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TNFα blockade in human diseases: An overview of efficacy and safety

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Abstract

Tumor necrosis factor-alpha (TNFα) antagonists including antibodies and soluble receptors have shown remarkable efficacy in various immune-mediated inflammatory diseases (IMID). As experience with these agents has matured, there is an emerging need to integrate and critically assess the utility of these agents across disease states and clinical sub-specialties. Their remarkable efficacy in reducing chronic damage in Crohn's disease and rheumatoid arthritis has led many investigators to propose a new, 'top down' paradigm for treating patients initially with aggressive regimens to quickly control disease. Intriguingly, in diseases such as rheumatoid arthritis and asthma, anti-TNFα agents appear to more profoundly benefit patients with more chronic stages of disease but have a relatively weaker or little effect in early disease. While the spectrum of therapeutic efficacy of TNFα antagonists widens to include diseases such as recalcitrant uveitis and vasculitis, these agents have failed or even exacerbated diseases such as heart failure and multiple sclerosis. Increasing use of these agents has also led to recognition of new toxicities as well as to understanding of their excellent long-term tolerability. Disconcertingly, new cases of active tuberculosis still occur in patients treated with all TNFα antagonists due to lack of compliance with recommendations to prevent reactivation of latent tuberculosis infection. These safety issues as well as guidelines to prevent treatment-associated complications are reviewed in detail in this article. New data on mechanisms of action and development of newer TNFα antagonists are discussed in a subsequent article in the Journal. It is hoped that these two review articles will stimulate a fresh assessment of the priorities for research and clinical innovation to improve and extend therapeutic use and safety of TNFα antagonism.

Keywords

Adalimumab; Ankylosing spondylitis; Autoimmune diseases; Biologic therapies; Bronchial asthma; Congestive heart failure; Crohn's disease; Cytokines; Etancerceot; Glomerulonephritis; Hepatitis; Immunotherapy; Infection; Inflammatory bowel disease; Inflammatory diseases; Infliximab; Juvenile idiopathic arthritis; Multiple sclerosis; Psoriasis; Psoriatic arthritis; Rheumatoid arthritis; Sarcoidosis; Tumor necrosis; factor-alpha; Ulcerative colitis; Vasculitis

Introduction

Worldwide about a million patients have been treated with tumor necrosis factor-alpha (TNFα) antagonists for indications that include rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriatic arthritis (PsA), juvenile chronic arthritis (JCA), psoriasis (Ps), and ankylosing spondylitis (AS). Currently, there are three TNFα antagonists licensed for clinical

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use in the United States: two monoclonal antibodies [adalimumab (ADA) and infliximab (INF)] and a soluble receptor [etanercept (ETA)] (Table 1). Since the first license for clinical use in 1998, the three approved TNFα antagonists have shown clear benefits in a series of randomized, controlled trials enrolling over 8000 patients with these diseases. Here, we focus on the human therapeutic experience to examine the utility of these agents across disease states.

TNFα in human diseases

Joint inflammation

Rheumatoid arthritis (RA)—RA is a chronic, progressive, systemic inflammatory disease that targets primarily the synovial tissues, resulting in destruction of cartilage and ultimately bone. Delayed treatment often leads to substantial disability, functional declines, economic losses, work disability, and premature mortality [1]. Non-steroidal anti-inflammatory drugs (NSAIDs) were used to alleviate symptoms prior to realization in 1970s–80s that certain drugs [disease-modifying anti-rheumatoid drugs (DMARD)] can modify the natural course of disease [2]. Many DMARDs can induce significant remission and retard disease progression in a substantial proportion of patients, but with a high complication rate and limited duration of benefit.

Animal studies in early 1990s discovered a major role of TNFα in the pathogenesis of inflammatory arthritis [3]. Simultaneous studies showed elevated levels of TNFα in serum and synovial fluids of patients with active RA, with 4–5-fold higher levels at the site of inflammation (synovial fluid) than in plasma [4]. Neutralization of TNFα in synovial membrane cultures led to reduced secretion of other pro-inflammatory mediators [5]. These studies made the case for TNFα blockade as a therapy for RA. This targeted bench-to-bedside research led to the development of TNFα inhibitors that interfere with the function of TNFα. These agents have been the focus of multiple clinical trials.

