



Infection complications associated with the use of biologic agents

Barry Bresnihan, MD, FRCPI, FRCP^{a,*},
Gayle Cunnane, MB, MRCPI, PhD^b

^a*Department of Rheumatology, St. Vincent's University Hospital, Dublin 4, Ireland*

^b*Department of Rheumatology, University of Leeds, Old Nurses' Home, Leeds General Infirmary, Leeds LS1 3EX, UK*

The advent of biologic agents that target proinflammatory cytokines such as interleukin-1 (IL-1) or tumor necrosis factor alpha (TNF α) has revolutionized the understanding of the pathophysiology of inflammatory diseases and has given new hope to patients suffering from these disorders. Both IL-1 and TNF α play pivotal roles in inflammation and enhance the pathologic events in rheumatoid arthritis (RA) and other inflammatory arthropathies. A variety of therapeutic interventions that specifically block the effects of these biologic agents have been examined in several clinical trials. Interleukin-1 receptor antagonist (IL-1Ra) has clinical, radiologic, and histologic benefits in patients with RA [1–3]. Anti-TNF α agents such as infliximab, etanercept, and adalimumab are also efficacious in the management of inflammatory arthropathies [4–18].

Targeting interleukin-1

Role of interleukin-1 in host defense mechanisms

The IL-1 family includes IL-1 α , IL-1 β and IL-1Ra [19]. Interleukin-1 α and IL-1 β are effector molecules that influence cell function by binding to IL-1 cell surface receptors (IL-1R); IL-1Ra is the naturally occurring antagonist of IL-1 α and IL-1 β , preventing their action by competitively binding to IL-1R. Interleukin-1 β is believed to be the major form of IL-1 released from cells, whereas IL-1 α is thought to play a predominantly intracellular role [20]. Induction of IL-1 expression may result from any cell perturbation, including trauma, infection, cell-

* Corresponding author.

E-mail address: c.walsh@st-vincent.ie (B. Bresnihan).

cell contact, or the presence of crystals, immune complexes, or complement components [21]. Although most cells are capable of IL-1 production, monocytes and macrophages are the main source [19]. Binding of IL-1 to IL-1R induces several important physiologic effects, including increases in cell adhesion molecule expression on vascular endothelium, lymphocytes, and monocytes, encouraging their migration into areas of inflammation [22]. Interleukin-1 also activates T cells and stimulates release of proteolytic enzymes, thereby contributing to tissue injury [23]. In animal models of arthritis, IL-1 exacerbates the inflammatory process, causing pannus formation and cartilage destruction [24–27].

In the presence of active inflammation or infection, IL-1 contributes to fever, anorexia, weight loss, and elevation of the acute-phase response [20,28,29]. Interleukin-1 also plays a critical part in the initiation of dermal contact hypersensitivity [30]. Interleukin-1 β knockout mice demonstrate impaired acute-phase inflammatory and pyrogenic responses. Although these mice succumb to infection with influenza virus, they are resistant to *Listeria monocytogenes*, suggesting that IL-1 and other cytokines may play a greater or lesser role in host defense depending on the microorganism involved [20].

Interleukin-1 receptor antagonist

Mode of action

Anakinra is a recombinant human form of IL-1Ra that binds to IL-1 receptors without activating the cell. Because most cells express an abundance of IL-1 receptors, however, an excess of IL-1Ra must be present to prevent IL-1-mediated cell activity [31]. Inflammatory diseases such as RA are characterized by a relative deficiency of IL-1Ra, making this cytokine inhibitor an attractive therapeutic target [1].

