

Adverse reactions to biological modifiers

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Purpose of review

Newer biologic immunomodulators such as interferons, tumor necrosis factor α (TNF α) inhibitors, and monoclonal antibodies have been introduced into the management of various inflammatory conditions. This review addresses adverse responses to these agents.

Recent findings

Both interferon- α and interferon- β have been associated with autoimmune phenomena. The ability of TNF α antagonists to cause significant adverse reactions appears to be substantial. These are either related to interference with TNF α activity or as consequence of the agents, either immunoglobulin or fusion protein, being recognized as foreign proteins, becoming themselves targets of an immune response.

Summary

Although advancing the management of inflammatory conditions, biologic modifiers are attended by significant concerns. Identification of at risk groups and careful selection of appropriate patients will minimize occurrence of adverse events.

Keywords

adverse reaction, biologic modifier, cytokine antagonist

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Introduction

The concept of modulating immune or inflammatory processes is not a new one, ranging from attempts to augment tumor cytotoxicity, to dampening the immune response in conditions such as rheumatoid arthritis and inflammatory bowel disease. What has greatly progressed over the past decade is the sharpness of the scope, or the narrowness of the target. Emphasis has shifted away from broad-spectrum agents such as ionizing radiation, cancer chemotherapy, or corticosteroids, to isolating a single mediator for augmentation or neutralization. For example, these newer biological immunomodulators include interferons, TNF- α inhibitors, IL-1 receptor antagonist, growth factors, monoclonal antibodies, and complement protein inhibitors (Table 1). In some arenas, this approach has met with impressive success, such as the use of TNF- α antagonists in rheumatoid arthritis. In 2003, Nelson and Ballou [1•] published a comprehensive review of immunomodulators spanning the use of drugs, cytokines, cytokine receptors, and antibodies. The authors provided background and cited studies up to 2002. Watts [2] had previously reviewed, in 2000, musculoskeletal and systemic reactions to biological agents used in autoimmune diseases. The present review will examine a number of these newer biological modifiers, but will emphasize the adverse reaction profile as reported in the literature within the recent past (2002–2004).

Interferons

IFN- α , IFN- β , and IFN- γ have been used for a number of years in a large variety of disorders for anti-infectious, anti-neoplastic, and anti-inflammatory effects (see Table 2). As reviewed by Watts [2], IFN- α and IFN- β have been especially associated with the development of lupus-like autoimmune disorders. In patients receiving IFN- α for chronic lymphocytic leukemia, low-titer, low-affinity IgM and IgG antibodies for single-stranded and double-stranded DNA could be detected. Clinical manifestations of autoimmune disease were not seen. In distinction, Kalkner and coworkers [3] reported 8% of 214 patients being treated with IFN- α for carcinoid or pancreatic tumors developed high affinity IgG anti-dsDNA antibodies after a mean duration of therapy of 35 months. One patient had polymyositis, and three developed myxedema. ANA antibodies were found in 22% of these patients. Bell and associates [4] found that the antecedent presence of low-level autoantibodies was predictive of autoimmune complications during IFN- α therapy.

Table 1. Newer biological agents in clinical usage

Cytokines
Interferons
Hematopoietic growth factors
IL-2
Polyclonal antibodies (intravenous immunoglobulin)
Monoclonal antibodies
Cytokine receptor inhibitors

Table 2. Interferons in human illness

Agent	Indication	Adverse effects
IFN- α	Melanoma, CLL, AIDS-related Kaposi's sarcoma, chronic HBV, HCV	LE-like syndrome, theophylline interaction, depression, 'flu-like syndrome, arthritis
IFN- β	Multiple sclerosis	LE-like syndrome, Raynaud's syndrome
IFN- γ	CGD, IPF, recurrent MAC infection	LE-like syndrome

See References [1,2]. CGD, Chronic granulomatous disease; CLL, chronic lymphocytic leukemia; HBV, hepatitis B virus; HCV, hepatitis C virus; IPF, idiopathic pulmonary fibrosis; LE, lupus erythematosus; MAC, *Mycobacterium avium-intracellulare* complex.