Most clinical trials included patients who had active disease despite receiving methotrexate (MTX) therapy, with continued MTX monotherapy serving as the control arm. Addition of an anti-TNF agent to MTX significantly improved patient outcomes [6–10]. Subsequent clinical trials evaluated whether the combination of a DMARD and an anti-TNFα agent was superior to either agent alone [11,12] or compared an anti-TNF agent with placebo [13,14]. Emboldened by the positive results of these trials, investigators probed a window of opportunity by asking whether treating patients with an anti-TNF agent in early stages (less than 3 years) of disease could ‘wipe out’ the disease and provide long-lasting remissions [12,15–17].

We performed a meta-analysis of 12 randomized, controlled clinical trials (Singh et al., manuscript submitted for publication). This analysis suggested a clear benefit effect of anti-TNF agents over placebo or MTX. Interestingly, our analysis also suggested that duration of disease predicts responsiveness to anti-TNF agents. Thus, patients with late disease appeared to have a higher response, irrespective of the anti-TNF agent used, than patients with intermediate to early disease (Singh et al., manuscript submitted for publication). Nevertheless, treatment with anti-TNF agents even in early disease did lead to a significant reduction in structural damage, i.e., radiographic progression.

Although there have been no head-to-head trials, our meta-analyses confirm the general clinical impression that all three currently approved agents have similar overall efficacy in RA. A further analysis of data in early RA patients reveals that whereas MTX and TNFα antagonists appear to be similar in suppression of symptoms and signs of disease, TNFα inhibitors appear to be superior in their ability to contain structural damage (radiographic changes). Moreover, combination of TNFα antagonists+MTX appears better than TNFα antagonists alone, which, in turn, appears better than MTX alone when data on structural damage are considered.

More than two third of patients with RA respond favorably to TNFα inhibitors. The currently available anti-TNF treatments have similar overall efficacy in RA. Even without clinical remission, some patients achieve radiological improvement on anti-TNF treatments. The dose should be tailored in patients to achieve a maximal response. Much lower than the conventional doses are enough in some patients.

Psoriatic arthritis (PsA)—Arthritis involving peripheral joints and axial skeleton affects 7–34% of patients with psoriasis. More than 40% of patients with PsA have deforming, erosive arthropathy and advanced radiological changes. Recent trials led to approval of anti-TNFα drugs for patients with active PsA that is not controlled with NSAIDs in the case of axial disease and sulfasalazine or MTX in the case of peripheral arthritis. Usual dose regimens include INF (5 mg/kg) at 6–12 week intervals, ETA (25 mg SC twice per week), and ADA (40 mg SC every 1–2 weeks) (Table 1). Clinical trials in PsA are summarized in Table 2.

ETA: Placebo-controlled trials of ETA have shown significant improvements in PsARC and ACR20 responses, skin lesions, and physical function in PsA patients with prolonged and active disease [18,19]. During a 6-month open-label extension, further improvements in skin were noted, suggesting that full response took longer to achieve. There was essentially no difference in response in the study arms, implying that ETA can be used as monotherapy or in combination. ETA treatment also significantly inhibited radiological disease progression, as defined by total Sharp score, similar to the effect in RA. However, no difference between treatment and placebo was found in PsA-specific radiologic changes [20].

INF: Highly favorable results in an open-label trial in PsA and in spondyloarthropathy patients with PsA [21] triggered a placebo-controlled trial IMPACT that showed significant improvement in ACR20, ACR50 and ACR70 responses in patients treated with INF. PsARC response was seen in 78% (INF) and 18% (placebo). Enthesitis and dactylitis also showed significant improvement. In a 1-year open-label follow-up, patients originally in the placebo group achieved similar results with INF and efficacy was maintained in those continuing INF treatment.

In the phase 3 IMPACT 2 trial, ACR20 response was seen in 58% of INF and 11% of placebo patients, PsARC in 77% and 27%, and PASI 75 in 65% and 2%, respectively [22], suggesting that the medication was highly effective in skin. The median PASI improvement in ACR20 responders was 87%, whereas the median improvement in ACR20 nonresponders was 74%, suggesting some disassociation of skin and joint response. INF treatment also slowed radiographic progression of joint damage (total modified van der Heijde–Sharp score change of −0.70 vs. 0.82 in the placebo group at 24 weeks). As with ETA, there was no difference between the treatment groups in PsA-specific radiographic features.