The plasma half-life of IL-1Ra is short, and animal studies have demonstrated that continuous infusion of IL-1Ra is more efficacious than intermittent injection [31,32]. In patients with RA, maximum plasma concentrations of IL-1Ra occurred 3 to 7 hours after subcutaneous administration, and the terminal half-life ranged from 4 to 6 hours. Interleukin-1Ra has a favorable effect in several forms of arthritis in animals [33–35]. It has been shown to inhibit prostaglandin production and leukocyte infiltration in inflamed joints [36]. It also decreases the increased IL-1-mediated protease expression by chondrocytes and synovial cells, and it reduces synovial cellular infiltration and adhesion molecule expression [3,37]. Transfer of the IL-1Ra gene to the knee joints of rabbits with monoarticular arthritis results in a marked chondroprotective effect accompanied by a lesser anti-inflammatory effect [38].

Efficacy

Interleukin-1Ra has been evaluated in several clinical trials of patients with RA [1,2,3,39,40]. The initial study was a dose-ranging trial of IL-1Ra in 175 patients with active RA [39]. Because of the multiple small treatment groups and lack of a placebo control arm, the efficacy of IL-1Ra was not ascertained,

although the results suggested that daily rather than weekly dosing had a more beneficial effect on disease activity measures. Following this study, a randomized, double-blind study was carried out using placebo or IL-1Ra, 30 mg, 75 mg or 150 mg/day, delivered by subcutaneous injection for 24 weeks [1]. The primary therapeutic endpoint was the American College of Rheumatology 20% (ACR20) response, and that endpoint was attained in 27% of the placebo group and in 43% of the cohort who received IL-1Ra 150 mg/day ($P=0.014$). Clinical responses were observed as soon as 2 weeks after start of treatment and were sustained throughout the duration of the trial. Furthermore, there was a statistically significant slowing of radiographic progression of joint damage in those patients who received IL-1Ra compared with placebo [1,41]. A small subgroup of patients in this trial underwent synovial biopsy before the trial and after 3 to 6 months of receiving IL-1Ra or placebo [3]. Treatment with IL-1Ra, 150 mg/day, resulted in marked reduction in synovial cellularity and adhesion molecule expression.

The patients who completed the 24-week trial had the option of entering a further 24-week extension study [40]. Those who had received placebo were randomly allocated to one of the IL-1Ra treatment arms; patients who were already receiving IL-1Ra continued their previous dosage regimens. On completion of the extension phase, significant clinical improvements were noted, particularly in those who had received IL-1Ra, 150 mg/day. Forty-nine percent of patients maintained an ACR20 response at 48 weeks, and the benefits regarding erosive disease continued through the extension study.

Interleukin-1Ra was also evaluated in combination with methotrexate in 419 patients with active RA [2]. The ACR20 responses at week 12 in the 5 active treatment plus methotrexate groups were significantly greater than in the placebo plus methotrexate cohort ($P=0.001$). At week 24, the ACR20 responses were consistent with the results at week 12. The authors concluded that the combination of IL-1Ra plus methotrexate provided significantly greater clinical benefit than methotrexate alone.

Safety

Interleukin-1Ra is well tolerated in most patients. In the published clinical trials, injection site reactions were the most common adverse events and were dose related. These reactions tended to be mild and transient and became less frequent with time. The second most common adverse effect in the methotrexate combination study was the occurrence of headaches, which were experienced by 15% of the placebo group and 14% to 34% of the treatment group. In addition, abdominal pain was reported more frequently by patients who received IL-1Ra than by those who were given placebo in the same study [2]. Malignancy developed in 2 patients in the monotherapy study (pulmonary cancer and thyroid cancer) and in 2 patients in the methotrexate combination trial (lung cancer and breast cancer). These malignancies were not considered to be related to IL-1Ra, but the patients were withdrawn from the studies.

Neutropenia has been observed in patients treated with IL-1Ra. This problem developed in 3 patients in the monotherapy study and in 5 patients in the methotrexate combination trial and did not seem to be dose-related. White cell counts returned to normal after discontinuation of treatment, and no patient developed fever or infection during the transient leukopenic episodes [1,2].

A small number of patients (<1%) exposed to IL-1Ra develop anti-IL-1Ra antibodies. No correlation between antibody development and clinical response or adverse events has been observed, and the long-term immunogenicity of IL-1Ra is unknown.

