Drug Saf (2014) 37:921–943
DOI 10.1007/s40264-014-0226-z

REVIEW ARTICLE

Side Effects of Cytokines Approved for Therapy

Brian A. Baldo

Published online: 1 October 2014

Abstract Cytokines, currently known to be more than 130 in number, are small MW (<30 kDa) key signaling proteins that modulate cellular activities in immunity, infection, inflammation and malignancy. Key to understanding their function is recognition of their pleiotropism and often overlapping and functional redundancies. Classified here into 9 main families, most of the 20 approved cytokine preparations (18 different cytokines; 3 pegylated), all in recombinant human (rh) form, are grouped in the hematopoietic growth factor, interferon, platelet-derived growth factor (PDGF) and transforming growth factor β (TGFβ) families. In the hematopoietin family, approved cytokines are aldesleukin (rhIL-2), oprelvekin (rhIL-11), filgrastim and tbo-filgrastim (rhG-CSF), sargramostim (rhGM-CSF), metreleptin (rh-leptin) and the rh-erythropoietins, epoetin and darbepoietin alfa. Anakinra, a recombinant receptor antagonist for IL-1, is in the IL-1 family; recombinant interferons alfa-1, alfa-2, beta-1 and gamma-1 make up the interferon family; palifermin (rhKGF) and becaplermin (rhPDGF) are in the PDGF family; and rhBMP-2 and rhBMP-7 represent the TGFβ family. The main physicochemical features, FDA-approved indications, modes of action and side effects of these approved cytokines are presented. Underlying each adverse events profile is their pleiotropism, potency and capacity to release other cytokines producing cytokine 'cocktails'. Side effects, some serious, occur despite cytokines being endogenous proteins, and this therefore demands caution in attempts to introduce individual members into the clinic. This caution is reflected in the relatively small number of cytokines currently approved by regulatory agencies and by the fact that 14 of the FDA-approved preparations carry warnings, with 10 being black box warnings.

Key Points

Of the so far more than 130 known cytokines, 18 (3 also in pegylated form) are approved for human therapy as recombinant preparations

Cytokines are pleiotropic proteins with short half-lives and sometimes functional redundancies and overlapping side effects. They may induce a range of flu-like symptoms as well as more severe hematologic, pulmonary, endocrine, autoimmune, neurologic, ischemic, infection, psychiatric and dermatologic adverse events

Fourteen of the 20 listed FDA-approved cytokine preparations carry warnings with 10 being boxed warnings. Despite this, cytokine side effects profiles do not generally negate benefits and sometimes observed toxicity may even correspond with improved outcomes

1 Introduction

Given their ubiquitous presence, diverse roles and importance in the body, it should not be surprising that proteins

B. A. Baldo was formerly affiliated with Molecular Immunology Unit, Royal North Shore Hospital of Sydney, Kolling Institute of Medical Research and Department of Medicine, University of Sydney, Sydney, Australia.

B. A. Baldo (✉)
11 Bent Street, Lindfield, NSW 2070, Australia
e-mail: babaldo@iinet.net.au

dominate the growing list of the more than 200 approved biotherapeutic agents used in medicine today [1–3]. From the abundant albumin, important for the osmolarity and volume of the blood; to vaccines; myriad enzymes, antibodies and receptors; so-called 'factors' involved in blood-clotting, homeostasis and thrombosis; down to the tiny concentrations of hormones and cytokines that act as signaling molecules; proteins, often in recombinant form, comprise the majority of Food and Drug Administration (FDA)- and European Medicines Agency (EMA)-approved biologics [1, 2].

Of the proteins studied and now exploited as therapeutic agents over the last 20 years, those of greatest recent interest are monoclonal antibodies (mAbs), some cytokines and targeted chimeric proteins, and a number of enzymes, some of which have been developed for clinical use via programs administered by the FDA Office of Orphan Products Development (OOPD). The OOPD provides incentives for the development of products (drugs, biologics, devices, medical foods) for the diagnosis and/or treatment of rare conditions, that is, diseases or disorders that affect fewer than 200,000 people in the US or where developers/manufacturers are not expected to cover the costs of developing and marketing the agents. Since 1983, more than 400 drugs and biologic products for rare diseases have been brought to market under the Orphan Drug Designation programs, a marked increase over the 10 industry-supported products developed and marketed in the decade prior to 1983 [4].

Over the last decade, it is probably true to say that no group of therapeutic agents has had such a successful history of use and wide disease application as the steadily growing collection of over 30 mAbs currently approved by the FDA [1, 5, 6]. From 16 different antibodies with approved indications covering blood, solid tumor and skin cancers to a range of others specifically developed for the management of a variety of diseases including chronic asthma, cryopyrin-associated periodic syndrome, macular degeneration, paroxymal nocturnal hemoglobinuria, autoimmune disorders such as Crohn's disease and rheumatoid arthritis, bone loss, psoriasis, systemic lupus erythematosus and prevention of organ rejection, mAb development continues to be extended and refined. The biotechnical advances, pharmacokinetics, clinical applications and adverse effects of these antibodies have been well reviewed [7–13]. Such close attention is yet to be directed at a relatively more slowly expanding list of cytokines [3, 14, 15], a number of which have been developed as orphan drugs and which are available in highly purified, well characterized recombinant form [1, 3, 4]. These biologics are generally reviewed, regulated and approved by the FDA Center for Drug Evaluation and Research (CDER) rather than the Center for Biologics Evaluation and Research which retains regulatory responsibility for bacterial and human cellular products, gene therapy products, vaccines, allergenic extracts, antitoxins, antivenoms, blood, blood components and plasma-derived products. Side effects of the currently approved cytokines in the CDER biologic product list [1] (as at June 2014) are reviewed here together with summaries of each product's approved indications, properties and mechanism of action.

2 Some Complexities of Protein Therapeutics. Perceived Advantages and Some Problems

Protein therapeutics prepared by recombinant DNA technology [16, 17] are often assumed to have fewer side effects including the expected lower immunogenicity due to their human origin [3, 4]. Not surprisingly, clinical experience often reveals significant departures from the expected outcomes. Unlike small drug molecules, protein therapeutics are typically more complex and there is the possibility of heterogeneity due to changes in amino acid sequence, the presence and degree of glycosylation, folding, and protein-protein interactions. Even small differences which are often difficult to control can affect a protein's purity, specificity, potency and safety. Many proteins have a short half-life in plasma requiring frequent parenteral administration and ultimately poor patient compliance. This may be offset to at least some extent by the degree of glycosylation [18] and that, in turn, may affect the protein's activity, potency and immunogenicity (for examples see later

3 Cytokines

3.1 General Characteristics

Cytokines, currently known to be more than 130 in number, are relatively small signaling proteins of MW < 30 kDa, usually glycosylated, and produced by a variety of different cells including those of the immune system, epithelia, endothelia and stroma. Cytokines are key modulators of the immune and inflammatory responses functioning in an autocrine, paracrine or endocrine manner stimulating or suppressing cellular activities in infection, innate and adaptive immunity, autoimmunity, inflammation and malignancy. Key to an understanding of these regulatory proteins is the recognition of their pleiotropism and sometimes overlapping activities, functional redundancies and side effects. Their secretion may be induced by an array of different stimuli associated with infection, inflammation or tumorigenesis, first releasing waves of (for example) pro-inflammatory molecules followed by anti-

inflammatory cytokines to restore homeostasis. Cytokines therefore induce a diverse range of biological responses including proliferation, differentiation, activation, inflammation, chemotaxis and cell death and the nature of an immune or inflammatory stimulus determines whether an immune response is humoral- or cell-mediated, cytotoxic, immunosuppressive or allergic [15, 19–22].

3.2 Classification

The many attempts to classify cytokines over the last three decades and the complexities in devising classifications based on structural and/or functional parameters are not hard to understand given the sheer number of imprecisely defined 'factors' identified in the early years and the difficulties and work involved in trying to accumulate details on functions and diseases. In their discussion of the evolution of cytokine biology and nomenclature, Steinke and Borish [20] draw attention to three phases of development in the identification and classification of cytokines. The identification of cytokines by their biologic activities (e.g., T cell growth) occurred in the first, or factor, stage. The production of recombinant cytokines and demonstration of their pleiotropism and redundancy led to much of our current understanding and this can be called the recombinant-cloning or second phase. Currently, we are experiencing the third, or genomic phase, where cytokines are being identified on the basis of homology with known, characterized cytokines. In the more recent progressive assemblages published by Tato and Cua [23–26] detailing each cytokine's receptor(s), source, targets, major function and disease association, the first 16 interleukins were grouped in order of their discovery. Many of these interleukins form homodimeric structures and have the γc and/or βc chains in their receptors [23]. More recently discovered interleukins have proven more difficult to classify in relation to their function in health and disease due to the complexity of their heterodimeric ligands and receptors [24]. For example, a homotrimeric motif for ligands and receptors and bi-directional signaling was found to be an important feature of the TNF family [25]. It should be pointed out that many original names are still in use and many of the originally described 'factors' share receptors with other interleukins [26].

For the purposes in this review where we focus on the 20 FDA-approved cytokine products from the CDER-approved Biologic Products list, the classification presented is based on the Kyoto Encyclopedia of Genes and Genomes [27] with input from Vacchelli et al. [22]. Nine main families are recognized (Table 1) with most of the cytokines of interest classified in the hematopoietic growth factor, interferon (IFN), platelet-derived growth factor (PDGF) and transforming growth factor β (TGFβ) families. In the hematopoietin family, approved cytokines manufactured by recombinant DNA technology are aldesleukin [rh-interleukin-2 (IL-2)], oprelvekin (rhIL-11), filgrastim and tbo-filgrastim [rh-granulocyte colony-stimulating factor (G-CSF)], sargramostim [rh-granulocyte macrophage (GM)-CSF], metreleptin (rh-leptin) and rh-erythropoietins, epoetin and darbepoietin alfa. Anakinra, a recombinant receptor antagonist for IL-1, is a representative of the IL-1 cytokine family; interferon recombinants interferons alfa-1, alfa-2, beta-1 and gamma-1 make up the interferon family; palifermin [rh-keratinocyte growth factor (KGF)] and becaplermin (rhPDGF-BB; see Sect. 3.3.4) are in the PDGF family; and rh-bone morphogenetic protein [BMP]-2 and rhBMP-7 represent the TGFβ family. Chemokines, placed here in group 9 (Table 1), behave as regulatory molecules for leukocytes and lymphoid tissue and have an important role in infectious, inflammatory, allergic and autoimmune responses as well as angiogenesis, hematopoiesis and tumor growth [21, 22]. No members of the chemokine family are yet approved for therapy.

3.3 Side Effects of Individual Approved Recombinant Cytokine Analogs

A number of the characteristics and properties of cytokines provide an insight into the possibility of adverse effects when these 'natural' agents are used therapeutically. These include, in particular, their pleiotropic nature; relatively short half-lives; the presence of other cytokines; their capacity to release other cytokines producing a cytokine 'cocktail'; and the existence of multiple receptors on different cells that bind the same cytokine with different affinities [22]. Overall, and as one might expect with biological systems involving genetically diverse patients; the diverse range of biological activities of cytokines; their action in causing the release of additional cytokines; the knock-on pharmacological effects of these secondarily released agents; and different disease statuses of patients; side effects of cytokines are not unusual, are to be expected, and patient-to-patient spectra of these effects will be variable.

For the common side effects of cytokines used as therapeutic agents, as well as for the less common but important hematologic, psychiatric, endocrine, neurologic, pulmonary and dermatologic adverse effects [31, 33, 110–113], space constraints and the many hundreds of relevant studies do not always allow the direct referencing of the many pertinent reports. Instead, one or more selected examples or studies that are particularly germane are provided. For those seeking a more comprehensive follow-up on a particular cytokine, comprehensive and ongoing collective review series such as the side effects of drugs annual (Elsevier) are suggested.

Table 1 Family classification of cytokines[a] relevant to this review

Family	Members
Hematopoietin[b]	IL-2; IL-6[c]; IL-11[c,d]; IL-12[e]; G-CSF[c]; GM-CSF; leptin[c,f]; EPO[g]; TPO[g]
IL-1	IL-1α; IL-1β; IL-18[h]
IL-10[i]	IL-10[j]
IL-17[k]	IL-17; IL-17B; IL-17C; IL-17D; IL-17E; IL-17F
Interferon[l]	IFNα-1; IFN α-2; IFNβ-1; IFNγ-1
PDGF[m]	EGF; KGF; M-CSF; PDGFA-D; PGF; VEGFA-D
TGFβ	BMP-2[n]; BMP-7[o]; TGFβ1[p]; TGFβ2[p]; TGFβ3[p]
TNF	TNF; TNFSF4[q]; TNFSF5[r]; TNFSF6[s]; TNFSF10[t], TNFSF11[u]; TNFSF12[v]
Chemokines	CC subfamily; CXC subfamily; C subfamily; CX3C subfamily[w]

BMP bone morphogenetic protein, *EGF* epidermal growth factor, *EPO* erythropoietin, *G-CSF* granulocyte colony-stimulating factor, *GM-CSF* granulocyte macrophage colony-stimulating factor, *IFN* interferon, *IL* interleukin, *KGF* keratino- cyte growth factor, *M-CSF* macrophage colony-stimulating factor, *PDGF* platelet- derived growth factor, *PGF* placenta growth factor, *TGFβ* transforming growth factor β, *TNF* tumor necrosis factor, *TNFSF* tumor necrosis factor ligand superfamily member, *TPO* thrombopoietin, *VEGF* vascular endothelial growth factor

[a] Based on the Kyoto Encyclopedia of Genes and Genomes [27] and Vacchelli et al. [22]

[b] Class I cytokines

[c] Member of IL-6 receptor subfamily that also includes IL-11, G-CSF and leptin. IL-6 involved in cytokine storm reactions

[d] Also called AGIF, adipogenesis inhibitory factor. Promotes platelet recovery after chemotherapy-induced thrombocytopenia

[e] Promotes Th1 responses and stimulates production of IFNγ and TNF from T and NK cells

[f] Homologous in structure to a cytokine. Included here according to [22] but often described as a hormone. Produced primarily in adipose tissue; regulates fat storage

[g] Member of single chain subfamily

[h] Proinflammatory but suppresses metastasis surveillance by NK cells

[i] Class II cytokines. Interferons sometimes classified in this family. Family also includes IL-19, -20, 22, -24, -26

[j] Anti-inflammatory and immunosuppressive

[k] Proinflammatory cytokines; stimulate release of other cytokines, e.g., IL-1β, IL-6, GM-CSF, TGFβ, TNF

[l] Class II cytokines. Comprise 3 types: type I (IFNα, IFNβ, IFNω1, IFNκ1, FNτ1), type II (IFNγ), type III (incl IL-28A, -28B, -29)

[m] PDGFs, PGF & VEGFs belong to subclass I of cysteine-knot growth factors. M-CSF is incl- uded in the 4-helix bundle growth factors

[n] BMP2 subfamily

[o] BMP5 subfamily

[p] Member of TGFβ subfamily

[q] Also called OX40L & CD252, the ligand for CD134. Expressed on the surface of activated B, T, dendritic and endothelial cells

[r] Also called CD40L & CD154. Costimulatory molecule with T cell receptor in activation of antigen presenting cells

[s] Also called FASL or Fas ligand. Binding with its receptor induces apoptosis

[t] Also called CD253 or TRAIL,TNF-related apoptosis-inducing ligand

[u] Also called RANKL, receptor activator of nuclear factor kappa-B ligand

[v] Also called TWEAK, TNF-related weak inducer of apoptosis

[w] Small peptides divided into 4 subfamilies on the basis of a cysteine motif

The main physicochemical features, FDA-approved indications, modes of action and side effects, as well as warnings, are summarized for the 20 recombinant cytokine preparations approved by the FDA CDER [1] (Table 2). They will now be considered individually.

3.3.1 Interferons

Interferons are a class of broad spectrum antiviral cytokines, seven of which occur in humans and which have overlapping, but also some individual, activities. They can be divided into three classes, types I, II and III. Of most interest for therapy are interferons alfa, beta and gamma. The former two, classified as type I interferons, bind to the interferon alfa receptor (IFNAR) consisting of IFNAR1 and IFNAR2 chains; interferon gamma, a type II interferon, binds the interferon gamma receptor (IFNGR) consisting of IFNGR1 and IFNGR2.