ADA: A large placebo-controlled trial, with 50% of PsA patients on background MTX, showed significant ACR20/50/70 and PASI 50/75/90 responses in ADA-treated as compared to placebo-treated patients at week 24 [23]. Responses in both joints and skin were seen as early as week 2. At week 24, ADA patients demonstrated a change of −0.2 modified Sharp points compared with +1.0 in the placebo group. A recent report showed that ADA improved joint and skin manifestations, reduced disability, and inhibited radiographic progression over 48 weeks in patients with PsA who were participants in ADEPT. ADA was well tolerated through week 48 and MTX use at baseline was not required for clinical or radiographic efficacy [24].

The three TNF inhibitors confer significant clinical and radiographic benefit in PsA. However, PsA-specific radiologic changes such as pencil-in-cup change, osteolysis, or periostitis seem to be unaffected with TNF inhibitor therapy, presumably because these are chronic and fixed

types of changes. It is not known whether early use of TNF inhibitors in PsA would prevent or retard the joint destruction seen in PsA.

Ankylosing spondylitis (AS)—AS is a chronic inflammatory disease characterized by inflammation of the sacroiliac joints, entheses, and spine. AS benefits from few therapeutic options other than symptomatic treatment dominated by the NSAIDs. Conventional DMARDs have not shown consistent efficacy, especially in the most typical forms of the disease, which involve predominantly the axial skeleton. ETA, INF, and ADA have been shown not only to significantly improve the signs and symptoms of spondyloarthropathy but also to improve functional status and quality of life and even to attenuate disease progression [25].

Initial open-label reports suggested efficacy of TNF inhibitors. These were followed by more stringent trials of INF [26–30], ETA [31–34], and most recently ADA [35], enrolling over 1000 patients with ankylosing spondylitis. These trials are summarized in Table 3.

INF: At week 12 of a randomized double-blind placebo-controlled study involving 70 patients, there was a 53% improvement in Bath AS Disease Activity Index (BASDAI) with INF vs. 9% for placebo, and 73% vs. 27% of patients who attained the Assessment in AS 20 response criteria [26]. Importantly, in the open-label extension, efficacy was maintained with up to 3 years of continuous treatment [27–29]. A similar improvement was seen in a larger scale randomized, double-blind, placebo-controlled 24-week study involving 279 patients [30].

ETA: Similar improvements have been reported in multiple randomized double-blind placebo-controlled trials using ETA [31–33]. At week 6, Brandt et al. reported BASDAI 50 of 57% vs. 6% in ETA group vs. placebo group in a study of 30 patients and ASAS 20 of 78.6% vs. 25% in ETA vs. placebo, respectively [32]. Calin et al. reported BASDAI 50 of 71.1% vs. 25.6% improvement in ETA group vs. placebo group, respectively, at 12 weeks [34].

ADA: In a randomized, double-blind, placebo-controlled 24-week study with 315 patients, significant improvement was reported [ASAS 20 of 58.2% (ADA) vs. 20.6% (placebo) at 12 weeks and 51% (ADA) vs. 19% (placebo) at 24 weeks] [35].

Considerations: Anti-TNF agents do not induce immunologic tolerance or long-term remission in AS. Virtually all patients with AS have a disease flare upon discontinuation of therapy, with a mean time to flare ranging from about 6 weeks with ETA to 17.5 weeks with INF [32,36]. However, readministration of INF after discontinuation of long-term treatment in 42 AS patients in a 3-year multicenter trial was generally safe and efficacious [37]. TNF inhibition therapy may also improve extra-articular inflammatory involvement in AS. In a systematic review [38] of double-blind, placebo-controlled clinical trials and open-label experience, it was observed that flares of anterior uveitis occurred less frequently under TNF inhibitor therapy (6.8/100 patient-years) compared with placebo (15.6/100 patient-years).

Analysis of treated patients has begun to identify patients, e.g., those with elevated CRP or ESR, who are most likely to benefit from TNF inhibitor therapy [27]. From a clinical standpoint, it will be interesting to see if there are differential responses to treatment in heterogeneous groups of AS patients. The ability of early treatment to reduce disease progression remains to be investigated, as does the question of whether patients with advanced AS will respond.