Infection and interleukin-1 receptor antagonist

Throughout the randomized, controlled trials of IL-1Ra in patients with RA, the incidence of infection was slightly higher in the treatment groups than in patients receiving placebo. In the monotherapy study, infections requiring antibiotic therapy occurred in 12% of patients in the placebo arm and in up to 17% of patients receiving IL-1Ra. Respiratory tract infections were the most common type of infection observed and were usually mild. Serious infections (defined as those requiring hospitalization) included elbow bursitis, infected union, and herpes zoster [1]. In the methotrexate combination study, upper respiratory tract infections developed in 22% of patients in the placebo group and in 14% to 24% of those in the IL-1Ra cohort. No serious infections occurred in this study [2].

The US Food and Drug Administration (FDA) Advisory Committee has reviewed a large database of almost 3000 patients who have received IL-1Ra. Of these, 2184 were treated for at least 6 months, and 2233 received doses of 100 mg/day or more. The incidence of any infectious episodes was similar in patients who were given IL-1Ra (39.3%) and in patients who received placebo (36.2%). The incidence of serious infectious episodes was 0.7%, 1.1%, 1.2%, and 2.0% in patients who received placebo, IL-1Ra doses below 100 mg/day, of 100 mg/day, or higher than 100 mg/day, respectively. Pneumonia was the most frequently reported serious infection overall and developed in 14 patients treated with IL-1Ra and in none of the patients given placebo. Nine of the 14 patients had significant comorbidities; 11 were taking concomitant disease-modifying treatment or corticosteroids. An analysis of exposure-adjusted event rates of serious infection across all of the IL-1Ra studies suggested that the risk of infection did not increase with time. There have been no reports of opportunistic infections in patients receiving IL-1Ra.

In considering patients for treatment with IL-1Ra, caution is advised in patients with several comorbid illnesses that may put them at increased risk of infection. A white blood cell count should be obtained before and during treatment, and IL-1Ra should be withdrawn if neutropenia develops. No data are yet available on the effects of vaccination in patients receiving this treatment, but live vaccines should not be administered concurrently with IL-1Ra. The use of IL-1Ra in clinical practice with larger numbers of patients will further help to determine the safety profile of this medication in people with RA.

Targeting tumor necrosis factor alpha

Role of tumor necrosis factor alpha in host defense mechanisms

Tumor necrosis factor was originally defined by its specific toxicity towards malignant cells [42]. More recently, however, it has been shown to have a central role in the pathophysiologic response to inflammation and infection. Tumor necrosis factor is produced by a variety of inflammatory cells, predominantly macrophages and lymphocytes and is active both as a membrane-bound and as a soluble protein [43]. Tumor necrosis factor alpha and TNF β (also known as lymphotoxin alpha or LT α) share the same cell surface receptors, p55 and p75, which have similar and differential activities depending on the cell type on which they are present [44]. p55 and p75 participate in programmed cell death or apoptosis, whereas p55 is associated with lymphocyte proliferation [45,46]. Tumor necrosis factor alpha increases the production of other proinflammatory cytokines such as IL-1 [47]. It also mediates cell-cell interactions, promotes differentiation of macrophages, influences release of proteolytic enzymes, and induces adhesion molecule expression to aid cellular trafficking into areas of inflammation [48,49].

The generation of TNF knockout mice has confirmed the importance of this cytokine in immunoregulation. Tumor necrosis factor-deficient mice are viable and fertile but are particularly susceptible to infections such as *Candida albicans* and *L monocytogenes* that are normally easily suppressed in immunocompetent mice [50]. In addition, granuloma formation is inhibited in these animals, and there is a notable absence of splenic primary B-cell follicles and germinal centers [51]. Further immunologic abnormalities include impairment of IgG and IgE antibody responses. Although isotype switching can occur in these mice, prolonged antibody responses are generally decreased, causing difficulties with sustained antigen presentation [51].