3.3.1.1 Interferon alfa It is said that virtually all patients treated with interferon alfa experience some adverse effect(s) at some time during therapy [33]. In fact, the

Table 2 Cytokines approved for human therapy[a]

Generic and trade names	Properties	Approved indications[a]	Mechanism(s) of action relevant to indications	Warnings and side effects, serious and common	Refs.
Peginterferon alfa-2a[b] (Pegasys®)	Covalent complex of recombinant interferon alfa-2a 127 amino acids MW ~ 20 kDa with PEG[c] linked by an amide bond to lysine	Chronic hepatitis C[d,e]; chronic hepatitis B[d] (HBeAg[f] + or - patients)	Not fully known[g]. IFN[h]α binds to its receptor, activating JAK1 and Tyk2[i] which phosphorylate receptors which bind STAT1 and STAT2[j]. These combine with IRF-9[k] leading to expression of multiple ISGs[l] Type I IFNs have antiviral and proliferative effects and modulate immune responses but their relative potencies differ. IFNα binds IFN receptors less stably than IFNβ	Boxed warnings: Neuropsychiatric, autoimmune, ischemic and infectious disorders[m] and ribavirin-associated effects[n]; Other effects: fatigue/ asthenia; pyrexia; headache; myalgia; cytopenias; autoimmunity; infection; colitis; pulmonary, CV[o] and cutaneous disorders	[28–34]
Interferon alfa-2b (Intron A®) Peginterferon alfa-2b (Pegintron®) (Sylatron®)	Recombinant protein MW ~ 19 kDa 165 amino acids with Arg 23; similar to leukocyte IFN Recombinant protein linked to PEG Recombinant protein linked to PEG	Chronic hepatitis B and C; MM[p]; HCL[q]; A-RKS[r]; FL[s]; condylomata acuminata Chronic hepatitis C with or without ribavirin Adjuvant treatment of melanoma		Boxed warnings: Neuropsychiatric, autoimmune, ischemic and infectious disorders[m]. Other effects: Flu-like symptoms of fever, fatigue, chills, headache, myalgia; neutropenia; pm[t] Boxed warnings: Neuropsychiatric, autoimmune, ischemic and infectious disorders[m] and ribavirin-associated effects[n]; Other effects: fatigue/ asthenia; fever; nausea; rigor, myalgia; pm[u] Boxed warnings: Depression and other neuropsychiatric disorders. Other: as above plus ↑ALT and AST[v]; pm[w]	[35–38] [37–40]
Interferon beta-1a (Avonex®; Rebif®)	Recombinant 166 amino acid glycoprotein MW 22.5 kDa; amino acid sequence identical to natural protein	Relapsing forms of multiple sclerosis	Not fully understood. IFNβ binds to receptor leading to complex events including ↑ expression of antiinflammatory agents and ↓ proinflammatory cytokines; gene products and markers include 2′,5-oligoadenylate synthetase, neopterin; CD56 killer cells increase	Flu-like symptoms—chills, fever, myalgia, asthenia; depression; immunogenicity; anaphylaxis; rash	[41–45]
Interferon beta-1b (Betaseron®; Extavia®)	Recombinant 165 amino acid protein MW 18.5 kDa; gene contains ser for cys at posn 17	Relapsing forms of multiple sclerosis		Flu-like symptoms; lymphopenia, leukopenia and neutropenia; isr[x]; myalgia; depression; hypertonia; abdominal pain; asthenia; rash; ↑ liver enzymes; immunogenicity; anaphylaxis	[42–46]
Interferon gamma -1b (Actimmune®)	Recombinant 140 amino acid polypeptide; non-covalent dimer of 2 identical 16.465 kDa monomers of 6 α-helices	Chronic granulomatous disease; malignant osteopetrosis	Interacts with heterodimeric receptor IFNγR1 and IFNγR2 activating JAK-STAT pathways and altering transcription of up to 30 genes	Most common: flu-like symptoms—fever; headache, chills, fatigue; isr[x]; rash; diarrhea. Other effects: neutropenia; thrombocytopenia; hepatotoxicity; CV, pulmonary, CNS and GI events;? Pulmonary toxicity	[47–51]
Filgrastim (Neupogen®;Nivestim®) Pegfilgrastim[y] (Neulasta®)	Recombinant hu-G-CSF[z]; 175 amino acid MW 18.8 kDa nonglycosylated protein; differs from natural by an *N*-terminal methionine	Cancer patients receiving: chemotherapy for AML[aa], myelosuppression or BMT[ab]; patients with chronic neutro- penia or undergoing pbpcct[ac]	Binds to G-CSF receptors on progenitor cells of neutrophil-granulocyte linage → proliferation, differentiation, activation. Enhances phagocytosis, chemotaxis, cytotoxicity of mature neutrophils[ad]	Warnings: Splenic rupture; Sickle cell crisis. Other effects: nausea/vomiting; fever; bone pain; hypersensitivity; ARDS[ae]; isr; alveolar hemorrhage; immunogenicity; osteoporosis; rash; cutaneous vasculitis; Sweet's syndrome	[52–57, 58]
Tbo-filgrastim (Granix®; Tevagrastim®)	Recombinant biosimilar non-glycosylated G-CSF expressed in *E. coli.* Formulated for short action	Severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs	As for filgrastim	Warnings: Splenic rupture; ARDS; allergic reactions; Sickle cell crisis. Other effects: bone pain; nausea/ vomiting; fever; diarrhea; immunogenicity; cutaneous vasculitis; Sweet's syndrome	[59–61]
Sargramostim (Leukine®)	Recombinant hu-GM-CSF[af], 3 molec species MWs 19.5, 16.8 15.5 kDa 127 amino acids; leu23 differs from natural factor	Patients receiving: chemotherapy for AML, BMT[ai] or undergoing pbpcct; myeloid recovery in NHL[ag], ALL[ah], BMT	Induces progenitor cells to prolif → neutrophils, monocytes, macrophages & enhances neutrophil function via specific receptors & signaling through JAK2, STAT, MAP & P13 kinase pathways & transcriptional changes	Warnings & precautions: Fluid retention; respiratory, CV, renal & hepatic symptoms. Other effects: fever; headache; nausea /vomiting; myalgia; malaise; anorexia; bone pain; diarrhea; alopecia; stomatitis; rash	[57, 62, 63]

Table 2 continued

Generic and trade names	Properties	Approved indications[a]	Mechanism(s) of action relevant to indications	Warnings and side effects, serious and common	Refs.
Oprelvekin (Neumega®)	Recombinant IL-11, nonglycosylated 177 amino acids (178 natural IL-11) MW 19 kDa	Prevention of thrombocytopenia & reduction of need for platelet transfusion after myelosuppressive chemotherapy	Stimulates megakaryocytopoiesis & thrombopoiesis → ↑platelet prod'n[ai]. Binds to IL-11Rα & gp130 activating JAK which phosphylates Tyr on gp130	Boxed warning: Allergic reactions including anaphylaxis. Warnings: fluid retention[aj]; dilutional anemia; CV events[ak]; papilledema; stroke. Other effects: nausea; vomiting; asthenia; abdominal & bone pain; myalgia; anorexia; chills; alopecia	[64–67]
Becaplermin (Regranex®)[al]	Recombinant PDGF[am] MW ~ 25 kDa; homodimer of 2 identical peptide chains of 109 amino acids -S-S-joined at cys43 & 52	Treatment of diabetic neuropathic ulcers that extend into subcutaneous tissue[an]	Binds to & activates PDGF receptors by dimerization & autophosphorylation binding SH_2 sites & activating signal pathways	Boxed warning: Increased rate of mortality secondary to malignancy[ao]. Other effects: erythematous skin rash; burning at application site; infection; urti; skin ulceration; cellulitis; osteomyelitis; skin hypertrophy; bullous eruption	[68–71]
Palifermin (Kepivance®)	Truncated recombinant human KGF[ap] 140 amino acids, nonglycosylated, MW 16.3 kDa	Severe oral mucositis in patients with hematologic malignancies	Binds to fibroblast growth factor receptor activating Ras-MAP kinase signaling & transcriptional activation of cell growth & survival	Warning: Potential for stimulation of tumor growth. Othereffects : fever; dysesthesia; tongue discoloration/thickening; arthralgias; ↑serum amylase; edema; rash; erythema; hand-foot syndrome; pruritus	[72–76]
Aldesleukin (Proleukin®)	Recombinant analog of human IL-2 MW 15.3 kDa; unlike IL-2, not glycosylated, ser for cys at position 125 & no *N*-terminal ala	Metastatic renal cell carcinoma; metastatic melanoma	Binds to IL-2 receptor → heterodimeriz ation of IL-2Rβ & -2Rγ → activation JAK3; phosphorylation of tyr on IL-2Rβ → activated receptor, signaling molecules & T cell stimulation	Boxed warning: Restrict to patients with normal cardiac & pulm functions; administer in hospital with ICU facility & specialists; cls[aq]; impaired neutrophil function[ar]; withhold in cases of lethargy & somnolence. Other: chills; diarrhea; hypotension; oliguria; thrombocytopenia; erythema; rash	[77–81]
Anakinra (Kineret®)	Recombinant receptor antag-onist for IL-1 (IL-1RA), 153 amino acids MW 17.3 kDa; has met added to amino terminal	Rheumatoid arthritis; cryopyrin-associated periodic syndrome (CAPS)	Binds to IL-1RI receptor blocking activity of IL-1α and β & acting as a biological response modifier, e.g., for cartilage degradation & bone resorption	isr; worsening rheumatoid arthritis; urti; headache; nausea; diarrhea; flu-like symptoms; arthralgia; abdominal pain; hypersensitivity (incl anaphylaxis, angioedema); sinusitis	[81–84]
Epoetin alfa (Epogen®; Procrit®; Eprex®; Erypo®)	Recombinant human erythro-poietin; glycoprotein, 165 amino acids (identical to natural product) MW 30.4 kDa	Treatment of anemia due to: chronic kidney disease; zidovudine in HIV patients; effects of chemotherapy; reduction of allogeneic red blood cells in surgery	Binds receptors on erythroid progenitor cells triggering conformational change, activation of JAK2 by transphosphorylation, Src signaling, STAT regulation of genes for cell division & differentiation	Boxed warning: ESAs increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access & tumor regression or recurrence. Other effects:pyrexia; arthralgias; nausea; hypersensitivity; headache; cough; isr; hypertension; rash; pruritus; stomatitis; myalgia; pure red cell aplasia[as]	[85–90]
Darbepoetin alfa (Aranesp®)	Recombinant human erythro-poietin, 165 amino acids, MW ~ 37 kDa; 2 amino acids substituted to enhance glycosylation	Treatment of anemia due to: chronic kidney disease; effects of concomitant mylosuppressive chemotherapy	As for epoetin alfa	Boxed warning: As for epoetin alfa. Other effects: hypertension; dyspnea; peripheral edema; cough; abdominal pain; prca; thrombovascular events; seizures; hypersensitivity (including anaphylaxis, angioedema, bronchospasm); rash/erythema	[91–93]
Bone morphogenetic protein 2 (InFUSE® Bone Graft/LT-Cage®)[at]	Recombinant human BMP-2 (rhBMP-2; dibotermin alfa); a disulfide-linked homodimer; glycosylated subunits 114 & 131 amino acids	Spinal fusion procedures in patients with degenerative disc disease	BMP binds to Ser/Thr kinase types I & II receptors forming activated complexes. SMAD proteins, part of type I receptors, relay BMP signal to target genes in the nucleus. This in turn induces transcription of osteogenic genes leading to cell proliferation and differentiation	Erythema; swelling over implant site; immunogenicity; ectopic/heterotopic ossification; myositis ossificans; wound-related complications; osteolysis; infections; radiculitis; compression of airways after spine fusion; urogenital events; retrograde ejaculation; allergy	[94–100]
Bone morphogenetic protein 7 (OP-1 Putty[au], OP-1 Implant[au]; Opgenra®[av]; Osigraft®[av])	Recombinant human BMP-7 (rhBMP-7; OP-1; eptotermin alfa). 30 kDa homodimeric glycoprotein prod by CHO cells; two 139 amino acid peptides corres to posns 293-431 of full length BMP-7[aw]	Opgenra: posterolateral lumbar spinal fusion with spondylolisthesis and failed autograft Osigraft: tibial nonunions of at least 9 months			[96, 101–104]

Table 2 continued

Generic and trade names	Properties	Approved indications[a]	Mechanism(s) of action relevant to indications	Warnings and side effects, serious and common	Refs.
Metreleptin[ax] (Myalept®)	Recombinant analog of leptin, 147 amino acids, nonglycosylated, MW 16.14 kDa; 1 more met than leptin at NH_2 terminal; 1 -S-S- at cys97-cys147	Complications of leptin deficiency in patients with congenital and acquired generalized lipodystrophy	Binds and alters conformation of homodimer receptor[ay] activating JAK2 which phosphorylates other Tyr residues within receptor JAK2 complex to mediate downstream signaling	Boxed warning: Anti-metreleptin antibodies with neutralizing activity worsening metabolic control &/or infection; T cell lymphoma. Warnings: hypoglycemia with concomitant insulin/insulin secretagogues; autoimmunity; hypersensitivity; benzyl alcohol toxicity. Other effect: immunogenicity	[105–109]

[a] Approved by FDA CDER or EMA or both*

[b] Peginterferon alfa-2a and ribavirin (Copegus®) are indicated for the treatment of adults not previously treated with interferon alfa and with chronic hepatitis C and liver disease. This drug combination is the only FDA-approved regimen for the treatment of chronic hepatitis C infected with both hepatitis C virus and HIV

[c] PEG, bis- monomethoxy polyethylene glycol

[d] In adults with compensated liver disease

[e] Combination therapy with ribavirin recommended

[f] HBeAg, hepatitis B 'e' antigen circulating in blood when the virus is replicating

[g] All type 1 interferons have antiviral, antiproliferative and immunomodulatory activities [28]

[h] IFN, interferon

[i] JAK1, Janus-activated kinase 1; Tyk2, tyrosine kinase 2

[j] STAT1 and STAT2, signal transducer and activator of transcription proteins 1 and 2

[k] IFN-regulatory factor 9

[l] IFN-stimulated genes

[m] Fatal or life-threatening

[n] Ribavirin may cause birth defects; avoid pregnancy. It is a potential carcinogen

[o] CV, cardiovascular

[p] MM, malignant melanoma

[q] HCL, hairy cell leukemia

[r] A-RKS, AIDS-related Kaposi's sarcoma

[s] FL, follicular lymphoma

[t] Reactions less commonly seen and/or seen during pm (post marketing) period include nephrotic syndrome; renal insufficiency and failure; pancreatitis; Stevens–Johnson syndrome (SJS); toxic epidermal necrolysis (TEN); erythema multiforme (EM), injection site necrosis; myositis; immune-mediated disorders including thrombocytopenia

[u] Less commonly seen and pm period: thrombocytopenia; cardiac disorders; renal insufficiency and failure; hearing and eye disorders; infections; immune disorders including anaphylaxis, angioedema, urticaria, SJS, TEN, systemic lupus erythematosus (SLE); EM and nervous system disorders such as peripheral neuropathy and seizures

[v] ALT, alanine aminotransferase, AST, aspartate aminotransferase

[w] Less commonly seen and pm period: CV; endocrinopathies; hepatic failure; retinopathy; ear, eye, pulmonary and immune (thrombocytopenic purpura, SLE, EM, SJS, TEN) disorders; pancreatitis; colitis; psoriasis

[x] isr, injection site reactions

[y] Indicated to decrease the incidence of infections in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs and associated with febrile neutropenia. Extends half-life to 42 h from ~3.5 h for filgrastim

[z] hu-G-CSF, human granulocyte colony-stimulating factor

[aa] AML, acute myeloid leukemia

[ab] BMT, bone marrow transplantation

[ac] pbpcct, peripheral blood progenitor cell collection therapy

[ad] Mechanisms still poorly understood

[ae] ARDS, acute respiratory distress syndrome

[af] hu-GM-CSF, human granulocyte macrophage colony-stimulating factor

[ag] NHL, non-Hodgkin lymphoma

[ah] ALL, acute lymphoblastic leukemia

[ai] Other actions: regulation of intestinal epithelium growth; inhibition of adipogenesis and proinflammatory cytokines; induction of acute phase protein synthesis (e.g., fibrinogen)

[aj] Pulmonary and peripheral edema, dyspnea, capillary leak syndrome (cls)

[ak] Arrhythmias, pulmonary edema

[al] Used topically as a gel

[am] PDGF, platelet-derived growth factor (also known as PDGF-BB)