MTX is not routinely used in combination with TNF inhibitors in AS because MTX is not effective for spinal disease. Given the potential for pharmacokinetic benefits with the mAb TNF inhibitors, it may be useful to more rigorously assess the utility of this combination in AS. Even with the impressive efficacy of TNF inhibitors, most patients have residual

inflammation on MRI. Additional therapeutic paradigms should be explored in order to optimize outcomes.

TNF inhibitors reproducibly induce substantial clinical improvement in AS. The extent of response in outcomes appears to be comparable among the three approved anti-TNF agents. Clinical improvement is rapid and can be seen as early as 2 weeks after the start of TNF inhibitor therapy. Continuous therapy with TNF inhibitors is likely to be necessary to maintain clinical benefit in patients with AS. Restarting therapy has successfully reinduced clinical improvement in most patients. Patients with AS with elevated CRP or ESR tend to respond better to TNF inhibitor therapy.

Juvenile chronic arthritis—Juvenile chronic arthritis (JCA) refers to a group of distinct but heterogeneous disorders characterized by chronic inflammatory arthritis in children. The JCA includes 7 subtypes. The initial study of ETA in polyarticular JCA [39] showed that the mean time to disease flare up was 116 days vs. 28 days with ETA vs. placebo, respectively (Table 4). Of 22 systemic onset juvenile idiopathic arthritis (SOJIA) patients in this study, 17 responded with active treatment. However, during the randomized withdrawal phase, 7 of 8 SOJIA placebo patients and 4 of 9 ETA patients flared, while only 18% of children with other subtypes flared in the ETA group. In the long-term, open-label extension [40], 47% of SOJIA patients compared with 62% with other disease-onset subtypes achieved 70% improvement. The study concluded that children with severe longstanding MTX-resistant poly-articular JRA sustained clinical improvement with >2 years of continuous ETA treatment.

Growing evidence suggests that more SOJIA patients on ETA had a disease flare and/or poor response to it in comparison to the other JCA subgroups [39–41]. In another study that examined response to ETA in MTX-resistant JCA, scores improved by ≥30% in 73% of patients after 3 months, but this proportion decreased to 39% after 12 months. Also, compared to oligoarticular- or polyarticular-onset JCA, SOJIA responded least frequently [42]. In a large cohort of children with refractory SOJIA, ≥50% response was observed in 46% patients [43]. In the German ETA registry with 322 JCA patients [44], 24% of 66 SOJIA patients compared with 54% of patients with other JCA subtypes had a 70% improvement at 12 months; 14 patients had discontinued because of lack of efficacy.

A double-blind placebo-controlled trial of INF in 122 polyarticular-course JRA patients reported clinical improvement at the 6-mg/kg dose but not at the 3-mg/kg dose. Anecdotal reports suggest that very high dose INF may be effective in SOJIA, but this is associated with increased risk of complications. Anecdotal reports on the use of ADA for SOJIA show varied results [45].

TNF inhibitors confer clinically important benefit in children with JCA but may fare less well in the SOJIA subtype.

Gut inflammation

Crohn's disease

INF: After case reports of successful use in patients with severe CD, an open-label study of INF in 10 steroid-resistant patients showed a marked decrease in CD activity index (CDAI) at week 8 [46]. This triggered the first multicenter, prospective, double-blind, placebo-controlled trial, which gave INF as a single dose of 5, 10, or 20 mg/kg and then followed the patients–clinical response for 12 weeks [47]. Patients who did not respond 4 weeks after infusion were given INF in an open-label fashion at 10 mg/kg and followed for an additional 12 weeks. Remarkably, 81% of patients given 5 mg/kg of INF had a clinical response at week 4, and 33% of patients treated with INF went into remission compared with 4% in the placebo group.

A phase III multicenter clinical trial, ACCENT-I, examined maintenance of patients with CD who responded to an induction dose. This study enrolled 573 patients with CDAI ≥220, who received a single dose of INF 5 mg/kg IV before being assigned to one of three arms: placebo at 2, 6, and then every 8 weeks until week 46 (episodic), 5 mg/kg INF at the same time course, or 5 mg/kg at weeks 2 and 6 followed by a dose of 10 mg/kg thereafter. 335 patients (58%) responded within 2 weeks of the induction dose of INF. At week 30, 23 of the patients (21%) given placebo were in remission compared with 44 (39%) in the 5 mg/kg only group and 50 (45%) in the escalated dose group. Median time for loss of response to INF was greater than 54 weeks in both groups on the maintenance dosing schedule. A similar study examined maintenance treatment of moderate to severe CD patients [48]. Maintenance dosing reduced the number of surgeries, hospitalizations, and procedures ($p<0.05$ for all outcomes). Furthermore, INF patients had an improved quality of life as measured by the IBD Questionnaire.