The link between TNF α and tuberculosis (TB) has also been demonstrated in several animal models in which TNF α plays an essential part in the host response to this infection. Administration of antibodies against TNF α causes reactivation of TB in a mouse model of latent infection [52]. Furthermore, transgenic expression of TNF receptors, leading to reduced TNF activity, results in increased susceptibility to TB [53]. Tumor necrosis factor alpha is thought to participate in host defense against TB by inducing apoptosis of infected cells. Macrophage apoptosis occurs in tuberculoid granulomas and may help contain the infection [54]. Interruption of the normal TNF α -controlled response to TB, leading to reduced apoptosis and absent granuloma formation, may predispose the host to disseminated infection.

Thus, TNF seems to play a fundamental role in both early and late inflammation. Initially, TNF augments the inflammatory process by encouraging cell trafficking to the injured area, helping to localize and destroy the inciting agent. Later, TNF acts to limit the damage by inducing apoptosis of infected cells, maintaining the formation of granulomas and limiting the extent of damage.

These essential functions may be blocked by anti-TNF agents, leaving the patient at risk of new infection or reactivation of latent disease.

Infliximab

Mode of action

Infliximab is a chimeric monoclonal antibody composed of 75% human and 25% mouse protein [55]. It binds with high avidity and specificity to both soluble and membrane-bound forms of TNF α and has been found to lyse TNF α -producing cells in vitro [56]. It does not bind to TNF β (LT α), thus limiting its effects on other biologic pathways and decreasing its potential for toxicity. Infliximab has been shown to neutralize TNF α in a dose-dependent manner, and higher doses provide better disease suppression and longer duration of response than lower dosage regimens [57–60]. Infliximab is administered by intravenous infusion, has a half-life of 8 to 12 days, and does not accumulate with repeated dosing [13].

Infliximab is thought to exert its beneficial effects by decreasing the inflammatory cascade, thus lowering the acute-phase response, inhibiting migration of inflammatory cells, and decreasing production of proteolytic enzymes. It causes an initial reduction in serum IL-6 concentrations followed by a decrease in C-reactive protein levels in patients with RA [61]. In the RA synovial membrane, cellularity is diminished after infliximab treatment, associated with decreased expression of adhesion molecules, reduced angiogenesis, and an increase in the number of circulating lymphocytes [49,62–64].

Efficacy

The efficacy of infliximab has been demonstrated in several clinical trials involving more than 1000 patients with RA [11,13,57,58]. Infliximab also has proven benefits in Crohn's disease and seronegative arthropathies such as ankylosing spondylitis (AS) and psoriatic arthritis [5,65,66]. Furthermore, infliximab is currently being evaluated in the management of vasculitis and myositis. The Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) investigated the clinical and radiologic benefits of various doses of infliximab in 428 methotrexate-treated patients with active RA [11,62]. Each of the four infliximab dosing regimens (3 or 10 mg/kg every 4 or 8 weeks) was associated with clinical improvement compared with placebo. The ACR20 clinical response rates at week 54 were significantly greater in the infliximab-treated groups than in those who received methotrexate monotherapy (42%–59% versus 17%; $P < 0.001$). Quality of life was also significantly better with the combination of infliximab and methotrexate than with methotrexate alone. Furthermore, stabilization of radiographic joint damage occurred in the infliximab-treated groups, whereas those patients given only methotrexate suffered an increase in joint damage over the observation period (mean change in radiographic score, 0.6 versus 7.0; $P < 0.001$).

A dose-response for infliximab was noted in this trial. Further analysis revealed that a significantly greater proportion of patients receiving the lower dose of 3 mg/kg every 8 weeks had undetectable trough serum infliximab levels compared with those treated with higher-dosage regimens [60]. Furthermore, greater clinical and radiologic benefits were observed in patients who had higher trough serum infliximab concentrations, suggesting that some patients with RA may benefit from higher doses or more frequent administration of this drug.

