the other above-mentioned criteria for the 'ideal' immunosuppressive agent are not met.

Research is now focused on developing more specific immunosuppressive agents. Monoclonal antibodies, other than muromonab CD3, that have either shown promise or are under investigation for the prophylaxis of transplant rejection include antibodies directed against CD4, CD6, CD7, CD8, CD11a, CD18, CD25, CD45 or intracellular adhesion molecules, anti–IL-2 receptor monoclonal antibodies, humanised (and entirely human) pan-lymphocyte monoclonal antibodies, monovalent anti-CD3 antibodies, muromonab CD3 $F(ab')_2$ fragments, growth factor antagonists and antisense oligonucleotides. Encouragingly, donor-specific tolerance has been induced in animal models by anti-CD4, anti-CD25 and anti-CD54 monoclonal antibodies.[4,37,131,146,213,214]

Other potential approaches to improving prophylactic immunosuppression include the development of anti-CD3 monoclonal antibodies of the IgG2b type (to reduce adverse events), humanised muromonab CD3 preparations that are less immunogenic and synthetic peptides that deviate alloreactive T cells; the modification of class I major histocompatibility complex antigens by site-directed mutagenesis; the use of several monoclonal antibodies, each targeting a different TCR epitope; the systemic administration of specific agents or the local administration of nonspecific agents; and the use of different monoclonal antibodies for prophylaxis and treatment.

In the meantime, however, muromonab CD3 is the only clinically available monoclonal antibody for the prevention of solid organ transplant rejection. The efficacy of sequential immunosuppression with this agent in reducing early acute rejection episodes is greater than that of standard triple therapy in renal and hepatic, but not cardiac, transplant recipients. The overall efficacy of muromonab CD3–based induction regimens appears to be similar to that of polyclonal–based regimens, although this requires confirmation. While the routine use of muromonab CD3 for the prevention of rejection in patients with primary graft function does not appear to be justified, prophylactic sequential muromonab CD3–based therapy has a role in high-risk patients, particularly those with primary allograft dysfunction or renal failure.

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Correspondence: *Michelle I. Wilde*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.

Erratum

Vol. 51, No. 2, page 314: In section 5.2, the second sentence in the third paragraph should read: 'Dialyser clearances of urea . . . (mean dosage 4335*IU* 3 times weekly) . . .'.

[Dunn CJ, Markham A. Epoetin beta: a review of its pharmacological properties and clinical use in the management of anaemia associated with chronic renal failure. Drugs 1996 Feb; 51 (2): 299-318]