In patients with draining abdominal or perianal fistulas ($n=94$) given placebo or 5 or 10 mg/kg INF IV at weeks 0, 2, and 6, 68% receiving 5 mg/kg achieved at least 50% reduction in the number of draining fistulas and 55% had closure of all of their fistulas [49]. In the double-blind, placebo-controlled ACCENT-II trial in 282 patients with fistulizing CD, 48% had a complete response to INF, defined as the absence of draining fistulas.

Pediatric CD: In a phase 3 study, 112 pediatric patients with moderate to severe CD despite treatment with an immunomodulator±steroids were treated with 5 mg/kg INF IV as induction therapy at 0, 2, and 6 weeks [50]. Patients were then randomized to receive the drug every 8 or 12 weeks. Patients who responded to induction but lost response during maintenance were offered higher or more frequent doses. 88% of patients had a clinical response, and 59% of patients were in clinical remission at week 10. At week 54, 33 of 52 patients receiving every 8-week dosing had a clinical response compared with 17 of 51 patients receiving INF every 12 weeks ($p=0.002$). Corticosteroid usage was also reduced significantly during the study period from baseline.

Step up vs. top down therapy: "Step up" therapy refers to the traditional initiation of steroids in a newly diagnosed CD patient, whereas "top down" therapy describes a new paradigm of treating patients initially with INF to quickly control disease activity. 129 steroid-naive patients diagnosed within 4 years with moderate to severe CD were randomized to receive INF 5 mg/kg IV plus azathioprine 2.5 mg/kg, or prednisone [51]. There was no difference in remission between groups at 6 and 12 months, but there was a striking difference in the percentage of patients in clinical remission without a steroid requirement: 75% vs. 48% (6 months) and 77% vs. 64% (12 months) in the "top down" versus "step up" groups. At month 12, 75% of the patients in the "top down" group had resolution of mucosal ulceration vs. 21% in the "step up" group. These findings bolster the effort to alter the natural history early in the course of chronic inflammation in IBD.

Effect on extraintestinal manifestations: Case reports have described successful use of INF in patients with manifestations such as uveitis, episcleritis, and arthritis [52]. In a randomized double-blind placebo-controlled study of 30 patients with pyoderma gangrenosum (5 mg/kg), 46% of patients had a favorable clinical response over placebo at 2 weeks ($p= 0.025$) [53]. Nonresponders at week 2 were offered open-label INF. By week 6, 69% of patients had responded. INF has also been shown to improve bone mineralization in a cohort of treated IBD patients [54].

ADA: In a small retrospective study, Papadakis et al. suggested utility for ADA in patients who lost their initial response to INF [54]. Seven of the 13 patients who were followed for the

total 6-month period had a complete response to treatment, while 4 had at least a partial response.

CLASSIC I was the first double-blind, placebo-controlled trial of ADA as induction therapy for moderate to severe CD. Remission rates were significant in the 80/40 and 160/80 mg dosing regimens when compared with placebo (p=0.04), but patients in the 80/40 group were less likely to achieve remission than those receiving the 160 and 80 mg doses. The authors identified the optimal dosing regimen as 160 mg at week 0 followed by 80 mg at week 2. Patients were then eligible for enrollment into a study of maintenance treatment [55]. The 275 patients who completed CLASSIC I were given 40 mg ADA SC at week 0 (week 4 of CLASSIC I) and week 2. Those who remained in remission were randomized to receive either ADA 40 mg weekly or every other week or placebo for as long as 1 year. Of the 55 patients who were in remission at week 2, 8/18 patients randomized to the placebo group remained in remission compared to 15/19 in the biweekly treated group and 17/18 in the weekly treated group at week 24, and similar results were obtained at weeks 48 and 56. These results suggest that nearly half of the patients who discontinued ADA maintained a response 6 weeks later.