A more recent study used an open-label design to assess the timing of onset of clinical benefit after the initial infusion of infliximab in 553 methotrexate-treated patients with active RA [67]. Infliximab was found to have a rapid onset of action with a 25% to 34% reduction in RA clinical symptoms and signs within 48 hours. By week 16, several clinical scores had improved by 52% to 63%, confirming that the initial benefits are sustained in many patients.

In AS, infliximab also has rapid and sustained clinical and laboratory benefits, with significant decreases in disease activity scores and C-reactive protein levels and improvements in quality-of-life measures. In addition, radiologic benefits using MR imaging of spinal inflammation have been demonstrated [5,66].

Safety

Although infliximab is generally well tolerated, several side effects have been described. In the clinical trials reported to date, adverse reactions, particularly upper respiratory tract infection and headaches, were common in all treatment groups, including placebo. Infusion reactions (defined as any adverse experience occurring during or up to 1 hour after infusion) developed more frequently in the infliximab-treated group than in the placebo arm. These problems mostly occurred during the first infusion and tended to be mild and short lived. No serious infusion reaction was reported in the ATTRACT trial, although four cases of severe hypersensitivity to infliximab occurred in the open-label study [67]. Delayed infusion reactions occurring up to 2 weeks after infusion have been described. Symptoms include fever, rash, arthralgias, dyspnea, and vomiting and are attributed to complement activation and immune complex formation [68]. Serious adverse events (requiring hospitalization) were uncommon in the clinical trials and happened with similar frequency in the infliximab-treated patients and those given only methotrexate.

New and recurrent cancer has been reported in infliximab-treated patients with RA or Crohn's disease. These cases have included lymphomas, breast carcinoma, skin tumors (squamous, basal cell, melanoma), and rectal cancer. Pancytopenia has also been found in a small number of patients treated with infliximab. Because of the relatively low incidence of these problems and their association with the use of concomitant immunosuppressants, the risk for cancer and bone marrow compromise with infliximab is not thought to be increased, although vigilance is required.

Neurologic disorders related to infliximab include aseptic meningitis, demyelination, optic neuritis, peripheral neuropathy, and Guillain-Barré syndrome [69–71]. Diseases resembling systemic lupus erythematosus (SLE) have also

been reported, although the incidence of autoantibody development without associated clinical symptoms is more common [72,73].

The development of human antichimeric antibodies (HACA) has been observed in some patients receiving infliximab. Maini et al [13] reported that the overall incidence of HACA was 17.4%. However, concomitant therapy with low-dose methotrexate significantly decreased the appearance of these antibodies, suggesting that methotrexate reduces the immunogenicity of this biologic agent.

Several patients treated with infliximab have suffered exacerbation of congestive heart failure (CHF). The Anti-TNF α Therapy Against Congestive Heart Failure (ATTACH) trial has shown higher mortality and hospitalization rates in patients with class III/IV CHF who were given infliximab infusions of 5 mg/kg or 10 mg/kg [68]. Thus, caution is advised when prescribing infliximab for patients at risk of heart failure.

Infection and infliximab

Infections have been reported with the use of infliximab. In the ATTRACT trial, the percentage of patients receiving antibiotics was higher in the infliximab-treated patients (44%) than in those taking methotrexate alone (35%). Furthermore, some infections tended to occur more frequently in the infliximab groups, particularly at higher dosages, than in those who received only methotrexate [62]. These infections included upper respiratory tract infections (34% versus 22%), sinusitis (17% versus 6%) and pharyngitis (11% versus 6%). The frequency of serious infections was similar in both treatment groups (8% versus 6%) [11]. Serious infections (defined as those requiring hospitalization) have included pneumonia, bronchitis, peritonitis, septicemia, pyelonephritis, cellulitis, fungal infection, and herpes zoster. In addition, reports continue to emerge associating infliximab therapy with TB, histoplasmosis, coccidioidomycosis, *P carinii* pneumonia, candidiasis, and aspergillosus [11,62,74–78].