Other than 'flu-like symptoms or injection site reactions that occurred in all patients, a short-term, although escalating, dosage schedule of IFN- β -1a was not met with any other abnormalities in a small group of ulcerative colitis patients [5]. Nousari and colleagues [6] described an arcuate, polycyclic photodermatitis after increased sun exposure developing in a patient after 5 months of IFN- β -1a therapy for multiple sclerosis. On biopsy, immunofluorescence revealed granular IgG, IgM, and complement C3 along the basement membrane. The ANA was positive at 1:1280 and anti-Ro antibodies were present; these decreased after the cessation of therapy. Festi and colleagues [7] recently reviewed the available trial data comparing the use of IFN- β versus IFN- α in the treatment of chronic hepatitis C virus hepatitis. The authors found that the former was attended with no greater, and frequently lesser, adverse side-effects than the latter, and was well tolerated in long-term treatment. In an older study, Colosimo and associates [8] did not find any increased incidence of autoantibodies during the treatment of multiple sclerosis with IFN- β -1a. Why these two classes of interferon should be attended by different degrees of autoimmune phenomena remains unclear, although it has been suggested that the induction of bcl-2 gene transcription by IFN- α may lead to diminished apoptosis [2].

TNF- α antagonists

Inhibiting the actions of TNF- α has proved very effective in the management of early and chronic rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Crohn's disease, see Table 3 and Table 4. Two agents, etanercept and infliximab, are in common

Table 3. Cytokine receptor inhibitors in human illness

Inhibitor	Target	Indication
Etanercept	TNF- α	Rheumatoid arthritis
Lenercept	TNF- α	Rheumatoid arthritis
Anakinra	IL-1	Rheumatoid arthritis
Denileukin diftitox	IL-2	CTCL that express CD25 component of IL-2 receptor

See References [1,9**]. CTCL, Cutaneous T-cell lymphoma.

Table 4. Monoclonal antibodies in human disease

Antibody	Target	Indication
Muronmonab	CD3 lymphocyte	Organ rejection
Infliximab	TNF- α	Rheumatoid arthritis, Crohn's
Adalimumab	TNF- α	Rheumatoid arthritis
Alemtuzumab	CD52+ cells	Chronic lymphocytic leukemia
Rituximab	CD20+ cells	Non-Hodgkin's lymphoma
Ibritumomab	CD20+ cells	Non-Hodgkin's lymphoma
Omalizumab	IgE Fc binding domain	Steroid-dependent asthma

See references [1,9**,10]. CD, cluster of differentiation; IgE Fc, crystallizable fragment immunoglobulin-E.

use, both acting as traps for TNF- α , with subsequent clearing of the complexes through the reticular-endothelial system. Etanercept is a fusion protein of two ligand-binding regions of human TNF- α receptor 2 (p75) attached at the hinge region of the Fc fragment of human IgG1. It acts as a competitive inhibitor for TNF- α . Lenercept is a similar fusion protein using the p55 TNF- α receptor protein. Infliximab is a chimeric IgG1 monoclonal antibody directed against TNF- α [9**].

The most common adverse effect of twice weekly subcutaneous etanercept treatment is an injection site reaction, seen in up to 42% of patients, usually during the first month of therapy and declining thereafter [11,12]. In a biopsy study in 2001, Zeltser and coworkers [13] defined the immunological make-up of these injection site reactions. There was perivascular cuffing without evidence of leukocytoclastic vasculitis. Infiltration was predominantly by activated cytotoxic T lymphocytes (HLA-DR⁺/CD3⁺/CD4⁻/CD8⁺) with a moderate number of degranulating eosinophils. Biopsy of a recall injection reaction site showed strong HLA-DR expression by keratinocytes. Werth and Levinson [11] pointed out that most delayed hypersensitivity reactions show predominant CD4 T cells rather than CD8 T cells, and those that do have a CD8 response may be triggered by haptens such as dinitrochlorobenzene and urushiol. The waning of the reactions suggests tolerance or desensitization. Although not seen in the study by Zeltser *et al.* [13], leukocytoclastic vasculitis has been reported occurring 2 weeks after the institution of etanercept [14]. Pruritic urticarial lesions distant from injection sites have also been described [15].