ETA: A randomized placebo-controlled trial of ETA (25 mg twice weekly) enrolled 48 patients with moderate to severe CD (median CDAI score of approximately 285). Patients treated with ETA fared no better than those given placebo at 4 weeks or at 8 weeks [56].

Placebo response: Many of the studies in the maintenance therapy of patients with moderate CD are plagued by a high placebo rate, averaging about 35%. One reason cited for this high placebo rate is the concurrent symptoms of irritable bowel syndrome in patients with CD [57]. To obviate this problem, many investigators have stratified patients by levels of CRP. For example, recent trials of certolizumab showed that stratifying patients by CRP led to a greater separation between drug response and placebo response groups.

In the “therapeutic pyramid” algorithm of treating patients with CD, INF has maintained its place near the peak, reserved for patients with moderate to severe CD who either do not respond to or are intolerant of conventional therapy (steroids or immunosuppressants azathioprine/6-mercaptopurine or MTX). INF is best for patients with active disease who have already been maintained on these immunosuppressants as these patients experience fewer antibodies, more prolonged efficacy, and less serum sickness [58]. Recommended maintenance treatment for moderate to severe CD is INF 5 mg/kg IV at weeks 0, 2, and 6 and every 8 weeks thereafter. This may be increased to 10 mg/kg for patients who lose efficacy with the lower dose due to antibodies. Anti-TNF biologics (INF and presumably ADA and certolizumab) are the first drugs shown to induce endoscopic and histologic healing in patients with CD, and this healing has now been established as a new benchmark by the FDA for the development of new pharmaceuticals for CD.

Ulcerative colitis (UC)—Evidence for efficacy of anti-TNF therapy in UC is scant. This paucity of data may be due to the dogma of UC as a Th2 mediated inflammatory process characterized by high levels of IL-4 and IL-13. Recent trials, however, have shown that anti-TNF drugs may have a place in UC treatment.

INF: ACT I and ACT II evaluated the use of INF in the induction and maintenance therapy of UC. Clinical response was defined as a decrease in the Mayo score of 3 points and 30% from baseline with a corresponding decrease in the rectal bleeding subscore. Primary endpoint was clinical response at week 8, which was statistically significant for INF versus placebo.

INF was recently FDA approved for adult patients with moderate to severe UC.

Skin inflammation

Psoriasis is an inflammatory skin disease. TNFα is thought to play a part in its pathogenesis. As summarized in Table 2B, all three anti-TNF agents have been found to be effective in the treatment of moderate-to-severe psoriasis, with a high percentage of patients achieving sustained PASI 75 and PASI 90 improvement through 1 year, along with significant improvement in health-related quality of life [59–62]. All three agents have been well tolerated in most patients.

Anti-TNF therapies have also been reported in a variety of dermatologic diseases, including cicatricial pemphigoid, Behcet's disease, hidradenitis suppuritiva, pyoderma gang-renosum, acne, apthous stomatitis, pityriasis rubra pilaris, eosinophilic fasciitis, and panniculitis, with excellent tolerance and varied success (reviewed in [63]).

INF and ETA have recently been approved for use in moderate to severe plaque psoriasis.

Other human diseases: successes and failures

Experimental and human studies suggest that TNFα plays a major role in pathogenesis of inflammation in a broad spectrum of diseases. A few examples of diseases where TNFα inhibitors have been used are described in the following sections.

Lung inflammation—In an open-label trial of 15 patients maximally treated for chronic severe asthma [64], 25 mg ETA administered SC twice a week for 12 weeks clearly improved lung function, attenuated airway hyperresponsiveness, and reduced overall asthma symptoms scores with all but 1 patient discontinuing regular bronchodilators by study end. In a 10-week, randomized placebo-controlled crossover trial of ETA (25 mg SC twice weekly) in 10 patients with chronic severe asthma refractory to treatment with inhaled corticosteroids, ETA-treated patients had attenuation in airway hyperresponsiveness and significant improvement in FEV1 and in overall asthma symptoms scores compared with placebo [65]. However, in patients with a mild form of the disease, treatment with ETA, 25 mg SC, twice weekly for 2 weeks, failed to attenuate pulmonary eosinophilia or reduce airway hyperresponsiveness to methacholine [66]. Thus, anti-TNF agents appear to benefit patients with a more severe chronic stages of the asthma but have little effect in early disease [65].