Tuberculosis has been the most frequently reported infection. In the United States, the background rate of TB in patients with RA is 6.2 cases/100,000/year. In contrast, recent reports state estimate the rate of TB in infliximab-treated patients with RA as 24.4 cases/100,000/year [74]. Why some patients who receive infliximab become profoundly immunosuppressed and develop these infections is the subject of ongoing investigation. Contributory factors such as concomitant immunosuppressive medication, chronic illness, comorbidity, ethnic background, and environmental exposure may play a part. No coinfection with the human immunodeficiency virus has been reported. In many cases, the diagnosis of TB was made only after considerable evaluation, because of atypical presentation and or disseminated disease. Several cases have been diagnosed post mortem. In the index case of TB, reported by Keane et al [74], the pathologic findings of the open-lung biopsy were also atypical, showing absent granuloma formation and scant evidence of macrophage apoptosis. These observations concur with findings in animal models of TB where TNF α activity is absent or suppressed. Development of TB in patients with RA treated with infliximab is thought to represent reactivation of latent disease because of the age of these

patients (median age, 57 years), the small number with known recent exposure to TB, and the low background incidence of TB in many countries in which the reports have been received [74]. In addition, there has tended to be a close temporal relationship between the commencement of infliximab therapy and the reporting of TB symptoms (median, 12 weeks). Given the role of $\text{TNF}\alpha$ in controlling the immune response to TB, it is likely that patients receiving infliximab also have increased susceptibility to primary TB infection.

The recommendations for patients with RA about to start infliximab treatment include a thorough evaluation to assess the risk for TB. Caution is advised with the use of tuberculin skin tests, because these may be falsely negative in immunocompromised hosts. Latent TB infection should be treated prophylactically before infliximab therapy is started. Furthermore, patients should be advised to seek medical attention if they develop symptoms consistent with TB during treatment with this agent.

Etanercept

Mode of action

Etanercept is a genetically engineered fusion protein, consisting of two identical chains of the recombinant extracellular human TNF-receptor p75 monomer linked to the Fc domain of human IgG1. Because it is composed of only human amino acid sequences, the immunogenic potential of etanercept is low. Etanercept effectively binds $\text{TNF}\alpha$ and $\text{LT}\alpha$ and inhibits their activity. The dimeric structure of etanercept results in high binding affinity for TNF and is approximately 1000 times more potent than native, monomeric TNF receptor in blocking the biologic activity of TNF [79]. In addition, the Fc part of human IgG extends the *in vivo* half-life of etanercept by five- to eightfold.

Etanercept is given by subcutaneous injection, with a typical regimen of 25 mg two times/week. The median time to peak serum concentration after a single subcutaneous dose of 25 mg is 72 hours (range, 48–96 hours). After administration of etanercept, TNF concentrations rise, and the half-life of TNF is prolonged. The TNF activity is reduced, however, because, once TNF is bound to etanercept, it is no longer biologically active [80].

Efficacy

Etanercept has been shown to be highly efficacious in many patients with active RA [4,14,81–83], adult-onset Still's disease [9], seronegative spondyloarthropathies [84,85], and in children with polyarticular juvenile arthritis [12]. The initial placebo-controlled clinical trials in RA demonstrated significant improvements in several disease activity measures, and a dose response was noted [71,82]. The benefits occurred within weeks of commencement of therapy and were sustained throughout the duration of the trials. Disease activity returned towards baseline within 2 months of stopping etanercept treatment, indicating the need for continued treatment. When etanercept was added to methotrexate in patients with active RA, a rapid and sustained improvement in ACR20 and