As commented on by Day [10], initial 6-month trials of etanercept in 323 patients revealed that 11% became ANA positive, with only 1.6% developing anti-dsDNA antibodies, and none developed clinical symptoms of lupus erythematosus. Shakoor and colleagues [16] reported four cases of etanercept-associated lupus erythematosus. Three were ANA positive, three anti-dsDNA, three anti-histone (one only anti-histone antibody positive), and one with anti-Sm, anti-RNP, and hypocomplementemia as well. All symptoms resolved within 2–6 weeks of discontinuation of etanercept.

Peno-Green and colleagues [17] described a case of malaise, cough, and dyspnea on exertion, associated with microscopic hematuria, creatinine of 2.0, and a non-pruritic plantar rash after 2 months of etanercept therapy. A transbronchial biopsy showed peribronchial and parenchymal non-caseating granuloma with polarized birefringent particles. Tissue stains for acid-fast bacilli, fungi, and parasites were all negative. *Mycobacterium avium-intracellulare* complex was isolated from broncho-alveolar lavage after 4 weeks of incubation. A skin biopsy of an acute lesion also showed non-caseating granuloma with birefringent particles. Symptoms stabilized with etanercept discontinuation, and improved dramatically with prednisone initiation, which was continued for 4 weeks. Abnormalities on high-resolution chest computed tomography scan took a year to resolve totally.

Neurological complications have been reported with TNF- α receptor fusion proteins. Lenercept was withdrawn from clinical trials because of the increased duration and severity of multiple sclerosis [10,18]. Day [10] cited four cases of demyelination with etanercept, which resolved with discontinuation, and two cases after infliximab. Transient aseptic meningitis has been reported with infliximab [19].

Like etanercept, lupus-like syndromes have been reported with the use of infliximab. Lipsky and associates [20] reported on a one-year trial of infliximab plus methotrexate versus methotrexate alone in 428 rheumatoid arthritis patients. Antinuclear antibodies developed in 53–68% of the infliximab group versus 26% of controls, and 7–10% developed anti-dsDNA antibodies compared with none of the controls. One patient in the infliximab group developed a cutaneous rash.

Baert and colleagues [21•] monitored 125 consecutive patients receiving infliximab infusions for fistula-forming or refractory Crohn's disease for the development of antibodies against the agent. None had specific antibodies at baseline, over 40% developed antibodies after the first infusion, and by the fifth infusion 61% did so. Further infusions did not raise the percentage higher.

The presence of antibodies was associated with a higher incidence of infusion reactions, and poorer clinical response. The use of immunosuppressive agents such as azathioprine, mercaptopurine, or methotrexate was associated with a lower incidence and lower titers of antibody. Corticosteroids or mesalamine had no impact on the development of specific antibodies.

A report on the use of infliximab in 57 children and adolescents with Crohn's disease revealed 35 reactions in 361 infusions [22]. Risk factors for reactions with the second infusion were female sex and immunosuppressive therapy for less than 4 months. A reaction at the second infusion increased the likelihood of a reaction with the third. Cheifetz and associates [23] characterized infusion reactions in 165 consecutive Crohn's disease patients receiving 479 infliximab infusions. Reactions occurred in 29 out of 479 infusions (6.1%), affecting 9.7% of patients. Delayed reactions occurred in three infusions. Acute reactions were mild in 15, moderate in six, and severe in five. All responded to treatment, and further events were prevented with prophylactic therapy except for a single patient sustaining a second severe reaction. Serum tryptase was negative in 14 reactions occurring in 11 patients, suggesting a non-IgE mechanism.