[an] Promotes chemotactic recruitment and proliferation of cells for wound healing and formation of granulation tissue

[ao] Gel should only be used when benefits are expected to outweigh the risks and used with caution in cancer patients with known malignancy

[ap] KGF, keratinocyte growth factor. rhKGF differs from endogenous protein by truncation of the *N*-terminal amino acid to increase stability

[aq] cls, capillary leak syndrome which results in hypotension, reduced organ perfusion and possibly death and may be associated with cardiac arrhythmias, angina, myocardial infarction, respiratory insufficiency, edema etc

[ar] Reduced chemotaxis therefore treat pre-existing infection prior to aldesleukin therapy; patients with indwelling central lines particularly at risk

[as] Severe anemia with erythrocyte count <1 and <0.5 % mature erythroblasts in bone marrow

[at] InFUSE® Bone Graft consists of rhBMP-2 absorbed to a collagen sponge. The LT-Cage® titanium alloy device is a small, hollow, perforated machined cylinder with one end closed and the other open for addition of the InFUSE® Bone Graft component

[au] Acquired by Olympus Biotech from Stryker Corp

[av] Equivalent to OP-1 Putty and Implant preparations, respectively

[aw] Several different recombinant mature forms starting at positions 293, 300, 315 and 316 have been identified

[ax] Leptin, often called a hormone, shows some structural homology to cytokines

[ay] Leptin receptors are members of the IL-6 class I cytokine receptor family

* Cytokines (and date) approved by: FDA—Peginterferon alfa-2a (2002); Interferon alfa-2b (1986); Peginterferon alfa-2b, Pegintron® (2001), Sylatron® (2011); Interferon beta-1a, Avonex® (1996), Rebif® (2002); Interferon beta-1b, Betaseron® (1993), Extavia® (2009); Interferon gamma-1b (1999); Filgrastim, Neupogen® (1991), Nivestim® (2010); Pegfilgrastim (2002); Tbo-filgrastim (2012); Sargramostim (1991); Oprelvekin (1997); Becaplermin (1997); Palifermin (2004); Aldesleukin (1992); Anakinra (2001); Epoetin alfa (1989); Darbepoetin alfa (2001); Bone morphogenetic protein 2 (2002, 2004 and 2007 for different indications); Bone morphogenetic protein 7 (2001); Metreleptin (2014)

EMA—Peginterferon alfa-2a (2002); Interferon alfa-2b (2000); Peginterferon alfa-2b, Pegintron® (2001); Interferon beta-1a, Avonex® (1997), Rebif® (1998); Interferon beta-1b, Betaferon® (1995), Extavia® (2008); Filgrastim, Neupogen® (1991), Nivestim® (2010); Pegfilgrastim (2002); Tbo-filgrastim (2008); Becaplermin (1999); Palifermin (2005); Aldesleukin (2006); Anakinra (2002); Epoetin alfa (2007); Darbepoetin alfa (2001); Bone morphogenetic protein 2 (2002); Bone morphogenetic protein 7 (2001). Metreleptin designated an orphan drug in 2012

literature on side effects to interferons is voluminous and probably greater than all the other approved, non mAb biologics literatures put together. Three interferon alfa preparations are in the CDER Biologic Products List [1]. Peginterferon alfa-2a together with ribavirin (Copegus®) are indicated for the treatment of chronic hepatitis C in adults who have compensated liver disease and were not previously treated with interferon alfa. This drug combination is also the approved treatment of patients infected with hepatitis C and HIV and peginterferon alfa-2a alone is approved for the treatment of patients with chronic hepatitis B who have compensated liver disease, viral replication and liver inflammation. Interferon alfa-2b is administered extensively for hepatitis B and C as well as several malignancies (Table 2) [114]. It upregulates the expression of MHC I proteins enhancing activation of CD8+ T cells and cytotoxic lymphocyte-mediated killing as well as inducing synthesis of several other antiviral agents including protein kinase R. Peginterferon alfa-2a and peginterferon alfa-2b are covalent conjugates of the recombinant interferon with a single branched bis-monomethoxy polyethylene glycol (PEG) chain, MW 40 kDa. Pegylation, which is FDA approved, non-toxic and contributes to water solubility, helps to protect the protein from immune recognition that is, it reduces the immunogenicity and antigenicity and increases the molecule's size thus extending protein half-life and circulatory time and reducing renal clearance [115]. For interferon alfa-2a, adverse events in patients treated with the pegylated form and ribavirin occur with a similar, or significantly less, frequency than those treated with standard interferon/ribavirin. For interferon alfa-2b, a number of adverse events occur more frequently with pegylated interferon/ribavirin [33]. In some reports on side effects, especially in the earlier literature, interferon alfa is often not distinguished as alfa-2a or alfa-2b although this can be important as demonstrated by some of the different effects induced by alfa-2a and alfa-2b interferons mentioned below.

Interferon alfa-induced neuropsychiatric disorders, particularly depression, cognitive dysfunction and mania are well known and have been intensively studied [31–33, 110–112]. Other symptoms include altered sleep pattern, anorexia and fatigue. Of the patients who develop severe depressive symptoms, most occur within the first 3 months of treatment and the incidence of depressive disorders has been estimated to be 23–41 % [116–118]. Symptoms may be prolonged for 6 months or more after the cessation of therapy. There is some evidence that the serotonergic system is involved in the pathophysiologic mechanism [119–121] although the central opioid, dopamine and glutamate neurotransmitter systems may also be involved [122]. A positive correlation between depression scores and serum concentrations of soluble ICAM (intracellular adhesion molecule)-1 in patients who received interferon alfa led to the suggestion that the cytokine may induce the adhesion molecule which then increases the permeability of the blood-brain-barrier, allowing the interferon to more easily enter the brain [123]. A number of susceptibility factors have been suggested [124] including a history of depression; high dose of interferon; long treatment duration; female sex; and possession of the apolipoprotein Eε4 allele, said to be associated with some neuropsychiatric disorders.

The appearance of autoantibodies and development or exacerbation of autoimmune diseases are known to occur in response to interferon alfa therapy. In one study, seven cases of autoimmune disease, including one of hypothyroidism, two each of immune-mediated hemolysis and systemic lupus erythematosus, one of Raynaud's disease and one case of mixed connective tissue disease were identified in 76 patients after a median of 19 months of treatment [125]. Reports of autoimmune reactions to interferon alfa or its combination with ribavirin are not rare and include cases of Hashimoto's thyroidtoxicosis followed by type 1 diabetes [126], autoimmune thyroiditis [127] and development [128–130] and exacerbation [131] of a lupus-like syndrome. See also 'Endocrine effects' below.

In addition to their neuropsychiatric and immune effects, interferon alfas occasionally provoke an extensive range of adverse reactions including cardiovascular, respiratory, endocrine, hematologic, metabolic, urinary tract and skin adverse events as well as adverse effects on the nervous and sensory systems. Cardiovascular complications such as pericarditis [132] and cardiomyopathy with left ventricular dilatation in patients with malignancies improved after withdrawal of the interferon and thereafter treatment with lower doses proved possible [133]. Pegylated interferon alfa-2b has been associated with acute myocardial infarction [134], pericarditis [135], pericardial effusion with tamponade [136] and sick sinus syndrome producing arrhythmias [137] and an orthotopic heart transplant patient died after allograft failure with death attributed to interferon toxicity [138]. Interstitial lung disease, reported for both interferon alfa-2a and 2b [139–144], is seen more frequently with the former agent and with high doses of the latter [145]. Potentially fatal interstitial pneumonitis [146], secondary to interferon alfa-ribavirin therapy for hepatitis C infection, is said to have an incidence of 0.03–0.3 % although an incidence of ~1.1 % was found in 558 Japanese patients [147]. Fatal interstitial pulmonary disease can occur with pegylated interferon alfa-2b as shown by a patient with interstitial pneumonitis who also developing adult respiratory distress syndrome [148]. Cases of bronchiolitis obliterans organizing pneumonia (BOOP), some fatal, are also known [139, 149].

Interferon alfa may have adverse effects on the nervous system in the form of seizures in patients with no history of epilepsy [150], involuntary facial movements and weakness [151, 152], features resembling multiple sclerosis [153, 154], restless legs syndrome [155], 17 reports of sensorimotor polyneuropathy [156] and Bell's palsy [157, 158]. Adverse effects on sensory systems, mainly the eyes but also the ears, occur particularly to interferon alfa-2b. Ocular complications include occlusive vasculitis, central retinal artery occlusion and anterior ischemic optic retinopathy [159, 160]. Twenty seven of 42 patients taking interferon alfa-2b/ribavirin developed a retinopathy: cotton wool spots, 27 patients; retinal hemorrhage, 6; subconjunctival hemorrhage, 2; optic nerve edema, 1. Other ocular complications described in patients treated with interferon alfa-2b include permanent loss of sight due to combined retinal artery and central retinal vein obstruction; development of an epiretinal membrane; and the T cell-mediated autoimmune syndrome, Vogt-Koyanagi-Harada disease [161].

Endocrine effects of interferon alfa are probably best illustrated by thyroid dysfunction which is not yet fully understood but may have an autoimmune mechanism. Thyroid dysfunction occurs with an incidence of 5–14 % in patients treated for chronic hepatitis C. Hypothroidism occurs more often than hyperthyroidism and resolution occurs in about 60 % of cases. Interferon alfa-2b can cause both conditions [162–164]. Although an autoimmune reaction is the most likely mechanism, some patients develop hypothyroidism without autoimmunity. A direct inhibitory effect of thyrocytes has been suggested as the possible mechanism [162].

Neutropenia induced by interferon alfa is fairly commonly seen [165] while other reported hematologic side effects include acute and autoimmune thrombocytopenia [166–168], pernicious anemia [169], bone marrow hypoplasia [170] which may be immune-mediated, and pure red cell aplasia [171].

A number of acute renal complications in response to interferon alfa have been well documented and include renal thrombotic microangiopathy [172], acute nephrotic syndrome [173], hemolytic-uremic syndrome [174], renal insufficiency due to interstitial nephritis [175], tubular necrosis and IgA nephropathy [176].

The list of cutaneous reactions to interferon alfa is extensive and includes injection site reactions (erythema, necrosis and vasculitis), pruritus, xerosis, urticaria, hyperpigmentation, psoriasis, alopecia, lichen planus, pityriasis rosea, sarcoid nodules, eosinophilic fasciitis, livedo reticularis, vitiligo and fixed drug eruption [177–181].

3.3.1.2 Interferon beta The transcriptional response to interferons beta-1a and beta-1b appear to be indistinguishable [44] but the biological and clinical responses may vary with the dosage schedules. A flu-like illness is the most commonly occurring adverse event following administration of the interferon beta proteins (Table 2) and injection site reactions are common [43, 182]. A comparison of interferon beta-1a, 30 μg, given intramuscularly (im) once per week with interferon beta-1b, 44 μg, subcutaneously (sc) every other day, showed that injection site reactions and antibodies were significantly more frequent in patients given the beta-1b preparation but after 2 years, clinical outcomes to this agent were superior [183]. The questions of the production of neutralizing antibodies to interferon beta and whether they reduce the therapeutic effectiveness in treated patients, especially in the treatment of multiple sclerosis, are important ones. Such antibodies are found in about a quarter of patients treated with sc administered interferon beta-1b and the consensus is that they neutralize or reduce the cytokine's activity. Some believe that this has the potential to significantly reduce the effectiveness of the therapy and it has been suggested that the immunogenic potential of interferon beta should therefore be considered as well as its safety [184]. Other immunologic effects observed are cases of a lupus-like syndrome to both beta interferons [185, 186] and cutaneous lymphocytic vasculitis to sc interferon beta-1b [187].

Unlike interferon alfa, results from studies do not support an association of interferon beta with depression but interferon beta can induce thyroid disorders notably hyperthyroidism [188] and a severe case of hypothyroidism to interferon beta-1a resembling Hashimoto's encephalopathy has been described [189]. Skin reactions reported include urticaria [190] to interferon beta-1a and an acneiform eruption to interferon beta-1b [191].

3.3.1.3 Interferon Gamma Interferon gamma, structurally distinct from other interferons [48, 49], is produced predominately by NK (TCR not expressed) and NKT cells and by CD4 and CD8 cytotoxic T lymphocytes in antigen-specific immunity. The cytokine shows a different biological activity spectrum, in particular in its action of differentiating normal and B lymphocytes, and as an immunomodulator of macrophage activity. It also has an important role in dealing with intracellular pathogens, including viruses, and tumor control [51, 192, 193].

Early phase I studies of the biological activity of, and tolerance to, recombinant interferon gamma showed the common appearance of flu-like symptoms and granulocytopenia [194]. In another early study, a 30 % fall in peripheral blood lymphocytes was seen after 10 days of interferon gamma therapy [195]. The occurrence of fatal acute respiratory failure in four patients treated with interferon gamma-1b for advanced idiopathic pulmonary

fibrosis [196] prompted further investigation in the form of a double blind study of the effect of the cytokine in 330 patients with that condition. No significant differences were found in lung function, gas exchange or quality of life but the patients experienced more frequent upper respiratory infections and pneumonia [197]. However, acute respiratory insufficiency has been reported in a single patient with idiopathic pulmonary fibrosis four months after receiving interferon gamma [198]. Cardiovascular toxicity to interferon gamma, particularly at higher doses, and including hypotension, arrhythmias, coronary vasospasm and ventricular tachycardia [199, 200] and renal toxicity, namely acute renal failure, nephrotic syndrome and tubular necrosis [201, 202], have been recorded. There appears to be few reports of cutaneous reactions to interferon gamma but severe erythroderma occurred in 5 of 10 bone marrow transplant patients given the drug [203].

3.3.2 *Colony-Stimulating Factors: Filgrastim, Sargramostim and Tbo-filgrastim*

CSFs [57], produced by most tissues and cell types, are glycoprotein cytokines with multiple actions on hematopoietic cells. Described by Metcalf [204] as "the master regulators of granulocyte and macrophage populations", the CSFs are used to treat chemotherapy-induced neutropenia, mobilize stem cells for transplantation, and enhance the immune response to cancer. Currently, approved members of the CSF family are filgrastim and pegfilgrastim, both G-CSFs, sargramostim, a GM-CSF, and tbo-filgrastim, a short acting biosimilar G-CSF (Table 2). The latter is used for severe neutropenia in patients with lung cancer receiving platinum drug chemotherapy. GM-CSF, used as an immunostimulant following bone marrow transplantation and chemotherapy, is also viewed as a potential immunoadjuvant for anti-cancer vaccines.

As well as the most common, and usually mild and transient reactions of headache, bone pain, myalgia, fever, flushing and rash for filgrastim and sargramostim, other more severe, but rare, respiratory, cardiovascular, hematologic and cutaneous reactions occur. Adult respiratory distress syndrome (ARDS) following G-CSF [205] is more likely when a rapid rise in the white cells occurs in patients taking pulmonary toxic drugs, when there is concomitant infections and in patients with HLA-B51 or HLA-B52 antigens. Other occasional respiratory side effects are pulmonary toxicities, particularly pulmonary edema which has proved fatal [206], and interstitial pneumonitis [207]. There has been speculation that GM-CSF might contribute to the development of acute coronary syndrome. In fact, cardiovascular complications have been observed. These include fluid retention, pulmonary edema and weight gain [208], aortitis to molgramostim [209] and capillary leak syndrome following G-CSF which can be severe and even fatal [210]. Recorded hematologic side effects to CSFs consist mainly of a number of cases of thrombocytopenia, some with an immune mechanism, [211, 212], splenomegaly [211], and splenic rupture (note FDA issued warning, Table 2) [213]. There is a belief that G-CSF may be a risk for the progression of myelodysplastic syndrome (MDS) but this has not been unequivocally established. MDS has been reported after G-CSF treatment [214] and the incidence of MDS or acute myeloid leukemia (AML) was found to be 11 % in patients treated with G-CSF but only 5.8 % in patients receiving immunosuppression alone [215]. In another more recent study [216], patients who received G-CSF had a 2.5-fold increased risk. Interpretation of results relevant to the alleged risk of G-CSF is not straight forward however. Findings that there is no significant relationship between G-CSF therapy and MDS/AML onset [217] are at odds with the belief that the risk of leukemia in severe congenital neutropenia patients increases with the G-CSF therapy [218]. Two other potentially life-threatening responses to CSFs, both the subject of warnings, are anaphylactic/anaphylactoid reactions [219] and severe adverse events such as acute chest syndrome, vaso-occlusive episodes, multi-organ failure and death seen in patients with sickle cell disease [220].