ACR50 responses was observed compared with methotrexate alone [83]. At 24 weeks, 71% of patients receiving the combination of etanercept plus methotrexate met the ACR20 criteria compared with 27% of those receiving only methotrexate. Furthermore, 39% of patients taking both etanercept and methotrexate achieved an ACR50 response compared with 3% of those taking methotrexate alone. In a separate randomized, double-blind trial, patients with early RA (<3 years) received either etanercept or oral methotrexate for at least 12 months [4]. There were significant benefits in clinical and radiologic scores in the etanercept-treated group. There were also fewer adverse events, including infections, in those who received etanercept. After 24 months of treatment, it was concluded that monotherapy with etanercept was superior to methotrexate in reducing disease activity, arresting structural damage, and decreasing disability in patients with early RA [81]. In a 4-month randomized, placebo-controlled trial of patients with active AS, etanercept treatment resulted in rapid and significant improvements in several measures of disease activity which were sustained throughout the study period [84].

Safety

Etanercept is well tolerated in most patients. Injection-site reactions are the most common adverse events associated with this drug. Such reactions occur in approximately 37% of patients, are generally mild, and tend to develop most frequently in the first month of use and to decrease with subsequent administration [82]. Other side effects are rare, but associations have been described between the use of etanercept and the development of vasculitis [86–88], nodulosis [87], diabetes mellitus [89], pancytopenia, and neurologic events such as demyelination, altered mental status, transverse myelitis, and seizures [71,90]. Cancer rates in the clinical trials of patients receiving etanercept were similar to those of age-, sex-, and disease-matched controls. The clinical trials did not describe an increase in immunogenicity with etanercept, and although a small number of patients developed anti-etanercept antibodies, these antibodies were non-neutralizing and did not compromise efficacy or safety. The development of SLE in four patients with RA who were receiving etanercept was recently reported [73]. In a small study by Ferraccioli et al [91], five of eight etanercept-treated patients had an increase in anticardiolipin (ACA) IgG associated with a *Staphylococcus aureus* nasal or bronchial infection. In four of the five patients, antibiotic treatment resulted in amelioration of the infection and a decrease in the ACA IgG levels to normal, suggesting that susceptibility to infection may predispose to autoantibody formation in patients in whom TNF α activity is inhibited.

Infection and etanercept

Infections are common in RA patients and have been described with the use of etanercept. In clinical trials, there was no significant difference in the infection rates between etanercept-treated patients and non-etanercept-treated disease controls. The most commonly reported infections were mild upper respiratory

tract infections. Serious infections were rare and did not increase in frequency with time. In the 2-year study of etanercept versus methotrexate in early RA, no cases of TB or other opportunistic infections were reported [81]. In postmarketing surveillance, infections in patients receiving etanercept have included pyelonephritis, bronchitis, septic arthritis, osteomyelitis, cellulitis, septicemia, abdominal and foot abscesses, and a psoas abscess caused by *Mycobacterium avium intracellulare* [92]. Viral pneumonia has been described in a separate case report [93]. Bacterial, viral, fungal, and protozoan infections have all been cited with etanercept, and some have been diagnosed within weeks of initiation of therapy. Furthermore, in patients with established sepsis, anti-TNF therapy may increase mortality [94]. Comorbid illnesses and concurrent immunosuppressive medication augment the susceptibility of these patients to such infections. In view of the known role of TNF α in containment of infection, extra vigilance is recommended for all patients receiving any anti-TNF α agents.

Adalimumab

Mode of action

Adalimumab (D2E7) is a fully humanized IgG1 anti-TNF monoclonal antibody. It is structurally identical to naturally occurring human antibodies, thus reducing the risk of immunogenicity [95]. It is specific for TNF and does not bind other cytokines. Preclinical experiments demonstrated the ability of adalimumab to neutralize TNF bioactivity *in vitro*; *in vivo* data showed that adalimumab could prevent the development of arthritis in TNF transgenic mice [96,97]. Adalimumab can be administered by intravenous or subcutaneous injection. Phase I human trials have indicated that the systemic drug exposure increases with higher doses. Adalimumab tends to remain within the intravascular space and has a half-life of approximately 2 weeks [95]. Recent studies have shown that adalimumab treatment decreases production of circulating matrix metalloproteinases and decreases markers of cartilage turnover and endothelial activation [8,98,99]. Adalimumab also reduces proinflammatory cytokine levels in the circulation and synovium [100].