A review of the Mayo Clinic experience was published by Colombel and co-workers in 2004 [24•]. Thirty patients (6%) suffered serious adverse reactions that were felt to be related to infliximab. Acute infusion reactions occurred in 3.8% of patients. A serum sickness-like syndrome occurred in 19 patients, and was attributed to infliximab in 14 (2.8%). Three patients developed drug-induced lupus, and one a demyelinating disease. Forty-one (8.2%) had infectious complications attributed to the drug, 20 were considered serious: two fatal sepsis; eight pneumonias, two fatal; six viral infections; two surgery-requiring abdominal abscesses; one arm cellulites; and one histoplasmosis. Nine patients had malignancy, with three possibly related to the drug. Ten patients died, half (1%) were felt possibly to be related to infliximab.

Recently, Feletar and co-workers [25] reported on the use of infliximab in a 12-month trial in 16 patients with refractory psoriatic arthritis, 11 of whom remained on methotrexate. Although the drug showed clinical efficacy, 31% stopped treatment because of adverse events: three with liver toxicity (two with concomitant methotrexate therapy), and two with allergic reactions, one severe (urticaria, chest tightness and shortness of breath). In addition, six patients suffered infectious complications: two pneumonias, one each of septic arthritis, epididymitis, perichondritis, and a surgical site abscess in a digit (interestingly, surgery was performed 2 years

previously). Eight patients seroconverted an ANA, and six became anti-dsDNA positive. No patients developed clinical features of a connective tissue disorder.

Several adverse skin reactions have been described with infliximab. Interestingly, as infliximab has been used for psoriatic arthritis, there is a report of psoriasiform lichenoid dermatitis in a patient with Crohn's disease after the second and third infliximab infusions [26]. Other cutaneous reactions reported with infliximab include leukocytoclastic vasculitis, lichenoid drug reaction, pemphigus-like eruption, granuloma annulare, and acute folliculitis [27].

Földvari and associates [28] described a case of acute cholecystitis after etanercept therapy, which remitted with discontinuation. Symptoms recurred after the institution of infliximab. Initial gall bladder puncture revealed no infectious agents, nor did an ultimate cholecystectomy.

TNF- α antagonists are frequently given in consort with disease-modifying antirheumatic drugs. Whether such combinations may suppress or augment adverse reactions is an open issue. In the case of immunosuppressive agents, as mentioned above, such therapy may diminish the development of antibodies, and thus infusion reactions [21•]. Leflunomide is an inhibitor of de novo pyrimidine synthesis [9••]. It has been implicated in a Stevens-Johnson type of severe erythema multiforme reaction [29]. A recent report collected multicenter data on combination therapy of leflunomide and infliximab in 88 rheumatoid arthritis patients [30]. Adverse events were in keeping with known risks of the individual agents. Infusion reactions with infliximab were uncommon (0.7%). Two patients developed rashes. Ten infections occurred, of which nine resolved, and one, bacterial pneumonia with acute respiratory disease, resulted in death. Viral infections were minor, requiring famciclovir for a case of shingles, and no therapy for four others with 'flu or upper respiratory infection. The remaining bacterial infections required hospitalization.

As TNF- α is a central cytokine in the inflammatory response to infection and in immune surveillance, its antagonism could lead to the increased incidence of serious infection or malignancy. As reviewed by Day in 2002 [10], however, clinical trials and open-label follow-ups of etanercept accounting for 4794 patient-years revealed a serious infection rate (requiring hospitalization or intravenous antibiotics) of 0.04 per patient-year of exposure, which was identical to the control group in the clinical trials. Similarly, 41 cancers developed, compared with 42 expected on the basis of US national cancer statistics. Furthermore, as of the fall of 2001, 13 cases of tuberculosis in patients on etanercept were reported,