There is a long list of adverse skin reactions provoked by CSFs. Perhaps the most commonly occurring cutaneous reactions are Sweet's syndrome seen after therapy with sargramostim as well as filgrastim [221–223] and psoriasis flare [224, 225] but other reports describe pyogenic granulomas [226], pruritic erythematous maculopapular eruptions [227], palmoplantar pustulosis [228], erythema multiforme [229] and neutrophilic dermatoses [230].

3.3.3 *Oprelvekin*

Recombinant human IL-11, or oprelvekin (Table 2), is used to prevent chemotherapy-induced thrombocytopenia and reduce the need for platelet transfusions in patients with nonmyeloid malignancies [67, 231]. The most commonly occurring adverse events seen in placebo-controlled studies were edema, dyspnea, tachycardia, palpitations, atrial fibrillation/flutter, pleural effusions, conjunctival injection and oral moniliasis, [232]. Fluid retention and an increase in plasma volume underlie many of the adverse events, for example, edema, dyspnea, pleural effusions, arrhythmia and dilutional anemia, and indicate that oprelvekin should be used with caution in patients with congestive heart failure. No evidence of cumulative toxicity or bone marrow exhaustion has been observed after sequential cycles of the cytokine and no proliferative effect on tumors has been noted [66, 67, 232]. Two other clinically important adverse reactions reported are papilledema

[67, 233] and periosteal bone formation [233]. An incidence of 3–4 % was found for anti-oprelvekin antibodies in treated patients [67, 233].

3.3.4 Becaplermin

Becaplermin is a recombinant human PDGF, a homodimer made up of two disulfide-bonded B chains and hence written as rhPDGF-BB. Naturally occurring PDGF has A and B chains in homodimeric or heterodimeric form. The PDGF-A chain binds to the α receptor whereas the PDGF-B chain binds to both the α and β receptors [234, 235]. rhPDGF-BB promotes the growth of granulation tissue and wound healing [236, 237] via interaction with receptors on fibroblasts (α and β) and endothelial cells (β receptors). Becaplermin has found use in gel form as a topical application for patients with lower extremity diabetic neuropathic ulcers [69, 238].

Growth factors cause cell proliferation so the possibility of increased cancer rates is considered for drugs with a cell growth-promoting property. In a retrospective study by the FDA of a medical claims database, cancer rates and deaths were compared for 1,622 becaplermin users and 2,809 matched non-users. The incidence rate ratios of becaplermin to matched controls for all cancers and for mortality from all cancers were 1.2 and 1.8, respectively and the incidence rates for mortality among patients who received 3 or more tubes of becaplermin and controls were 3.9 and 0.9 per 1,000 patient-years, respectively. The rate ratio for cancer mortality in the patient group receiving 3 or more tubes was 5.2 (95 % CI 1.6–17.60). Following an earlier safety study in 2001, where more cancers were found in the becaplermin group than a non-user group, the FDA in 2008 issued a boxed warning for Regranex® Gel stating that "malignancies distant from the site of application have occurred in becaplermin users… and an increased rate of death from systemic malignancies was seen in patients who have received 3 or more tubes". As a consequence, it was stated that "becaplermin should be used with caution in patients with known malignancy" and only used "when the benefits can be expected to outweigh the risks" [239]. In 2010, the EMA's Committee for Medicinal Products for Human Use recommended that becaplermin should not be used in patients with a pre-existing cancer but, at the same time, admitted that there was no evidence either way to establish, or rule out, a link between therapeutic use of the cytokine and cancer. Apart from this major potential adverse event and the known side effects listed in Table 2, there is a dearth of subsequent studies on the side effects of becaplermin, including case reports. This is probably because clinical experience with the agent has not lived up to the initial high expectations and it has not become widely used.

3.3.5 Palifermin

Palifermin, a recombinant human keratinocyte growth factor produced by mesenchymal cells and fibroblasts, stimulates differentiation, proliferation and migration of epithelial cells via interaction with its complementary receptors on epithelial cells widely distributed in numerous tissues including skin, hair follicles, tongue, stomach, intestine, lung, liver, kidney, lens of the eye and many other tissues and organs [74]. The recombinant molecule is a nonglycosylated, 16.3 kDa, 140 amino acid protein belonging to the fibroblast growth factor family that has been genetically modified to increase stability by shortening the natural protein at the *N*-terminal end [72]. Palifermin is an important agent in oncological supportive care, aiding the management of mucositis in cancer patients by protecting the mucosal epithelium and aiding its regeneration after chemotherapy- and radiation-induced injury [74].

Reported adverse events following palifermin administration in a phase III double-blind, placebo-controlled trial were rash, pruritus, erythema, paresthesia, edema, taste alteration, rhinitis, arthralgia, thickening of the tongue and numbness [75]. The keratinocyte growth stimulation properties of palifermin may underlie a number of cutaneous reactions seen following its administration. Cases of palmoplantar erythrodysesthesia (acral erythema; hand-foot syndrome), a papulopustular (acne-like) eruption on the head and trunk, hyperpigmented papillomatous plaques in the axillae and inguinal areas and a case of lichenoid papules have been described. The latter reaction consisted of a cutaneous eruption of planar papules resembling lichen planus, together with erythema mainly in an intertriginous distribution and confluent white plaques on the oral mucosa [76]. Being a growth factor, palifermin carries a warning of potential stimulation of tumor growth (Table 2).

3.3.6 Aldesleukin

Interleukin-2 (IL-2) is one of the best studied cytokines after its discovery as an activator of T lymphocytes nearly 40 years ago. Because it possesses a wide range of immune effects regulating T cells and immune activation and homeostasis, IL-2 was one of the first cytokines characterized at the molecular level. The recombinant form, called aldesleukin, differs from the natural cytokine by absence of glycan residues and at position 125 and the end terminal amino acid (Table 2). It has been applied clinically in a number of ways, particularly for melanoma and renal cell carcinoma, and from its earliest applications showed a wide range of the sort of side effects often seen with cytokines including fever, chills, myalgia, nausea, vomiting, diarrhea, hypotension, oliguria and edema [81,

240, 241] (Table 2) plus a number of more severe cardiovascular, hematologic [81], endocrine, kidney, central nervous system, infectious and cutaneous toxicities.

Cardiovascular adverse events are the main dose-limiting toxicities of aldesleukin with recorded cases of hypotension, tachycardia, peripheral edema, pleural effusions, myocarditis, myocardial infarction, heart block, arrhythmias, cardiac eosinophilic infiltration and coronary ischemic changes [241–244]. An important occasional and serious adverse event of IL-2 therapy is capillary (sometimes called vascular) leak syndrome which causes hypovolemia and fluid accumulation in the extravascular spaces and may lead to oliguria, ischemia and confusion. Aldesleukin therapy can induce increased vascular permeability, interstitial edema and ultimately organ failure seen as an increase in body weight, fluid retention, peripheral edema, ascites, pleural and pericardial effusions and ultimately pulmonary and cardiovascular failure [245, 246]. Pulmonary side effects to aldesleukin are usually related to capillary leak syndrome and are more likely, and more severe, (e.g. as pulmonary edema and respiratory distress), in patients with existing cardiac problems. Hematologic adverse effects, particularly anemia, leukopenia and thrombocytopenia [247, 248], occur but are rarely severe or dose limiting. Eosinophilia may occur in the later stages of therapy accompanied by rash and pruritus [245]. Endocrine effects usually manifest as hypothyroidism which may affect up to one third of patients, or as the far less common hyperthyroidism [249]. Renal toxicity [250], especially oliguria, and gastrointestinal toxicities are also seen, the latter being particularly common in the form of nausea, vomiting, diarrhea, anorexia, gastritis and mucositis. Gastrointestinal perforation has also been reported [251]. IL-2-induced infectious toxicities may occur at venous catheter sites and in the urinary tract. Such infections, usually due to *Staphylococcus* species, are thought to arise from the known affect of IL-2 on neutrophil chemotaxis. Neurological effects, especially to high doses during IL-2 therapy, include anxiety, depression, altered sleep patterns, somnolence, emotional fragility, vivid dreams and confusion [252]. The list of aldesleukin-induced cutaneous reactions is extensive, ranging from mild erythema, pruritus, injection site reactions and vitiligo, to urticaria, angioedema, reactivation of eczema, exacerbation of psoriasis, generalized erythema followed by desquamation, vasculitis, and severe manifestations like pemphigus, IgA bullous dermatosis and toxic epidermal necrolysis [5, 253, 254]. A curious case involved the implication of high dose IL-2 therapy in the occurrence of multifocal fixed drug eruptions after the administration of other drugs, namely, ondansetron, granisetron, paracetamol and indomethacin [255].

3.3.7 Anakinra

Interleukin-1 (IL-1) is a cytokine produced in response to inflammatory stimuli in a number of immunological reactions including rheumatoid arthritis. The receptor for IL-1 (IL-1R), in membrane or soluble form, is widely expressed on tissues and organs and exists as two types, type I which is responsible for the expression of the inflammatory effects of IL-1 and type II which may compete for IL-1 and act as a suppressor of the cytokine. Anakinra is a recombinant specific receptor antagonist (IL-1RA) for IL-1 differing from the natural receptor by the addition of a single methionine at the amino terminal end (Table 2). Anakinra therefore acts as a biological response modifier in the treatment of diseases like rheumatoid arthritis. The side effects profile of anakinra is not large with two adverse events, injection site reactions (122 events per 100 patient years) [256] and infection episodes, the most commonly seen detrimental responses to the agent. Injection site reactions occur in up to 73 % of patients but cause cessation of treatment in less than 5 % of affected individuals. Infections, particularly upper respiratory tract infections (URTI), involving a wide variety of organisms have been reported but it has been suggested that the risk of infection is associated with high doses of anakinra and in patients with comorbidities. Septicemia due to *S. aureus*, hemolytic streptococci and *E. coli* occurred after anakinra was added to prednisolone for rheumatoid arthritis [257]. Anakinra provoked reactivation of pulmonary tuberculosis [258] and adenovirus, gastroenteritis, varicella pneumonitis, visceral leishmaniasis and acute Epstein-Barr virus infection occurred in juvenile idiopathic arthritis patients treated with anakinra [259]. A patient with Still's disease treated with anakinra developed systemic inflammatory response syndrome (SIRS) together with ARDS and some other patients with this disease had the cytokine withdrawn because of infections or severe skin reactions [260]. Other reported side effects of anakinra include progression of rheumatoid arthritis [256], exacerbation of Crohn's disease [261], anaphylaxis with a positive skin test to the cytokine [262], cellulitis at injection sites [263] and an interstitial granulomatous reaction which resolved after withdrawal of anakinra and recurred on challenge [264].

3.3.8 Epoetins

Erythropoietin (EPO) is a heavily glycosylated cytokine with three *N*-linked and one *O*-linked oligosaccharide chains that are important for the protein's biological activity and stability. Activity is also dependent on two disulfide bonds between cysteines 7 and 160 and 29 and 32. In both native human EPO and rhEPO (epoetin alfa), the originally secreted molecule is a 166 amino acid peptide

before the carboxy-terminal arginine is removed to give the final active protein of 165 amino acids [86, 265].

In an early study of rhEPO in anemic patients with end-stage renal disease, the main observed adverse effects and their incidences were myalgias 5 %, iron deficiency 43 %, elevated blood pressure 35 % and seizures 5.4 % [266]. Hypertension is a common side effect with approximately one third of dialysis patients affected [267] and hypertension and increased viscosity due to rhEPO may lead to encephalopathy, convulsions, cerebral edema and seizures [268]. Thromboembolism is said to be a potential outcome from EPO therapy but controlled studies have not always provided support for this claim [269]. Nevertheless, controlled studies on cancer patients revealed a 1.55-fold higher risk of thromboembolic events with rhEPO therapy than controls [270]. Cerebral ischemia with increased metabolic rate and blood viscosity is a potentially severe side effect of EPO therapy and it has been pointed out that this could limit or halt the use of EPO for neurovascular diseases [265]. EPO receptors have been demonstrated in tumor tissue and the cytokine may assist with tumor angiogenesis, suggesting the possibility of EPO initiating tumor growth or aiding tumor progression [271].

Pure red cell aplasia (PRCA) [272], caused by neutralizing antibodies to epoetin that cross-react with natural erythropoietin, produces a rapid decline in hemaglobin concentration, severe anemia, low reticulocyte count and an almost total absence of red cell precursors. In cases of transfusion-dependent PRCA with neutralizing serum antibodies to EPO, patients should not be switched to another epoetin such as darbepoetin alfa [268]. Development of wheals at former epoetin alfa subcutaneous injection sites on a patient with PRCA following intravenous injection with epoetin beta and darbepoetin alfa, provoked a systemic anaphylaxis/anaphylactoid response and anti-EPO antibodies cross-reactive with epoetin beta and darbepoetin alfa were detected in the serum [273]. Other cases of anaphylaxis to epoetin alfa have occurred [274] and a delayed hypersensitivity reaction in the form of acute exanthematous pustulosis following replacement of epoetin alfa with darbepoetin alfa was reported [5].

In a large randomized, double-blind controlled trial comparing two different administration schedules of darbepoetin alfa for the treatment of chemotherapy-induced anemia [92], serious adverse events that were treatment-related occurred in 3 % of the 672 patients. Deep vein thrombosis was seen in 1.1–1.7 % of patients, pulmonary embolism in 0.8 % and hypertension in 0.3–1.1 %. No antibodies to darbepoetin alfa were found in the serum of any patient. An investigation of the effect of darbepoetin alfa on exercise tolerance in anemic patients with symptomatic chronic heart failure revealed three events with a >5 % difference in incidence between the treatment and placebo groups: neurological signs and symptoms; upper respiratory tract infections; and joint-related signs and symptoms [93].

3.3.9 *Bone Morphogenetic Proteins*

BMPs are growth factors inducing the formation of bone and cartilage and important signaling proteins in some disease states such as adenocarcinoma and the progression of colon cancer. Of the 20 BMPs so far identified [275, 276], six, numbers 2 to 7, belong to the TGFβ cytokine family (Table 1). BMP-2 and BMP-7 promote the differentiation of osteoblasts and, on the basis of this action, recombinant forms of both cytokines (rhBMP-2 and rhBMP-7) are approved by the FDA for specific uses in orthopedic, oral and maxillofacial surgery and implant dentistry although up to 85 % of their usage is said to be off-label [277].

Safety studies on BMPs have a curious and troubling history of discrepancies due to the possible involvement of inadequate peer review and editorial oversight [97]. More recent results with rhBMP-2 indicate a much higher incidence of side effects and complications than reported in the original peer reviewed and industry-sponsored work. No adverse events following rhBMP-2 administration were reported in thirteen of the original studies involving analyses of 780 patients due, it seems, to methodological bias against the control group. Identification of previously unpublished adverse effects, study inconsistencies, and a comparative review of FDA material, revealed an adverse events frequency associated with rhBMP-2 in spine fusion of 10–50 % [97]. In a retrospective review of adverse events associated with the use of rhBMP-2 in spinal surgery, a search of the Manufacturer and User Facility Device Experience Database for the period July 2002 to August 2011 was undertaken. Only 4 of 834 reports described procedures using rhBMP-2 in accordance with the approved indication while 370 reports (44.4 %) stated that the patient required revision surgery or other invasive interventions to deal with the adverse event. The adverse events reported were swelling; fluid collection; osteolysis; pain/radiculopathy; heterotropic bone; pseudarthrosis; surgical site infections and other wound complications; thromboembolic events; respiratory distress; cancer; and some others [98]. In an examination of the prevalence and complications of BMP use in spinal fusion procedures, Cahill et al. [278] identified the following complications and incidences: vertebral osteolysis 44 %; graft migration 31 %; graft subsidence 27 %; formation of neutralizing antibodies to BMP-2 26 %; ectopic/heterotopic bone formation 7 %; and hematoma 3 %.