Given the similarities between chronic severe asthma and COPD, anti-TNFα has been tried in the treatment of COPD. However, a phase II trial of INF in patients with mild-to-moderate COPD failed to reach any definite conclusions about its effectiveness in COPD. More definitive conclusions about effectiveness of anti-TNFα drugs in COPD will require carefully designed studies with large numbers of patients with adequate disease severity.

Neurological inflammation—Elevated TNFα serum levels have been demonstrated in serum and CSF of some patients with MS, acute inflammatory demyelinating polyradiculopathy (Guillain Barre Syndrome), chronic inflammatory demyelinating polyradiculopathy, and nerve injury [67]. In chronic progressive MS, CSF levels of TNFα correlate well with disability and rate of neurologic deterioration [67]. An uncontrolled, retrospective study suggested that ETA may be effective in refractory cases of chronic inflammatory demyelinating polyneuropathy, but trials with TNFα antagonists in MS have not been promising [68]. A phase II randomized double-blind placebo-controlled trial of 168 MS patients treated with Lenercept, a TNFα receptor IgG1 fusion protein, resulted in an increase in MS exacerbations and a shortened time to flare [69]. In an open-label, phase I safety study, INF was given to two patients with rapidly progressive MS [70]. Both patients had transient increases in the number of lesions on MRI and increases in CSF leukocyte counts and IgG levels, suggesting increased disease activity.

Ocular inflammation—More experience is needed to clarify the indications and risks of TNF inhibitors in ocular inflammatory diseases. Some studies have suggested that INF might be more effective than ETA in the treatment of recalcitrant uveitis [71].

Graft-versus-host disease (GVHD)—The association of higher serum TNFα levels with worse outcome in patients with GVHD provided the rationale for the use of TNFα antagonists. Early studies show that TNFα antagonists are well tolerated and can induce a high response rate in patients with steroid-refractory acute and chronic GVHD [72].

Uncommon systemic diseases—TNFα antagonists have been used, anecdotally, with success in patients with refractory cases of Behcet's, rheumatoid vasculitis, Churg Strauss syndrome, Kawasaki's arteritis, Takayasu's arteritis, giant cell arteritis, polyarteritis nodosa, and cryoglobulinemic vasculitis [73].

Diseases where anti-TNF agents have failed—Levels of TNFα are elevated in patients with congestive heart failure (CHF) [74]. Elevated levels of TNFα correlate with a worse New York Heart Association (NYHA) functional status for CHF, a greater number of hospitalizations, and increased mortality. Studies with animal heart models revealed that high concentrations of TNFα had negative inotropic effects and caused left ventricular dilatation, resulting in depression in function. Clinical and experimental research suggests that elevated levels of TNFα appear to mediate cardiac injury. These data resulted in clinical trials to study a possible therapeutic role of TNFα inhibition in CHF. However, two large trials with ETA and a pilot trial with INF in clinical heart failure failed to show any improvement in morbidity and mortality [75,76]. While these disappointing results may have various explanations, anti-TNF agents should not be used to treat patients with NYHA Class III or IV heart failure, given the lack of evidence of beneficial effect. Further details are discussed in the following section.

TNFα may accelerate inflammatory processes in sarcoidosis. Hence, INF and ETA have been studied in patients with pulmonary and extrapulmonary sarcoidosis refractory to steroids. ETA was assessed in a preliminary trial of patients with progressive sarcoidosis, but the trial was stopped because of treatment failure in majority of participants [77]. A more recent phase 2 clinical trial using INF showed a statistically significant improvement in % predicted FVC at week 24, supporting further evaluation of anti-TNF therapy for sarcoidosis [78].

In summary, early reports suggest the clinical utility of TNF inhibitors in a variety of inflammatory diseases, as discussed above. In other diseases, such as multiple sclerosis, TNF inhibitors have been unsuccessful so far.

Adverse consequences of TNFα blockade therapies

Infections

Most infection data related to TNFα blockers come from postmarketing studies, which provide longer term risk estimates but are not well controlled for selection bias or bias by indication. Varying definitions of a "significant" or "serious"infection are a further complication. Of seven major reports on infections, increased frequency of "serious" infections with anti-TNF agents was reported in 3, while the other 4 showed no difference compared to other DMARDs [9, 79–81]. A recent meta-analysis investigated serious infections and malignancies in RA patients [82]. Serious infections were reported in 126 of 3493 (3.6%) of patients treated with anti-TNF antibodies and in 26 of 1512 (1.7%) of controls. Data interpretation is complicated by factors such as the time of exposure (the authors did not normalize for exposure), heterogeneity of the patient populations, and omission of ETA from this analysis.