primarily from eastern Europe. This was marginally higher than the 11 age-matched cases expected. Day [10] stated that it was plausible and likely that TNF- α inhibitory therapy would unmask latent tuberculosis, and that patients with risk factors should be screened for infection and possibly treated prophylactically for tuberculosis before TNF- α blocker therapy [10]. Not unexpectedly then, Gómez-Reino and coworkers [31••] reported in 2003 an increased risk of active tuberculosis in 1540 Spanish rheumatoid arthritis patients on infliximab or etanercept. A national database (BIOBADASER) had been initiated in February 2000 for the follow-up of rheumatic disease patients on biological modifiers. After 2 years, 1540 patients were enrolled, and another 61 patients had retrospective data collected. There were 1578 drug initiations, 86% of these were infliximab and 14% were etanercept; in 38 cases one drug was started after the discontinuation of the other. Therapy was stopped in 14% of patients as a result of adverse reactions: infections in 118 patients, cutaneous reactions in 44, and infusion reactions to infliximab in 31. Lower respiratory tract infections occurred in 21% of patients, skin infections in 13%, urinary tract in 11%, and upper respiratory in 9%. Ten patients developed sepsis. Organisms included *Mycobacterium tuberculosis* in 17 patients, herpes zoster in eight, *Staphylococcus* in five, *Salmonella* in four, and undisclosed bacteria in 15. The incidence of tuberculosis was 1893 per 100 000 in 2000, and 1113 per 100 000 in 2001; the background incidence of tuberculosis in Spain in 2000 was 21 per 100 000. Rheumatoid arthritis patients not on TNF- α inhibitors had an incidence of 95 per 100 000. It is therefore obvious that the risk of activating latent tuberculosis in this susceptible population is increased over a hundred-fold with the use of TNF- α inhibitors.

Elevated levels of TNF- α in advanced heart failure provided the rationale for the use of TNF- α antagonists in congestive heart failure. As commented on by Kwon and associates [32••], however, trials of etanercept were stopped early because of a lack of effectiveness, and a phase II trial of infliximab was attended by increased hospitalization and mortality in the active group. These authors therefore reviewed reports to the US Food and Drug Administration MedWatch programme for evidence of worsening or new-onset heart failure after treatment with TNF- α antagonists. This programme monitors post-marketing spontaneous reports of adverse events from several sources, to include manufacturers and physicians. Despite the underreporting inherent in such a system, they found 38 patients on TNF- α antagonists with new-onset heart failure, and nine with worsening congestive heart failure; the median duration of treatment was 3.5 and 4 months, respectively [32••]. Of those with worsening congestive heart failure, three were on etanercept and six were on infliximab. Of the

new-onset heart failure patients, 19 had no risk factors (12 on etanercept and seven on infliximab). Another 19 had risk factors such as previous myocardial infarction, coronary artery disease, hypertension, or diabetes (14 on etanercept and five on infliximab). Ten patients with new-onset heart failure were under the age of 50 years. Of these 10, with the discontinuation of TNF- α antagonists and the institution of heart failure therapy, three completely resolved, six improved, and one died. The authors pointed out that these spontaneous reports are not sufficient to prove causality, the improvement or resolution of heart failure in the younger patients after discontinuation strongly supports a causal relationship.

IL-1 receptor antagonist

Similar to TNF- α , IL-1 has been felt to be an important pro-inflammatory mediator of synovialitis. Anakinra is a recombinant IL-1 receptor antagonist (r-metHuIL-1ra), which has shown efficacy in rheumatoid arthritis. Kary and Burmester [33] and Fleischmann [34] summarized the experience with clinical trials of 10 000 rheumatoid arthritis patients, and found, similar to TNF- α antagonists, injection site reactions as the most frequent adverse event, followed by a mild increase in infections. No activation of tuberculosis was reported. A double-blind, placebo-controlled trial of anakinra in rheumatoid arthritis patients on methotrexate was recently published [35]. Two hundred and fifty and 251 patients were randomly assigned to anakinra plus methotrexate and placebo plus methotrexate, respectively. Injection site reactions were more common in the active group (65 versus 24%). Respiratory infectious events were similar, 21% with anakinra and 16% with placebo. Serious infections were rare, 0.8% in both groups.