In accordance with the classification followed in the recent review of rhBMP-2-associated complications by

Tannoury and Howard [99], the main adverse events to this cytokine are considered under the headings of those occurring during lumbar spine surgery and those seen in or after cervical spine surgery. In posterior and transforaminal interbody fusions in particular, postoperative radiculitis may occur after BMP-2 use during lumbar spine surgery, occurring, it seems, without neural compression and possibly because of the formation of ectopic bone. Postoperative radiculitis was estimated to occur in 11.4 % of patients who underwent a minimally invasive transforaminal interbody fusion procedure [279]. Postoperative nerve injury and ectopic bone formation with the use of rhBMP-2 has been reported, the latter with an incidence of 20.8 % compared to 8.3 % in the absence of the cytokine. Other major adverse events seen following BMP-2 use in lumbar spine surgery include vertebral osteolysis, edema and retrograde ejaculation [99, 280]. Although the formation of neutralizing antibodies to the bone growth protein is a theoretical concern, there is so far no clinical evidence that that has occurred. Reviews of complications after the use of rhBMP-2 in cervical spine surgery have revealed an incidence of 43 % for osteolysis and graft subsidence and 5.5–17 % for dysphagia and swelling (in particular, the neck) with respiratory difficulties [278, 281]. Other adverse events include hematoma with high doses of rhBMP-2; lucency and subsidence of fusion levels amongst allograft and demineralized bone matrix patients; and complications in posterior cervical fusion with BMP such as neurologic decline, wound complications and asymptomatic heterotopic ossification [99].

Besides being a growth factor, BMP-2 receptors are expressed on some tumor cells and it is therefore not surprising that the cytokine has been investigated as a potential carcinogen in studies on breast cancer cells, malignant human gastric epithelial cells, oral cell carcinoma and the risk of subsequent pancreatic cancer. Concern for the carcinogenic potential of rhBMP-2 was somewhat reinforced by a 2010 FDA Orthopedic and Rehabilitation Devices Advisory Panel report on the Amplify™ rhBMP-2 matrix [282] showing increased cancer rates among BMP-2-treated patients. At $\leq$24 months cancer incidences were patients 5 % and controls 0.9 %; at 60 months, patients 5 %, controls 2.1 % [282]. Other studies have reported tumor-enhancing, tumor-suppressing, or no dependence effects [99, 283, 284] so, in this situation of uncertainty, it may be prudent to very carefully consider the question of the use of BMPs together with the risk to benefit ratio for cancer patients requiring spinal fusion.

Less widely used than rhBMP-2 which promotes better bone growth, rhBMP-7, also known as osteogenic protein 1 (OP-1), is a multifunctional growth factor thought to have other possible therapeutic applications besides bone and cartilage growth and development. These hoped-for potential applications include identification and treatment of cancer, and a beneficial role in Parkinson's disease, ankylosing spondylitis, diabetes and asthma as well as some diseases of the kidney, liver, intestine, brain, adipose tissue and cardiovascular system [104]. Apart from an FDA Public Health Notification of life-threatening complications associated with rhBMP, including rhBMP-7, in cervical spine fusion, and the reminder that rhBMPs are contraindicated in skeletally immature or pregnant patients and those with hypersensitivity to the protein, studies on, and reports of, adverse events to BMP-7 are not yet extensive. This is in contrast to the large and rapidly growing literature on rhBMP-2 induced adverse events. In an early clinical trial designed to evaluate rhBMP-7 in the treatment of tibial reunions, adverse events were reported to be mild or moderate and non-serious, for example, fever, nausea and vomiting, leg edema and discomfort and hematoma at the operative site. Low levels of anti-BMP-7 antibodies were detected in 10 % of the treated patients but all titres were low with no related adverse events [285]. With the possibility in mind that risks following the use of rhBMP-7 in anterior cervical fusion procedures might not be as high as seen with BMP-2, the safety of rhBMP-7 was examined in 123 patients undergoing anterior cervical discectomy and fusion using interbody cages. Assessed over the first 30 days, there were no deaths or reoperations but 2.4 % of patients experienced brachalgia and dysphagia [286]. Although a slight increase on post-operative prevertebral swelling was seen on radiological evaluation, this was judged to be not clinically significant. The authors concluded that BMP-7 can be used safely in anterior cervical fusion surgery.

Pleomorphic sarcomas around heterotropic bone nodules were found in some animals during a study of rhBMP-7 in rats and 5 cancers, 4 nonosseous and 1 a recurrence of chondrosarcoma, occurred in 570 humans receiving OP-1. Note, however, published material on BMP-7 and carcinogenesis that is not related to manufacturers does not appear to be available [287].

3.3.10 Metreleptin

Leptin, a 167 amino acid protein of MW 16 kDa produced by a number of different cells in different organs but primarily adipocytes, helps to control energy homeostasis and body weight by adjusting hunger and energy expenditure to regulate fat stores [288]. It also regulates some neuroendocrine functions and other physiological processes, many yet to be defined. In February 2014, the FDA approved metreleptin, a recombinant analog of leptin (Table 2) as replacement therapy to treat leptin deficiency in patients with congenital or acquired generalized lipodystrophy.

Metreleptin is not to be used in patients with general obesity, for HIV-related lipodystrophy or in patients with metabolic diseases (e.g., diabetes mellitus) without concurrent generalized lipodystrophy. Neutralizing antibodies may develop to metreleptin and because of this and the possibility of the occurrence of T cell lymphoma in patients with acquired generalized lipodystrophy, the protein is only available under the Myalept Risk Evaluation and Mitigation Strategy Program.

Kinetic studies on metreleptin in relation to age, sex, production and clearance, demonstrated that the recombinant cytokine's half-life was 3.4 ± 1.5 h, older subjects show decreased production and clearance rates, and females have higher baseline levels which increase with increasing adiposity. In fact, an increased body mass is associated with higher endogenous leptin levels, a higher rate of production and a longer half-life [289].

Common side effects observed in early clinical trials were headache, weight loss, hypoglycemia and abdominal pain. In a randomized, double-blind study designed to evaluate the weight-lowering effect in human obesity of an amylin/leptin drug combination using pramlintide/metreleptin, adverse events specifically due to metreleptin occurring with an incidence of ≥5 % were injection site reactions 66.7 %, nausea 25.9 %, nasopharyngitis 7.4 %, headache 7.4 %, hypersensitivity 7.4 % and vomiting 7.4 % [108]. Injection site reactions often include inflammation, erythema and ecchymoses. Other potentially more serious reported adverse events to metreleptin include the worsening of renal disease [290], the production of anti-metreleptin antibodies [291, 292] and development of T cell lymphomas [292, 293].

4 Concluding Remarks

Cytokines have already had a revolutionary impact on our understanding of cellular functions and extracellular messaging but although their biological effects seem to offer great potential for the treatment of a wide range of human conditions, their pleiotropism, potency, and complexity to produce cytokine 'cocktails' with signaling cascades and accompanying side effects, demands caution in attempts to introduce individual members into the clinic. The range of biological events set in motion even by individual cytokines, warns of the possibility of unwanted side effects and the resultant caution is reflected by the relatively small number of cytokines currently approved by regulatory agencies and reviewed here. Good examples of the sorts of doubts that exist and why clinical developments proceed so cautiously, have been illustrated with interferons, aldesleukin, becaplermin, palifermin and bone morphogenetic proteins. A glance at Table 2 shows that 14 of the 20 listed FDA-approved cytokine preparations (18 different cytokines with 3 also in pegylated form) carry warnings with 10 of these being black box warnings. Having been used in human therapy for many years, interferon alfa preparations are well known for a number of often widely different, potentially serious, side effects specified in boxed warnings. The diverse nature of these side effects concerning neuropsychiatric, autoimmune, ischemic and infection adverse events, together with the therapeutic benefits of interferons are a good illustration of the two-edged nature of cytokine pleiotropism. Becaplermin, a growth factor, causes cell proliferation so the possibility of malignancy with its continued use needs to be kept in mind, especially in patients with known cancers. Likewise, palifermin, another growth factor and a valuable treatment for mucositis in cancer patients, has with it the potential for stimulation of tumor growth, especially since its complementary receptors occur widely on many different cell types in the body. Aldesleukin, the recombinant IL-2, is a potent activator of T lymphocytes and stimulates immune responses to cancer, producing regression of tumors in metastatic renal cell carcinoma and melanoma. However, this activity can also lead to a range of adverse cardiac and pulmonary events. Perhaps the best example of the safety uncertainties and benefits-to-risk ratios associated with these heterogeneous, pleiotropic cell regulators, is seen with the bone morphogenetic proteins BMP-2 and BMP-7. Already with a troubled history of under-reported adverse events, in the post-marketing period these growth factors are currently a focus of attention and speculation as potential carcinogens. BMP-2 receptors are expressed on some tumor cells and increased rates of cancer following its use have been reported but, in keeping with the complexity of cytokine-induced responses, and the difficulty of ascribing adverse effects to causes, tumor-suppressing or no dependence effects have also been reported.

In any consideration of adverse event profiles of approved biologics, two other potentially important contributing factors need to be recognized. Any drug brought to market under the Orphan Drug Designation program where development was mediated because of the rarity of a condition, may not reveal its full spectrum of adverse effects until well into its post-marketing period since a relatively smaller number of administrations results from a smaller pool of patients. The dose of a particular cytokine may also be of critical importance in avoiding dangerous side effects by narrowing the spectrum of activity of the pleiotropic agent and tipping the balance to a specific biological activity [15].

Lest the attention drawn in this review to the known and potential toxicities of cytokines obscures their often substantial benefits and the improved outcomes they can produce, readers are reminded that the focus here on side

effects does not negate the clear clinical improvements each of the approved cytokines can bring. Cytokines may indeed sometimes provoke a wide range and number of toxicities and adverse events but, overall, the second edge of their pleiotropism usually more than offsets the side effects profiles and this is reflected in their lists of indications and approved regulatory status. In fact, in some cases, toxicities correspond with improved outcomes. For example, in an assessment of the significance of autoimmunity in melanoma patients treated with interferon alfa-2b, interferon-induced autoimmunity was found to be a prognostic marker for improved relapse-free, and overall, survival [294].

Together with monoclonal antibodies, chimeric fusion proteins, vaccines, a range of recombinant enzymes, hormones, various receptor proteins, a few purified approved toxins and some cell-based and non-specific adjuvant therapies, the pool of over 130 cytokines seems to offer, via genetically engineered preparations or modifications of the natural proteins, the potential of a major expansion of biologic therapies, some revolutionary, over the forthcoming decade or less. Meanwhile, the relatively few currently approved recombinant cytokines are already revealing their true natures in relation to their efficacy and side effects, influenced above all by their pleiotropism, redundancies and potencies. The large range of activities displayed by the family of cytokine proteins, together with their potential for the treatment of many different diseases and our steadily accumulating knowledge and experience with the small number currently used clinically, may indeed end up helping to achieve the prediction that the future of therapy belongs to the emerging biologics.

Conflict of Interest No sources of funding were used to assist in the preparation of this study. Brian A. Baldo has no conflicts of interest that are directly relevant to the content of this study.

References

1. FDA. CDER Therapeutic Biologic Products. CDER billable biologic product list. http://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/default.htm. Accessed 1 June 2014.
2. FDA. User fee billable biologic products and potencies approved under section 351 of the PHS Act. http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm122936.htm. Accessed 1 June 2014.
3. Leader B, Baca QJ, Golan DE. Protein therapeutics: a summary and pharmacological classification. Nat Rev Drug Discov. 2008;7:21–39.
4. FDA. For Industry. Developing products for rare diseases and conditions. http://www.fda.gov/forindustry/DevelopingProductsforrareDiseasesConditions/default.htm. Accessed 1 June 2014.
5. Baldo BA, Pham NH. Drug allergy. Clinical aspects, diagnosis, mechanisms, structure-activity relationships. New York: Springer; 2013.
6. Ducancel F, Muller BH. Molecular engineering of antibodies for therapeutic and diagnostic purposes. mAbs 2012;4:445–57.
7. Kaneko E, Niwa R. Optimizing therapeutic antibody function: progress with Fc domain engineering. BioDrugs. 2011;25:1–11.
8. European Medicines Agency. Committee for medicinal products for human use. Guidelines on the clinical investigation of the pharmacokinetics of therapeutic proteins. 2005. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003031.pdf. Accessed 1 June 2014.
9. Alley SC, Okeley NM, Senter PD. Antibody-drug conjugates: targeted drug delivery for cancer. Curr Opin Chem Biol. 2010;14:529–37.
10. Hansel TT, Kropshofer H, Singer T, et al. The safety and side effects of monoclonal antibodies. Nat Rev Drug Discov. 2010;9:325–38.
11. Baldo BA. Adverse events to monoclonal antibodies used for cancer therapy. Focus on hypersensitivity responses. OncoImmunology 2013;e26333. http://dx.doi.org/10.4161/onci.26333.
12. Dy GK, Adjei AA. Understanding, recognizing, and managing toxicities of targeted anticancer therapies. CA Cancer J Clin. 2013;63:249–79.
13. Baldo BA, Pagani M. Adverse events to non-targeted and targeted chemotherapeutic agents: emphasis on hypersensitivity responses. Immunol Allergy Clin N Am. 2014;34:565–96.
14. Vazquez-Lombardi R, Roome B, Christ D. Molecular engineering of therapeutic cytokines. Antibodies. 2013;2:426–51.
15. Vacchelli E, Eggermont A, Fridman WH, et al. Immunostimulatory cytokines. OncoImmunology. 2013;e24850. http://dx.doi.org/10.4161/onci.24850.
16. Wurm F, Bernard A. Large-scale transient expression in mammalian cells for recombinant protein production. Curr Opin Biotechnol. 1999;10:156–9.
17. Brannigan JA, Wilkinson AJ. Protein engineering 20 years on. Nature Rev Mol Cell Biol. 2002;3:964–70.
18. Egrie JC, Browne JK. Development and characterization of novel erythropoiesis stimulating protein (NESP). Brit J Cancer. 2001;84(Suppl. 1):3–10.
19. Borish LC, Steinke JW. 2. Cytokines and chemokines. J Allergy Clin Immunol. 2003;111:S460–75.
20. Steinke JW, Borish L. 3. Cytokines and chemokines. J Allergy Clin Immunol. 2006;117:S441–5.
21. Tayal V, Kalra BS. Cytokines and anti-cytokines as therapeutics—an update. Eur J Pharmacol. 2008;579:1–12.
22. Vacchelli E, Galluzzi L, Eggermont A, et al. Immunostimulatory cytokines. OncoImmunology. 2012;1:493–506. http://dx.doi.org/10.4161/onci.20459.
23. Tato CM, Cua DJ. Snapshot: Cytokines I. Cell. 2008;132:324-e1.
24. Tato CM, Cua DJ. Snapshot: Cytokines II. Cell. 2008;132:500-e1.
25. Tato CM, Cua DJ. Snapshot: Cytokines III. Cell. 2008;132:900-e1.
26. Tato CM, Cua DJ. Snapshot: Cytokines IV. Cell. 2008;132:1062-e1.
27. Kyoto Encyclopedia of Genes and Genomes. http://www.genome.jp/kegg/.
28. Feld JJ, Hoofnagle JH. Mechanism of action of interferon and ribavirin in treatment of hepatitis C. Nature. 2005;436:967–72.
29. Pegasys® (Peginterferon alfa-2a). FDA: Highlights of prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103964s5204lbl.pdf. Accessed 1 June 2014.
30. Pegasys® (Peginterferon alfa-2a). EMA: Scientific discussion. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Scientific_Discussion/human/000395/WC500039192.pdf. Accessed 1 June 2014.
31. Fried MW. Side effects of therapy of hepatitis C and their management. Hepatology. 2002;36:s237–44.
32. Constant A, Castera L, Dantzer R, et al. Mood alterations during interferon-alfa therapy in patients with chronic hepatitis C: evidence for an overlap between manic/hypomanic and depressive symptoms. J Clin Psychiatry. 2005;66:1050–7.