Efficacy

Most of the published data on adalimumab is in abstract form at present, and the official publication of long-term clinical trials is awaited. Several studies of up to 2.5 years in duration have examined the efficacy of adalimumab as monotherapy or in combination with other disease-modifying agents in patients with active RA [6,7,10,15–18]. Adalimumab has been shown to have a rapid onset of action, with improvement in several clinical measures within 2 weeks of commencement of therapy. Furthermore, the clinical benefits are typically sustained throughout the course of treatment. When used in patients with active disease despite concurrent methotrexate, adalimumab therapy results in significant clinical improvements. Furthermore, adalimumab has demonstrable benefits on physical function and health-related quality of life in patients with active RA

[17]. Many of the patients in whom disease activity regressed with adalimumab have had resistant RA refractory to several other disease-modifying agents.

Safety and infections

Adalimumab is well tolerated in patients with RA. Reported side effects include injection-site reactions, headache, and rash. In the ARMADA trial, a 12-month efficacy and safety trial using the combination of adalimumab with methotrexate in 231 patients with active RA, the number of serious adverse events with adalimumab was 0.11/patient/year in the first 6 months of the study and 0.13/patient/year in the second 6 months. The rate of serious infections was 0.02/patient/year and 0.03/patient/year in the first and second 6 months, respectively [10]. The Safety Trial of Adalimumab in RA (STAR) demonstrated a higher number of injection-site reactions with adalimumab than with placebo (8.8% versus 0.6%). The number of serious adverse events (5.3 versus 6.9%), infections (52.2 versus 49.4%), or serious infections (1.3 versus 1.9%) did not differ significantly between the adalimumab and placebo groups [16]. There have been no reported cases of TB or other opportunistic infections in association with adalimumab in any of the clinical trials to date.

Summary

Despite the considerable clinical, radiologic, and functional benefits of biologic inhibitors in inflammatory arthritides, some concern exists regarding the occurrence of infections in patients treated with these agents. Clearly, comorbidities such as diabetes mellitus, heart disease, disability, and concurrent immunosuppressive medication all contribute to the risk of infection. Increased and closer observation may be in part responsible for some of the reported increases in the rates of mild infections with these drugs. The development of serious infections, particularly TB, in patients taking infliximab seems to be greater than would be expected in this population. Furthermore, experimental data from *in vitro* investigations and animal models demonstrate a link between decreased TNF α activity and increased susceptibility to TB. Why some patients, but not others, succumb to rapidly disseminated infection is unknown but may be related to the extent of TNF inhibition in different individuals. This difference in inhibition may also explain why the incidence of TB seems to be increased with infliximab in comparison with the other TNF blockers. Attribution analysis is the method used to assess the likelihood of a connection between two occurrences and includes such factors as temporal association, few alternative explanations, analogy with similar cases, and biologic plausibility. The putative relationship between anti-TNF treatment and infection is further strengthened by the presence of these factors [101].

Continued vigilance is therefore required in the use of biologic agents in patients with RA, most of whom are already in some way immunocompromised. Everyone who is under consideration for such treatment should be carefully

evaluated for the presence of infection, and prophylactic antituberculous therapy should be used if latent TB is discovered. Both patients and primary physicians need to be aware of the possibility that serious infection may develop; if such a problem is diagnosed, the biologic inhibitor should be discontinued until adequate treatment has been completed. Caution is advised in patients with recurring infections and in those with severe comorbidities, for example, poorly controlled diabetes mellitus or heart failure. Administration of live vaccines to patients taking these drugs is not recommended, but patients should be brought up-to-date with all immunizations relevant to their age group before commencement of therapy. Physicians prescribing biologic agents should be encouraged to report any suspected drug-related adverse event. Long-term observation will be required to determine the exact nature of the relationship between cytokine inhibition and infection.

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