Omalizumab

Omalizumab is a human/murine chimeric monoclonal antibody directed against the C ϵ 3 binding site for the high affinity IgE receptor. The antibody-binding site is murine, whereas the remaining IgG molecule is of human derivation. It prevents soluble IgE from attaching to mast cells and other effector cells, and thereby blunts IgE-mediated inflammatory responses. The downregulation of CD23 may ultimately shift the cytokine milieu away from a T helper cell type 2 proclivity [36 $\bullet$]. As the molecule is 95% human immunoglobulin, the likelihood of developing anti-murine antibodies directed against the binding site should be no greater than that with any anti-idiotypic response.

Usage so far has revealed little in the way of adverse reactions. Lanier and co-workers [37] reported on 460 patients (aged 12–74 years) who were continued for 52 weeks in a double-blind, placebo-controlled fashion; 245 patients received omalizumab [37]. Headache was reported in three active patients and one placebo. No

systemic immunological reactions were reported. In a 52-week trial of omalizumab in 309 children with allergic asthma [38], headache and upper respiratory infections were commonly reported as adverse events, 42.7 and 47.1%, respectively. Eleven patients developed urticaria (4.9%), which responded to antihistamines, or remitted spontaneously in 10. One patient was discontinued because of severe urticaria. No anaphylaxis or serum sickness-like illness occurred. No anti-omalizumab antibodies were detected. Holgate and colleagues [39] recently published the results of an international double-blind, placebo-controlled trial with 246 patients (aged 12–75 years). The most common effects were transient local injection site bruising in 20.4% compared with 10.3% placebo: bruising, itching warm and redness. Urticaria was only seen in one active treatment (and in three placebo patients). A Cochrane meta-analysis of eight trials involving 2037 mild to severe asthmatic patients came to the conclusion that omalizumab was well tolerated, but the safety profile required longer-term assessment [40]. Concern was raised that the incidence of malignancy was greater in the active treatment group than in the placebo arms of the index Food and Drug Administration studies. This appeared to be caused by an incidence in the placebo group that was lower than reported in the general population (Novartis, data on file). A White Paper Consensus Meeting was convened in June 2003 to address the risk of malignancy, and found that 23 out of 31 reports were unrelated to the study drug, and the remainder were unlikely to very unlikely to be related (Novartis, report on file).

Conclusion

Although providing great strides in the management of inflammatory conditions such as arthritis and inflammatory bowel disease, biological modifiers are attended by not inconsequential concerns. What mechanisms lead to the propensity to develop systemic lupus erythematosus-related autoantibodies as well as those seen more classically with drug-induced lupus with interferon therapy is unclear. That the large percentage of these appear to be low-affinity antibodies not associated with clinical manifestations is somewhat reassuring. The fact that IFN- β is perhaps less likely to induce such antibodies is also reassuring.

The ability to cause significant adverse reactions appears to be substantial with TNF- α antagonists. These are either related to interference with TNF- α activity or as a consequence of the agents, either immunoglobulin or fusion protein, being recognized as foreign proteins, becoming themselves targets of an immune response. As such, it has been suggested that infliximab and similar antibodies may have a greater likelihood of causing adverse events [10]. Certain reactions such as infusion reactions or injection site reactions are to be expected,

and can be successfully prophylaxed. Because several patient groups are at greater risk of either infection or other adverse events, practice guidelines need to be refined to exclude such patients from therapy, or to evaluate them properly and treat prophylactically. Although the mechanism is unclear, the risk of worsening disease in patients with histories of demyelinating disorders should preclude these patients from TNF- α antagonist therapy. The risk of infection, especially with mycobacteria, is a serious concern in areas in which the prevalence of such infection is greater. It can be argued that all patients should at least be screened for risk before the inception of therapy. In distinction to the other monoclonal antibody therapy reviewed, omalizumab therapy appears to be attended by a very low incidence of adverse reactions.

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