33. Negro F. Adverse effects of drugs in the treatment of viral hepatitis. Best Pract Res Clin Gastroenterol. 2010;24:183–92.
34. Poreaux C, Bronowicki J-P, Debouverie M, et al. Managing generalized interferon-induced eruptions and the effectiveness of desensitization. Clin Exp Allergy. 2014;44:756–64.
35. Intron®A (Interferon alfa-2b). FDA: Product information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103132s5096lbl.pdf. Accessed 1 June 2014.
36. Kraus MR, Schäfer A, Faller H, et al. Psychiatric symptoms in patients with chronic hepatitis C receiving interferon alfa-2b therapy. J Clin Psychiatry. 2003;64:708–14.
37. Laguno M, Murillas J, Blanco JL, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin plus ribavirin for treatment of HIV/HCV co-infected patients. AIDS. 2004;18:F27–36.
38. Kraus MR, Schäfer A, Csef H, et al. Psychiatric side effects of pegylated interferon alfa-2b as compared to conventional interferon alfa-2b in patients with chronic hepatitis C. World J Gastroenterol. 2005;11:1769–74.
39. PegIntron® (Peginterferon alfa-2b). FDA: Highlights of prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/103949s5172lbl.pdf. Accessed 1 June 2014.
40. Sylatron® (Peginterferon alfa-2b). FDA: Highlights of prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103949s5153lbl.pdf. Accessed 1 June 2014.
41. Avonex® (Interferon beta-1a). FDA: Highlights of prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103628s5189lbl.pdf. Accessed 1 June 2014.
42. Rudick RA, Ransohoff RM, Lee JC, et al. In vivo effects of interferon beta-1a on immunosuppressive cytokines in multiple sclerosis. Neurology. 1998;50:1294–300.
43. Walther EU, Hohlfeld R. Multiple sclerosis: side effects of interferon beta therapy and their management. Neurology. 1999;53:1622–7.
44. Markowitz CE. Interferon-beta. Mechanism of action and dosing issues. Neurology. 2007;68(suppl 4):S8–11.
45. Kieseier BC. The mechanism of action of interferon-β in relapsing multiple sclerosis. CNS Drugs. 2011;25:491–502.
46. Betaseron® (Interferon beta-1b). FDA: Highlights of prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103471s5185lbl.pdf. Accessed 5 June 2014.
47. Actimmune® (Interferon gamma-1b). FDA: Highlights of prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103836s5098LBL.pdf. Accessed 5 June 2014.
48. Ealick SE, Cook WJ, Vijay-Kumar S, et al. Three-dimensional structure of recombinant human interferon-gamma. Science. 1991;252:698–702.
49. Thiel DJ, le Du MH, Walter RL, et al. Observation of an unexpected third receptor molecule in the crystal structure of human interferon-gamma receptor complex. Structure. 2000;8:927–36.
50. Schroder K, Hertzog PJ, Ravasi T, et al. Interferon-gamma: an overview of signals, mechanisms and functions. J Leukoc Biol. 2004;75:163–89.
51. Schoenborn JR, Wilson CB. Regulation of interferon-gamma during innate and adaptive immune responses. Adv Immunol. 2007;96:41–101.
52. Neupogen® (Filgrastim). FDA: Highlights of prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103353s5147lbl.pdf. Accessed 5 June 2014.
53. Nivestim® (Filgrastim). EMA: CHMP Assessment Report. 2. Scientific discussion, p. 4. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Public_assessment_report/human/001142/WC500093664.pdf. Accessed 5 June 2014.
54. Bonilla MA, Dale D, Zeidler C, et al. Long-term safety of treatment with recombinant human granulocyte colony-stimulating factor (r-metHuG-CSF) in patients with severe congenital neutropenias. Br J Haematol. 1994;88:723–30.
55. Cottle TE, Fier CJ, Donadieu J, et al. Risk and benefit of treatment of severe chronic neutropenia with granulocyte colony-stimulating factor. Semin Hematol. 2002;39:134–40.
56. Molineux G. The design and development of pegfilgrastim (PEG-rmetHuG-CSF, Neulasta). Curr Pharm Des. 2004;10:1235–44.
57. Metcalf D. The CSFs and cancer. Nat Rev Cancer. 2010;10:425–34.
58. Neulasta® (Pegfilgrastim). FDA: Physician package insert. http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/pegfamg013102LB.pdf. Accessed 5 June 2014.
59. Tbo-filgrastim. FDA: Highlights of prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125294s0000lbl.pdf. Accessed 5 June 2014.
60. del Giglio A, Eniu A, Ganea-Motan D, et al. XM02 is superior to placebo and equivalent to Neupogen® in reducing the duration of severe neutropenia and the incidence of febrile neutropenia in cycle I in breast cancer patients receiving docetaxel/doxorubicin chemotherapy. BMC Cancer. 2008;8:332–8.
61. Devine MM. Tbo-filgrastim: The first biosimilar G-CSF. Hematology/Oncology Pharmacy Association. http://www.hoparx.org/apps/ws_resource/index.php?task=view_article&article_id=137&category_id=243&section_id=20. Accessed 5 June 2014.
62. Leukine® (Sargramostim). FDA Advisory Committee Briefing Package, May 3, 2013. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM350156.pdf. Accessed 5 June 2014.
63. Hercus TR, Broughton SE, Ekert PG, et al. The GM-CSF receptor family: mechanism of activation and implications for disease. Growth Factors. 2012;30:63–75.
64. Neumega® (Oprelvekin). FDA label information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/103694s1008lbl.pdf. Accessed 5 June 2014.
65. Heinrich PC, Behrmann I, Haan S, et al. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. Biochem J. 2003;374:1–20.
66. Vredenburgh JJ, Hussein A, Fisher D, et al. A randomized trial of recombinant human interleukin-11 following autologous bone marrow transplantation with peripheral blood progenitor cells support in patients with breast cancer. Biol Blood Marrow Transplant. 1998;4:134–41.
67. Kaye JA. FDA licensure of Neumega® to prevent severe chemotherapy-induced thrombocytopenia. Stem Cells. 1998;16(suppl 2):207–23.
68. Regranex® (Becaplermin). FDA: Highlights of prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103691s5095lbl.pdf. Accessed 5 June 2014.
69. Steed DL, the Diabetic Ulcer Study Group. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. J Vasc Surg. 1995;21:71–81.
70. Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. Diabetes Care. 1998;21:822–7.
71. Barman Balfour JA, Noble S. Becaplermin. BioDrugs. 1999;11:359–64.
72. Rubin JS, Osada H, Finch PW. Purification and characterization of a newly identified growth factor specific for epithelial cells. Proc Nat Acad Sci. 1989;86:802–6.
73. Kepivance® (Palifermin). FDA: Highlights of prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125103s0120lbl.pdf. Accessed 5 June 2014.

74. Blijlevens N, Sonis S. Palifermin (recombinant keratinocyte growth factor-1): a pleiotropic growth factor with multiple biological activities in preventing chemotherapy- and radiotherapy-induced mucositis. Annals Oncol. 2006;18:817–26.
75. Spielberger R, Stiff P, Bensinger W. Palifermin for oral mucositis after intensive therapy for hematologic malignancies. N Engl J Med. 2004;351:2590–8.
76. King B, Knopp E, Galan A, et al. Palifermin-associated papular eruption. Arch Dermatol. 2009;145:179–82.
77. Proleukin® (Aldesleukin). FDA label information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103293s5130lbl.pdf. http://www.bccancer.bc.ca/NR/rdonlyres/D97FCE53-F952-4718-ACAD-A2DCFF619EE5/64258/Aldesleukin_monograph_1June2013_formatted.pdf. Accessed 5 June 2014.
78. Ravaud A, Negrier S, Lakdja F, et al. Adverse effects of interleukin 2 [Article in French]. Bull Cancer. 1991;78:989–1005.
79. Aldesleukin. BC Cancer Agency Cancer Drug Manual. http://www.bccancer.bc.ca/NR/rdonlyres/D97FCE53-F952-4718-ACAD-A2DCFF619EE5/64258/Aldesleukin_monograph_1June2013_formatted.pdf. Accessed 5 June 2014.
80. Geertsen PF, Gore ME, Negrier S, et al. Safety and efficacy of subcutaneous and continuous intravenous infusion rIL-2 in patients with metastatic renal cell carcinoma. Br J Cancer. 2004;90:1156–62.
81. Spoerl D, Bircher AJ. Drugs that act on the immune system: cytokines and monoclonal antibodies. In: Aronson JK, editor. Side effects of drugs annual 33. Amsterdam: Elsevier; 2011. p. 777–8.
82. Kineret® (Anakinra). FDA: Highlights of prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103950s5136lbl.pdf. Accessed 5 June 2014.
83. Fleischmann RM, Schechtman J, Bennett R, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis. Arthritis Rheum. 2003;48:927–34.
84. Swart JF, Barug D, Möhlmann M, et al. The efficacy and safety of interleukin-1-receptor antagonist anakinra in the treatment of systemic juvenile idiopathic arthritis. Expert Opin Biol Therapy. 2010;10:1743–52.
85. Epogen® (Epoetin alfa). FDA: Highlights of prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103234Orig1s5166_103234Orig1s5266lbl.pdf. Accessed 5 June 2014.
86. Elliott SG, Foote M, Molineux G, editors. Erythropoietins, erythropoietic factors, and erythropoiesis: Molecular, cellular, preclinical, and clinical biology. 2nd ed. Basel: Birkhauser Verlag; 2009.
87. Cheung JY, Miller BA. Molecular mechanisms of erythropoietin signaling. Nephron. 2001;87:215–22.
88. Smith KJ, Bleyer AJ, Little WC, et al. The cardiovascular effects of erythropoietin. Cardiovasc Res. 2003;59:538–48.
89. McKoy JM, Stonecash RE, Cournoyer D, et al. Epoetin-associated pure red cell aplasia: past, present, and future considerations. Transfusion. 2008;48:1754–62.
90. McCullough PA, Barnhart HX, Inrig JK, et al. Cardiovascular toxicity of epoetin alfa in patients with chronic kidney disease. Am J Nephrol. 2013;37:549–58.
91. Aranesp® (Darbepoietin alfa). FDA: Highlights of prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103951Orig1s5173_103951Orig1s5258lbl.pdf. Accessed 5 June 2014.
92. Canon J-L, Vansteenkiste J, Bodoky G, et al. Randomized, double-blind, active-controlled trial of every-3-week darbepoietin alfa for the treatment of chemotherapy-induced anemia. J Natl Cancer Inst. 2006;98:273–84.
93. Ponikowski P, Anker SD, Szachniewicz J, et al. Effect of darbepoietin alfa on exercize tolerance in anemic patients with symptomatic chronic heart failure. J Am Coll Cardiol. 2007;49:753–62.
94. Infuse® Bone Graft/LT-Cage® lumbar tapered fusion device. FDA: Summary of safety and effectiveness data. http://www.accessdata.fda.gov/cdrh_docs/pdf/P000058b.pdf. Accessed 5 June 2014.
95. Chen D, Zhao M, Mundy GR. Bone morphogenetic proteins. Growth Factors. 2004;22:233–41.
96. Bessa PC, Casal M, Reis RL. Bone morphogenetic proteins in tissue engineering: the road from the laboratory to the clinic, part I (basic concepts). J Tissue Eng Regen Med. 2008;2:1–13.
97. Carragee EJ, Hurwitz EL, Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. Spine J. 2011;11:471–91.
98. Woo EJ. Recombinant human bone morphogenetic protein-2: adverse events reported to the Manufacturer and User Facility Device Experience Database. Spine J. 2012;12:894–9.
99. Tannoury CA, An HS. Complications with the use of bone morphogenetic protein 2 (BMP-2) in spine surgery. Spine J. 2014;14:552–9.
100. Baldo BA. Drugs that act on the immune system: cytokines and monoclonal antibodies. In: Aronson JK, editor. Side effects of drugs annual 36. Amsterdam: Elsevier; 2015 (In press).
101. Osigraft® (Bone morphogenetic protein-7). EMA: Scientific discussion. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000293/WC500050378.pdf. Accessed 5 June 2014.
102. Marcias-Silva M, Hoodless PA, Tang SJ, et al. Specific activation of Smad1 signaling pathways by the BMP7 type I receptor, ALK2. J Biol Chem. 1998;273:25628–36.
103. OP-1 Putty (Bone morphogenetic protein-7 putty). FDA: Postmarketing safety surveillance. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM153635.pdf. Accessed 5 June 2014.
104. Recombinant human BMP-7/OP-1: scientific background and collaboration opportunity. http:// http://www.sbhsciences.com/BMP7_info.asp. Accessed 5 June 2014.
105. Myalept® (Metreleptin). FDA: Highlights of prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125390s000lbl.pdf. Accessed 5 June 2014.
106. Tartaglia LA. The leptin receptor. J Biol Chem. 1997;272:6093–6.
107. Myers MG, Cowley MA, Münzberg H. Mechanisms of leptin action and leptin resistance. Annu Rev Physiol. 2008;70:537–56.
108. Ravussin E, Smith SR, Mitchell JA, et al. Enhanced weight loss with pramlintide/metreleptin: an integrated neurohormonal approach to obesity pharmacotherapy. Obesity. 2009;17:1736–43.
109. Margetic S, Gazzola C, Pegg GG, et al. Leptin: a review of its peripheral actions and interactions. Int J Obesity. 2002;26:1407–33.
110. Fattovich G, Giustina G, Favarato S, et al. A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alfa interferon. J Hepatol. 1996;24:38–47.
111. Okanoue T, Sakamoto S, Itoh Y, et al. Side effects of high-dose interferon therapy for chronic hepatitis C. J Hepatol. 1996;25:283–91.
112. Dusheiko G (1997) Side effects of alpha interferon in chronic hepatitis C. Hepatology 26(Issue 3):112S–121S).
113. Fontaine H, Pol S. Side effects of interferon-α in treating hepatitis C virus infection. Transpl Proc. 2001;33:2327–9.

114. Ningrum RA. Human interferon alpha-2b: a therapeutic protein for cancer treatment. Scientifica. 2014. http://dx.doi.org/10.1155/2014/970315.
115. Veronese FM, Pasut G. PEGylation, successful approach to drug delivery. Drug Discov Today. 2005;10:1451–8.
116. Bonaccorso S, Marino V, Biondi M, et al. Depression induced by treatment with interferon-alpha in patients affected by hepatitis C virus. J Affect Discord. 2002;72:237–41.
117. Dieperink E, Ho SB, Thuras P, et al. A prospective study of neuropsychiatric symptoms associated with interferon-alpha-2b and ribavirin therapy for patients with chronic hepatitis C. Psychosomatics. 2003;44:104–12.
118. Hauser P, Khosla J, Aurora H, et al. A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. Mol Psychiatry. 2002;7:942–7.
119. Bonaccorso S, Marino V, Puzella A, et al. Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. J Clin Psychopharmacol. 2002;22:86–90.
120. Kraus MR, Schafer A, Faller H, et al. Paroxetine for the treatment of interferon-alpha-induced depression in chronic hepatitis C. Aliment Pharmacol Ther. 2002;16:1091–9.
121. Capuron L, Neurauter G, Musselman DL, et al. Interferon-alpha-induced changes in tryptophan metabolism. Relationship to depression and paroxetine treatment. Biol Psychiatry. 2003;54:906–14.
122. Schaefer M, Schwaiger M, Pich M, et al. Neurotransmitter changes by interferon-alpha and therapeutic implications. Pharmacopsychiatry. 2003;36(Suppl 3):S203–6.
123. Schaefer M, Horn M, Schmidt F, et al. Correlation betweensI-CAM-1 and depressive symptoms during adjuvant treatment of melanoma with interferon alpha. Brain Behav Immun. 2004;18:555–62.
124. Raison CL, Demetrashvili M, Capuron L, et al. Neuropsychiatric adverse effects of interferon-alpha: recognition and management. CNS Drugs. 2005;19:105–23.
125. Tóthová E, Kafková A, Stecová N, et al. Immune-mediated complications during interferon alpha therapy in chronic myelogenous leukemia. Neoplasma. 2002;49:91–4.
126. Yagyu H, Okada K, Sato S, et al. Pegylated interferon-alpha2b and ribavirin combination therapy induces Hashitoxicosis followed by type 1 diabetes mellitus. Diabetes Res Clin Pract. 2012;95:e52–4.
127. Pinto JL, Pinto ME. Tiroiditis autoinmune inducida por interferón en pacientes con infección por virus de la hepatitis C [Interferon-induced autoimmune thyroiditis in a patient with hepatitis C virus infection.]. Rev Peru Med Exp Salud Publica. 2011;28:382–4.
128. Yılmaz S, Cimen KA. Pegylated interferon alfa-2b induced lupus in a patient with chronic hepatitis B virus infection: case report. Clin Rheumatol. 2009;28:1241–3.
129. Ho V, Mclean A, Shaughan T. Severe systemic lupus erythematosus induced by antiviral treatment for hepatitis C. J Clin Rheumatol. 2008;14:166–8.
130. Abbott IJ, Chang CC, Skinner MJ, et al. Development and management of systemic lupus erythematosus in an HIV-infected man with hepatitis C and B co-infection following interferon therapy: a case report. J Med Case Rep. 2009;3:7289.
131. Agarwal SK, Lal C, Zaidi SH. Lupus activation with cerebritis following pegylated interferon in a hemodialysis patient. Nat Rev Nephrol. 2009;5:599–603.
132. Popescu C, Arama V, Gliga S. Acute pericarditis due to pegylated interferon alpha therapy for chronic HCV hepatitis—case report. BMC Gastroenterol. 2011;11:30.
133. Kuwara A, Ohashi M, Sugiyama M, et al. A case of reversible dilated cardiomyopathy after alpha-interferon therapy in a patient with renal cell carcinoma. Am J Med Sci. 2002;324:331–4.
134. Gupta SK, Glue P, Jacobs S, et al. Single-dose pharmacokinetics and tolerability of pegylated interferon-alpha2b in young and elderly healthy subjects. Br j Clin Pharmacol. 2003;56:131–4.
135. Gressens B, Gohy P. Pericarditis due to interferon-alpha therapy during treatment for chronic hepatitis C. Acta Gastroenterol Belg. 2004;67:301–2.
136. Rauw J, Ahmed S, Petrella T. Pericardial effusion and tamponade following interferon alpha treatment for locally advanced melanoma. Med Oncol. 2012;29:1304–7.
137. Sakabe M, Yoshioka R, Fujiki A. Sick sinus syndrome induced by interferon and ribavirin therapy in a patient with chronic hepatitis C. J Cardiol Cases. 2013;8:173–5.
138. Wang BY, Chang HH, Chen IM, et al. Peginterferon alpha-2b and acute allograft failure in a heart transplant recipient. Ann Thorac Surg. 2010;89:1645–7.
139. Kumar KS, Russo MW, Borczuk AC, et al. Significant pulmonary toxicity associated with interferon and ribavirin therapy for hepatitis C. Am J Gastroenterol. 2002;97:2432–40.
140. Midturi J, Sierra-Hoffman M, Hurley D, et al. Spectrum of pulmonary toxicity associated with the use of interferon therapy for hepatitis C: case report and review of the literature. Clin Infect Dis. 2004;39:1724–9.
141. Kaneko R, Ogawa M, Iwata T, et al. Ursodeoxycholic acid exacerbates peginterferon-induced interstitial pneumonia in a patient with hepatitis C. Clin J Gastroenterol. 2009;2(4):296–9. doi:10.1007/s12328-009-0075-y.
142. Ando S, Kawai K, Kuriyagawa K, et al. Extremely acute exacerbation of interstitial pneumonia after interferonalpha treatment for metastatic renal cell carcinoma. Int J Clin Oncol. 2009;14:171–3.
143. Olivieri D. Desquamative interstitial pneumonitis (DIP) occurring during treatment with pegylated interferon and ribavirin. Respir Med CME. 2009;2:77–9.
144. Kang EJ, Kim DK, Jeon SR, et al. Interstitial pneumonitis in a patient with chronic hepatitis C and chronic renal failure on interferon therapy. Korean J Gastroenterol. 2011;58:47–52.
145. Foster GR, Zeuzem S, Pianko S, et al. Decline in pulmonary function during chronic hepatitis C virus therapy with modified interferon alfa and ribavirin. J Viral Hepat. 2013;20:e115–23.
146. Yamamoto S, Tomita Y, Hoshida Y, et al. Interstitial pneumonia induced by combined intraarterial 5-fluorouracil and subcutaneous interferon-alpha therapy for advanced hepatocellular carcinoma. J Gastroenterol. 2004;39:793–7.
147. Tokita H, Fukui H, Tanaka A, et al. Circulating KL-6 level at baseline is a predictive indicator for the occurrence of interstitial pneumonia during interferon treatment for chronic hepatitis C. Hepat Res. 2003;26:91–7.
148. Abi-Nassif S, Mark EJ, Fogel RB, et al. Pegylated interferon and ribavirin-induced pneumonitis with ARDS. Chest. 2003;124:406–10.
149. Kalambokis G, Stefanou D, Arkoumani E, et al. Fulminant bronchiolitis obliterans organizing pneumonia following 2 d of treatment with hydroxyurea, interferon-alpha and oral cytarabine ocfosfate for chronic myelogenous leukemia. Eur J Haematol. 2004;73:67–70.
150. Legroux-Crespel E, Lafaye S, Mahé E, et al. Seizures during interferon alpha therapy: three cases in dermatology [Article in French]. Ann Dermatol Venereol. 2003;130:202–4.
151. Tan EK, Chan LL, Lo YL. "Myorhythmia" slow facial tremor from chronic interferon alpha-2a usage. Neurology. 2003;61:1302–3.
152. Jabbari H, Fakharzadeh E, Merat S, et al. Bell's palsy associated with chronic HCV infection before and during peginterferon alfa and ribavirin therapy. Arch Iran Med. 2011;14:204–5.

153. Kataoka I, Shinagawa K, Shiro Y, et al. Multiple sclerosis associated with interferon-alpha therapy for chronic myelogenous leukemia. Am J Hematol. 2002;70:149–53.
154. Matsuo T, Takabatake R. Multiple sclerosis-like disease secondary to alpha interferon. Ocul Immunol Inflamm. 2002;10: 299–304.
155. LaRochelle JS, Karp BI. Restless legs syndrome due to interferon-alpha. Mov Disord. 2004;19:730–1.
156. Boonyapisit K, Katirji B. Severe exacerbation of hepatitis C-associated vasculitic neuropathy following treatment with interferon alpha: a case report and literature review. Muscle Nerve. 2002;25:909–13.
157. Hwang I, Calvit TB, Cash BD, et al. Bell's palsy: a rare complication of interferon therapy for hepatitis C. Dig Dis Sci. 2004;49:619–20.
158. Hoare M, Woodall T, Alexander GJ. Bell's palsy associated with IFN-alpha and ribavirin therapy for hepatitis C virus infection. J Interferon Cytokine Res. 2005;25:174–6.
159. Perlemuter G, Bodaghi B, Le Hoang P, et al. Visual loss during interferon-alpha therapy in hepatitis C virus infection. J Hepatol. 2002;37:701–2.
160. Gupta R, Singh S, Tang R, et al. Anterior ischemic optic neuropathy caused by interferon alpha therapy. Am J Med. 2002;112:683–4.
161. Vial T, Descotes J, Braun F, et al. Drugs that act on the immune system: cytokines and monoclonal antibodies. In: Aronson JK, editor. Side effects of drugs annual 28. Amsterdam: Elsevier; 2005. p. 418–9.
162. Monzani F, Caraccio N, Dardano A, et al. Thyroid autoimmunity and disfunction associated with type I interferon therapy. Clin Exp Med. 2004;3:199–210.
163. Prummel MF, Laurberg P. Interferon-alpha and autoimmune thyroid disease. Thyroid. 2003;13:547–51.
164. Tran HA, Reeves GEM, Jones TL. The natural history of interferon-a2b-induced thyroiditis and its exclusivity in a cohort of patients with chronic hepatitis C infection. Q J Med. 2009;102:117–22.
165. Soza A, Everhart JE, Ghany MG, et al. Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. Hepatology. 2002;36:1273–9.
166. Herishanu Y, Trestman S, Kirgner I, et al. Autoimmune thrombocytopenia in chronic myeloid leukemia treated with interferon-alpha: differential diagnosis and possible pathogenesis. Leuk Lymphoma. 2003;44:2103–8.
167. Fujii H, Kitada T, Yamada T, et al. Life-threatening severe immune thrombocytopenia during alpha-interferon therapy for chronic hepatitis C. Hepatogastroenterology. 2003;50:841–2.
168. Arimura K, Arima N, Ohtsubo H, et al. Severe autoimmune thrombocytopenic purpura during interferon-alpha therapy for chronic myelogenous leukemia. Acta Haematol. 2004;112: 217–8.
169. Andres E, Loukili NH, Ben Abdelghani M, et al. Pernicious anemia associated with interferon-alpha therapy and chronic hepatitis C infection. J Clin Gastroenterol. 2004;38:382.
170. Alabdulaaly A, Rifkind J, Solow H, et al. Rescue of interferon induced bone marrow aplasia in a patient with chronic myeloid leukemia by allogeneic bone marrow transplant. Leuk Lymphoma. 2004;45:175–7.
171. Chang CS, Yan SL, Lin HY, et al. Pure red cell aplasia caused by pegylated interferon-a-2a plus ribavirin in the treatment of chronic hepatitis C. World J Gastroenterol. 2011;17:2155–8.
172. Zuber J, Martinez F, Droz D, et al. Alpha-interferon-associated thrombotic microangiopathy: a clinicopathologic study of 8 patients and review of the literature. Med (Baltimore). 2002;81: 321–31.
173. Nishimura S, Miura H, Yamada H, et al. Acute onset of nephrotic syndrome during interferon-alpha retreatment for chronic active hepatitis C. J Gastroenterol. 2002;37:854–8.
174. Ohashi N, Yonemura K, Sugiura T, et al. Withdrawal of interferon-alpha results in prompt resolution of thrombocytopenia and hemolysis but not renal failure in hemolytic uremic syndrome caused by interferon-alpha. Am J Kidney Dis. 2003;41:E10.
175. Fisher ME, Rossini M, Simmons E, et al. A woman with chronic hepatitis C infection and nephrotic syndrome who developed multiple renal lesions after interferon alfa therapy. Am J Kidney Dis. 2004;44:567–73.
176. Gordon A, Menahem S, Mitchell J, et al. Combination pegylated interferon and ribavirin therapy precipitating acute renal failure and exacerbating IgA nephropathy. Nephrol Dial Transplant. 2004;19:2155.
177. Stadler R, Mayer-da-Silva A, Bratzke B, et al. Interferons in dermatology. J Am Acad Dermatol. 1989;20:650–6.
178. Asnis LA, Gaspari AA. Cutaneous reactions to recombinant cytokine therapy. J Am Acad Dermatol. 1995;33:393–410.
179. Seckin D, Durusoy C, Sahin S. Concomitant vitiligo and psoriasis in a patient treated with interferon alfa-2a for chronic hepatitis B infection. Pediatr Dermatol. 2004;21:577–9.
180. Grossmann S, Teixeira R, de Aguiar MCF, et al. Exacerbation of oral lichen planus lesions during treatment of chronic hepatitis C with pegylated interferon and ribavirin. Eur J Gastroenterol Hepatol. 2008;20:702–6.
181. Sato M, Sueki H, Iijima M. Repeated episodes of fixed eruption 3 months after discontinuing pegylated interferon-alpha-2b plus ribavirin combination therapy in a patient with chronic hepatitis C virus infection. Clin Exp Dermatol. 2009;34:e814–7.
182. Benito-León J, Borbujo J, Cortés L. Cutaneous mucinoses complicating interferon beta-1b therapy. Eur Neurol. 2002;47:123–4.
183. Durelli L, Verdun E, Barbero P, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet. 2002;359:1453–60.
184. Hartung HP, Munschauer F III, Schellekens H. Significance of neutralizing antibodies to interferon beta during treatment of multiple sclerosis: expert opinions based on the Proceedings of an International Consensus Conference. Eur J Neurol. 2005;12:588–601.
185. Bahri DM, Khiari H, Essouri A, et al. Systemic lupus erythematosus induced by interferon beta1 therapy in a patient with multiple sclerosis. Fundam Clin Pharmacol. 2012;26:210–1.
186. Sladkova V, Mares J, Lubenova B, et al. Drug-induced systemic lupus erythematosus in interferon beta-1b therapy. Neuro Endocrinol Lett. 2011;32:4–6.
187. Szilasiová J, Gdovinová Z, Jautová J, et al. Cutaneous vasculitis associated with interferon [beta]-1b treatment for multiple sclerosis. Clin Neuropharmacol. 2009;32:301–3.
188. Kreisler A, de Seze J, Stojkovic T, et al. Multiple sclerosis, interferon beta and clinical thyroid dysfunction. Acta Neurol Scand. 2003;107:154–7.
189. Polman CH, Jansen PH, Jansen C, et al. A rare, treatable cause of relapsing encephalopathy in an MS patient on interferon beta therapy. Neurology. 2003;61:719.
190. Guijarro C, Benito-León J, Bermejo-Pareja F. Widespread urticaria due to intramuscular interferon beta-1a therapy for multiple sclerosis. Neurol Sci. 2011;32:309–11.
191. Rosa DJ, de Matias FA, Cedrim SD, et al. Acute acneiform eruption induced by interferon beta-1b during treatment for multiple sclerosis. An Bras Dermatol. 2011;86:336–8.
192. Nathan CF, Murray HW, Wiebe ME, et al. Identification of interferon-gamma as the lymphokine that activates human

macrophage oxidative metabolism and antimicrobial activity. J Exp Med. 1983;158:670–89.
193. Sidman CL, Marshall JD, Shultz LD, et al. Gammainterferon is one of several direct B cell-maturing lymphokines. Nature. 1984;309:801–3.
194. Kurzrock R, Quesada JR, Talpaz M, et al. Phase I study of multiple dose intramuscularly administered recombinant gamma interferon. J Clin Oncol. 1986;4:1101–9.
195. Kahan A, Amor B, Menkes CJ, et al. Recombinant interferon-gamma in the treatment of systemic sclerosis. Am J Med. 1989;87:273–7.
196. Honoré I, Nunes H, Groussard O, et al. Acute respiratory failure after interferon-gamma therapy of end-stage pulmonary fibrosis. Am J Respir Crit Care Med. 2003;167:953–7.
197. Raghu G, Brown KK, Bradford WZ, et al. Idiopathic Pulmonary Fibrosis Study Group. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2004;350:125–33.
198. Carvalho CR, Kairalla RA, Schettino GP. Acute respiratory failure after interferon-gamma therapy in IPF. Am J Respir Crit Care Med. 2004;169:543–4.
199. Vlachoyiannopoulos PG, Tsifetaki N, Dimitriou I, et al. Safety and efficacy of recombinant gamma interferon in the treatment of systemic sclerosis. Ann Rheum Dis. 1996;55:761–8.
200. Yamamoto N, Nishigaki K, Ban Y, et al. Coronary vasospasm after interferon administration. Br J Urol. 1998;81:916–7.
201. Ault BH, Stapleton FB, Gaber L, et al. Acute renal failure during therapy with recombinant human gamma interferon. N Engl J Med. 1988;319:1397–400.
202. Nair S, Ernstoff MS, Bahnson RR, et al. Interferon-induced reversible acute renal failure with nephrotic syndrome. Urology. 1992;39:169–72.
203. Horn TD, Altomonte V, Vogelsang G, et al. Erythroderma after autologous bone marrow transplantation modified by administration of cyclosporine and interferon gamma for breast cancer. J Am Acad Dermatol. 1996;34:413–7.
204. Metcalf D. The colony-stimulating factors and cancer. Cancer Immunol Res. 2013;1:351–6.
205. Takatsuka H, Takemoto Y, Mori A, et al. Common features in the onset of ARDS after administration of granulocyte colony-stimulating factor. Chest. 2002;121:1716–20.
206. Gertz MA, Lacy MQ, Bjornsson J, et al. Fatal pulmonary toxicity related to the administration of granulocyte colony-stimulating factor in amyloidosis: a report and review of growth factor-induced pulmonary toxicity. J Hematother Stem Cell Res. 2000;9:635–43.
207. Couderc LJ, Stelianides S, Frachon I, et al. Pulmonary toxicity of chemotherapy and G/GM-CSF: a report of five cases. Respir Med. 1999;93:65–8.
208. Hast R, Hellström-Lindberg E, Ohm L, et al. No benefit from adding GM-CSF to induction chemotherapy in transforming myelodysplastic syndromes: better outcome in patients with less proliferative disease. Leukemia. 2003;17:1827–33.
209. Darie C, Boutalba S, Fichter P, et al. Aortite après injections deG-CSF. Rev Med Interne. 2004;25:225–9 (Article in French).
210. Deeren DH, Zachee P, Malbrain ML. Granulocyte colony-stimulating factor-induced capillary leak syndrome confirmed by extravascular lung water measurements. Ann Hematol. 2005;84(2):89–94.
211. Wang S, Degar BA, Zieske A, et al. Hemophagocytosis exacerbated byG-CSF/GM-CSF treatment in a patient with myelodysplasia. Am J Hematol. 2004;77:391–6.
212. Kovacic JC, Macdonald P, Freund J, et al. Profound thrombocytopenia related to G-CSF. Am J Hematol. 2007;82:229–30.
213. Nuamah NM, Goker H, Kilic YA, et al. Spontaneous splenic rupture in a healthy allogeneic donor of peripheral-blood stem cell following the administration of granulocyte colony-stimulating factor (g-csf). A case report and review of the literature. Haematologica. 2006;91(5 Suppl):08.
214. Dagdas S, Ozet G, Alanoglu G, et al. Unusual extramedullary hematopoiesis in a patient receiving granulocyte colony-stimulating factor. Acta Haematol. 2006;116:198–202.
215. Socie G, Mary JY, Schrezenmeier H, et al. Granulocyte-stimulating factor and severe aplastic anemia: a survey by the European Group for Blood and Marrow Transplantation (EBMT). Blood. 2007;109:2794–6.
216. Gruschkus SK, Lairson D, Dunn JK, et al. Use of white blood cell growth factors and risk of acute myeloid leukemia or myelodysplastic syndrome among elderly patients with non-Hodgkin lymphoma. Cancer. 2010;116:5279–89.
217. Freedman MH, Alter BP. Risk of myelodysplastic syndrome and acute myeloid leukemia in congenital neutropenias. Semin Hematol. 2002;39:128–33.
218. Donadieu J, Leblanc T, Bader Meunier B, et al. Analysis of risk factors for myelodysplasias, leukemias and death from infection among patients with congenital neutropenia. Experience of the French Severe Chronic Neutropenia Study Group. Haematologica. 2005;90:45–53.
219. Keung YK, Suwanvecho S, Cobos E. Anaphylactoid reaction to granulocyte colony-stimulating factor used in mobilization of peripheral blood stem cell. Bone Marrow Transplant. 1999;23:200–1.
220. Fitzhugh CD, Hsieh MM, Bolan CD, et al. Granulocyte colony-stimulating factor (G-CSF) administration in individuals with sickle cell disease: time for a moratorium? Cytotherapy. 2009;11:464–71.
221. Kumar G, Bernstein JM, Waibel JS, et al. Sweet's syndrome associated with sargramostim (granulocyte-macrophage colony stimulating factor) treatment. Am J Hematol. 2004;76:283–5.
222. Thompson MA, Dyson SW, Faderl S. Sweet's syndrome in chronic lymphocytic leukemia associated with neutropenic fever and granulocyte colony stimulation factor. Am J Hematol. 2006;81:703–5.
223. Oiso N, Watanabe K, Kawada A. Granulocyte colony-stimulating factor-induced Sweet syndrome in a healthy donor. Br J Haematol. 2006;135:148.
224. Feliu J, Díaz R, Contreras F, et al. Worsening psoriasis after treatment with G-CSF in a patient with small-cell lung cancer. J Natl Cancer Inst. 1997;89:1315–6.
225. Kavanaugh A. Flare of psoriasis and psoriatic arthritis following treatment with granulocyte colony-stimulating factor. Am J Med. 1996;101:567–8.
226. Lenczowski JM[1], Cassarino DS, Jain A, et al. Disseminated vascular papules in an immunodeficient patient being treated with granulocyte colony-stimulating factor. J Am Acad Dermatol. 2003;49:105–8.
227. Alvarez-Ruiz S, Penas PF, Fernandez-Herrera J, et al. Maculopapular eruption with enlarged macrophages in eight patients receiving G-CSF or GM-CSF. J Eur Acad Dermatol Venereol. 2004;18:310–3.
228. Kurokawa I, Umehara M, Iwai T, et al. Exacerbation of palmoplantar pustulosis by granulocyte colony-stimulating factor. Int J Dermatol. 2005;44:529–30.
229. Mori T, Sato N, Watanabe R, et al. Erythema exudativum multiforme induced by granulocyte colony-stimulating factor in an allogeneic peripheral blood stem cell donor. Bone Marrow Transplant. 2000;26:239–40.
230. Prendiville J, Thiessen P, Mallory SB. Neutrophilic dermatoses in two children with idiopathic neutropenia: association with granulocyte colony-stimulating factor (G-CSF) therapy. Pediatr Dermatol. 2001;18:417–21.

231. Du X, Williams DA. Interleukin-11: Review of molecular, cell biology, and clinical use. Blood. 1997;89:3897–9.
232. Smith JW. Tolerability and side-effect profile of rhIL-11. Oncology. 2000;14(9 Suppl 8):41–7.
233. Cairo MS, Davenport V, Bessmertny O, et al. PhaseI/II dose escalation study of recombinant human interleukin-11 following ifosfamide, carboplatin and etoposide in children, adolescents and young adults with solid tumours or lymphoma: a clinical, haematological and biological study. Br J Haematol. 2005;128:49–58.
234. Hart CE, Forstrom JD, Kelly RA, et al. Two classes of PGDF receptors recognize different isoforms of PGDF. Science. 1988;240:1529–31.
235. Seifert RA, Hart CE, Phillips PE, et al. Two different subunits associate to create isoform-specific platelet-derived growth factor receptors. J Biol Chem. 1989;264:8771–8.
236. Pierce GF, Mustoe TA, Altrock BW, et al. Role of platelet-derived growth factor in wound healing. J Cell Biochem. 1991;45:319–26.
237. Pierce GF, Tarpley JE, Allman RM, et al. Tissue repair processes in healing chronic pressure ulcers treated with recombinant platelet-derived growth factor BB. Am J Pathol. 1994;145:1399–410.
238. Robson MC, Phillips LG, Thomason A, et al. Platelet-derived growth factor BB for the treatment of chronic pressure ulcers. Lancet. 1992;339:23–5.
239. Regranex® (Becaplermin). Safety labeling changes approved by FDA Center for Drug Evaluation and Research (CDER)—October 2008. Summary of changes to contraindications and warnings. http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm121631.htm. Accessed 7 June 2014.
240. Rosenberg SA, Lotze MT, Muul LM, et al. A progress report on the treatment of 157 patients with advanced cancer using lymphokine-activated killer cells and interleukin-2 or high-dose interleukin-2 alone. N Eng J Med. 1987;316:889–97.
241. Thompson JA, Lee DJ, Lindgren CG, et al. Influence of schedule of interleukin 2 administration on therapy with interleukin 2 and lymphokine activated killer cells. Cancer Res. 1989;49:235–40.
242. Lee RE, Lotze MT, Scibber JM, et al. Cardiorespiratory effects of immunotherapy with interleukin-2. J Clin Oncol. 1989;7:7–20.
243. Osanto S, Cluitmans FHM, Franks CR, et al. Myocardial injury after interleukin-2 therapy. Lancet. 1988;2:48–9.
244. Thavendiranathan P, Verhaert D, Kendra KL, et al. Fulminant myocarditis owing to high-dose interleukin-2 therapy for metastatic melanoma. Br J Radiol. 2011;84:e99–102.
245. Schwartz RN, Stover L, Dutcher J. Managing toxicities of high-dose interleukin-2. Oncology. 2002;16(11 Suppl 13):11–20.
246. Nora R, Abrams JS, Tait NS, et al. Myocardial toxic effects during recombinant interleukin-2 therapy. J Natl Cancer Inst. 1989;81:59–63.
247. Eton O, Legha SS, Bedikian AY, et al. Sequential biochemotherapy versus chemotherapy for metastatic melanoma: results from a phase III randomized trial. J Clin Oncol. 2002;20:2045–52.
248. MacFarlane PM, Yang JC, Guleria AJ, et al. The hematologic toxicity of interleukin-2 in patients with metastatic melanoma and renal cell carcinoma. Cancer. 1995;75:1030–7.
249. Krouse RS, Royal RE, Heywood G, et al. Thyroid dysfunction in 281 patients with metastatic melanoma or renal carcinoma treated with interleukin-2 alone. J Immunother. 1996;18:272–8.
250. Cormier JN, Hurst R, Vasselli J, et al. A prospective randomized evaluation of the prophylactic use of low-dose dopamine in cancer patients receiving interleukin-2. J Immunother. 1997;20:292–300.
251. Heimann DM, Schwartzentruber DJ. Gastrointestinal perforations associated with interleukin- 2 administration. J Immunother. 2004;27:254–8.
252. Pizzi C, Caraglia M, Cianciulli M, et al. Low-dose recombinant IL-2 induces psychological changes: monitoring by Minnesota Multiphasic Personality Inventory (MMPI). Anticancer Res. 2002;22:727–32.
253. Tranvan A, Pezen DS, Medenica M, et al. Interleukin-2 associated linear IgA bullous dermatosis. J Am Acad Dermatol. 1996;35:865–7.
254. Segura Huerta AA, Tordera P, Cercós AC, et al. Toxic epidermal necrolysis associated with interleukin-2. Ann Pharmacother. 2002;36:1171–4.
255. O'Reilly F, Feldman E, Yang J, et al. Recurring cutaneous eruption in a patient with metastatic renal cell carcinoma being treated with high-dose interleukin 2. J Am Acad Dermatol. 2003;48:602–4.
256. Fleischmann RM, Tesser J, Schiff MH, et al. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. Ann Rheum Dis. 2006;65:1006–12.
257. Turesson C, Riesbeck K. Septicemia with Staphylococcus aureus, beta-hemolytic streptococci group B and G, and Escherichia coli in a patient with rheumatoid arthritis treated with a recombinant human interleukin 1 receptor antagonist (anakinra). J Rheumatol. 2004;31:1876.
258. Settas LD, Tsimirikas G, Vosvotekas G, et al. Reactivation of pulmonary tuberculosis in a patient with rheumatoid arthritis during treatment with IL-1 receptor antagonists (anakinra). J Clin Rheumatol. 2007;13:219–20.
259. Swart JF, Barug D, Mohlmann M, et al. The efficacy and safety of interleukin-1-receptor antagonist anakinra in the treatment of systemic juvenile idiopathic arthritis. Expert Opin Biol Ther. 2010;10:1743–52.
260. Lequerré T, Quartier P, Rosellini D, et al. Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. Ann Rheum Dis. 2008;67:302–8.
261. Carter JD, Valeriano J, Vasey FB. Crohn disease worsened by anakinra administration. J Clin Rheumatol. 2003;9:276–7.
262. Desai D, Goldbach-Mansky R, Milner JD, et al. Anaphylactic reaction to anakinra in a rheumatoid arthritis patient intolerant to multiple nonbiologic and biologic disease-modifying antirheumatic drugs. Ann Pharmacother. 2009;43:967–72.
263. Livory M, Wechsler J, Revuz J, et al. Cellulite de Wells et dermohypodermite bactérienne nécrosante induites par l'anakinra [Wells' cellulitis and bacterial necrotizing cellulitis induced by anakinra.]. Ann Dermatol Venereol. 2008;135:839–42.
264. Regula CG, Hennessy J, Clarke LE, et al. Interstitial granulomatous drug reaction to anakinra. J Am Acad Dermatol. 2008;59(2 Suppl 1):S25–7.
265. Maiese K, Chong ZZ, Shang YC. Raves and risks for erythropoietin. Cytokine Growth Factor Rev. 2008;19:145–55.
266. Eschbach JW, Abdulhadi MH, Browne JK, et al. Recombinant human erythropoietin in anemic patients with endstage renal disease. Results of a phase III multicenter clinical trial. Ann Intern Med. 1989;111:992–1000.
267. Nowicki M. Erythropoietin and hypertension. J Hum Hypertens. 1995;9:81–8.
268. Manolis AS, Tzeis S, Triantafyllou K, et al. Erythropoietin in heart failure and other cardiovascular diseases: hematopoietic and pleiotropic effects. Curr Drug Targets—Cardiovasc Haematol Disorders. 2005;5:355–75.
269. Sowade B, Sowade O, Mocks J, et al. The safety of treatment with recombinant human erythropoietin in clinical use: a review of controlled studies. Int J Mol Med. 1998;1:303–14.

270. Bokemeyer C, Aapro MS, Courdi A, et al. EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer. Eur J Cancer. 2004;40:2201–16.
271. Maiese K, Li F, Chong ZZ. Erythropoietin and cancer. JAMA. 2005;293:1858–9. doi:10.1001/jama.293.15.1858-b.
272. Bennett CL, Luminari S, Nissenson AR, et al. Pure red-cell aplasia and epoetin therapy. N Engl J Med. 2004;351:1403–8.
273. Weber G, Gross J, Kromminga A, et al. Allergic skin and systemic reactions in a patient with pure red cell aplasia and anti-erythropoietin antibodies challenged with different epoetins. J Am Soc Nephrol. 2002;13:2381–3.
274. Garcia JE, Senent C, Pascual C, et al. Anaphylactic reaction to recombinant human erythropoietin. Nephron. 1993;65:636–7.
275. Bessa PC, Casal M, Reis RL. Bone morphogenetic proteins in tissue engineering: the road from the laboratory to the clinic, part II (BMP delivery). J Tissue Eng Regen Med. 2008;2:81–96.
276. Bragdon B, Moseychuk O, Saldanha S, et al. Bone morphogenetic proteins: a critical review. Cell Signal. 2011;23:609–20.
277. Ong KL, Villarraga ML, Lau E, et al. Off-label use of bone morphogenetic proteins in the United States using administrative data. Spine (Phila, Pa). 2010;35:1794–800.
278. Cahill KS, Chi JH, Day A, et al. Prevalence, complications and hospital charges associated with the use of bone-morphogenetic proteins in spinal fusion procedures. JAMA. 2009;302:58–66.
279. Mindea SA, Shih P, Song JK. Recombinant human bone morphogenetic protein-2-induced radiculitis in elective minimally invasive transforaminal lumbar interbody fusions: a series review. Spine. 2009;34:1480–4.
280. Comer GC, Smith MW, Hurwitz EL, et al. Retrograde ejaculation after anterior lumbar interbody fusion with and without bone morphogenetic protein-2 augmentation: a 10-year cohort controlled study. Spine J. 2012;12:881–90.
281. Mroz TE, Wang JC, Hashimoto R, et al. Complications related to osteobiologics use in spine surgery: a systematic review. Spine. 2010;35(Suppl 9):S86–104.
282. FDA Executive summary for P050036 Medtronic's AMPLIFY™ rhBMP-2 Matrix. Orthopedic and Rehabilitation Devices Advisory Panel. July 27, 2010. http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/medicaldevices/medicaldevicesadvisorycommittee/orthopaedicandrehabilitationdevicespanel/ucm220079.pdf. Accessed 7 June 2014.
283. Koehler SM, Latridis JC, Hecht A, et al. Does BMP-2 really cause cancer? A systematic review of the literature—NASS meeting 2012. Spine J. 2012;12:S143–4.
284. Simmonds MC, Brown JV, Heirs MK, et al. Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion: a meta-analysis of individual participant data. Ann Intern Med. 2013;158:177–9.
285. Friedlaender GE, Perry CR, Cole JD, et al. Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions: a prospective, randomized clinical trial comparing rhOP-1 with fresh bone autograft. J Bone Joint Surg Am. 2001;83-A(Suppl 1,Pt 2):S151–8.
286. Leach J, Bittar RG. BMP-7 (OP-1®) safety in anterior cervical fusion surgery. J Clin Neurosci. 2009;16:1417–20.
287. Gitelis S, Wilkins RM, Yasko AW. BMPs and cancer: Is the risk real? http://www.aaos.org/news/aaosnow/may08/research7.asp. Accessed 7 June 2014.
288. Kelesidis T, Kelesidis I, Chou S, et al. Narrative review: the role of leptin in human physiology: EMERGING clinical applications. Ann Intern Med. 2010;152:93–100.
289. Wong SL, Depaoli AM, Lee JH, et al. Leptin hormonal kinetics in the fed state: effects of adiposity, age, and gender on endogenous leptin production and clearance rates. J Clin Endocrinol Metabol. 2004;89:2672–7.
290. Javor ED, Moran SA, Ryan J, et al. Proteinuric nephropathy in acquired and congenital generalized lipodystrophy: baseline characteristics and course during recombinant leptin therapy. J Clin Endocrinol Metabol. 2004;89:3199–207.
291. Beltrand J, Lahlou N, Charpentier T, et al. Resistance to leptin-replacement therapy in Berardinelli- Seip congenital lipodystrophy: an immunological origin. Eur J Endocrinol. 2010;162:1083–91.
292. Housa D, Housová J, Vernerová Z, et al. Adipocytokines and Cancer. Physiol Res. 2006;55:233–44.
293. Bristol-Myers Squibb, AstraZeneca: Endocrinologic and Metabolic Drugs Advisory Committee Briefing Document Metreleptin (BLA STN125390). 11 December 2013. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM377929.pdf. Accessed 7 June 2014.
294. Gogas H, Ioannovich J, Dafni U, et al. Prognostic significance of autoimmunity during treatment of melanoma with interferon. N Engl J Med. 2006;354:709–18.