The CORRONA database examined 5596 RA patients, followed for 6817 patient-years, comparing patients on TNF inhibitors (3012 patients and 2722 patient-years; 48% INF, 40% ETA, and 12% ADA) to those not using TNF blockers. Thirty-seven infections occurred per 100 patient-years with TNF inhibitors, compared with 29 per 100 patient-years in those not on TNF inhibitors. After adjusting for age, gender, disease duration and activity, comorbid conditions, previous DMARDs, and prednisone, there was a small increase in infections with TNF inhibitors (incident rate ratio 1.16, 95% CI: 1.06, 1.28, p= 0.002) [83]. The German Biologics Registry reported relative risk of all infections of 2.13 to 2.16 (CI>1) after adjusting for propensity scoring [84]. Pulmonary and skin infections, particularly herpes, were more frequent, while infections of the GI tract bone or joint did not appear to be increased. The United Kingdom nationwide registry compared patients on TNFα antagonists (2247 ETA patients, 2398 INF patients, 659 ADA patients) to 648 patients on DMARDs [81]. Serious infections were defined as those requiring hospitalization and IV antibiotics or resulting in death. After adjustments, there were no differences between serious infection rates in those using ETA, INF, or ADA compared to DMARD controls.

Some evidence suggests a small increase in infections in patients taking anti-TNF agents. Unfortunately, the data regarding “serious” infections are somewhat inconsistent.

Chronic and serious viral infections—A review of published case reports suggests that INF±MTX might reactivate chronic HBV infection, yet concurrent treatment of INF±MTX with lamivudine can stabilize HBV disease activity. There are no consensus guidelines regarding screening or treatment strategies for prevention of HBV reactivation in patients receiving anti-TNF therapy. It is prudent to screen all patients for hepatitis B prior to treatment with anti-TNF therapy using hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody. For patients with chronic hepatitis B, one should consider using anti-TNF therapy only in concert with hepatitis B treatment with antiviral agents and following with periodic serum aminotransferases and serum HBV DNA levels. However, studies are needed to determine any long-term side effects of concomitant therapy with lamivudine or other antiviral treatment.

Chronic hepatitis C virus (HCV) infection is endemic in many areas of the world. Case reports, a small prospective study, and a randomized, double-blind, placebo-controlled study, suggest that anti-TNF therapy may be safe and even beneficial in chronic HCV. However, these data are very preliminary and one must exercise great caution when considering anti-TNF therapy in chronic HCV infection. Interval monitoring of serum aminotransferases and HCV viral load is recommended.

HIV infection is associated with inflammatory arthritis, reactive arthritis, psoriasis, myositis, and vasculitis. Elevated TNFα levels are seen throughout all stages of HIV infection. Several case reports and controlled trials have examined anti-TNF therapy in patients with underlying HIV infection [85,86]. One of seventeen patients given single doses of ETA or INF had an adverse event (elevated creatinine) and 13 patients with HIV and active TB given 4 weeks of ETA had no adverse events. Of three patients using INF (2 patients) or ETA (1 patient) for 6 weeks to 18 months, rheumatic response was dramatic but the ETA-treated patient developed multiple infections leading to death. The data on anti-TNF treatment of HIV-infected individuals are extremely limited and TNF blocking agents should be used very carefully, given the risk of activation of infections in this immunocompromised population. In addition, a thorough discussion of the relative risks and benefits is needed before initiation of anti-TNF therapy.

Fungal infections—Fungal infections were not significantly increased in anti-TNF studies. However, a systematic review of the FDA Adverse Events Reporting System (AERS) database

from January 1998 to September of 2002 showed that granulomatous infections with INF were reported 3.25 times that of ETA and that 72% of INF-associated infections occurred within the first 90 days [87]. Although the incidence of fungal infections after anti-TNF therapy is extremely low and there is no clear indication that any one agent predisposes patients to fungal infections, a number of fungal infections have been reported to the FDA AERS. Based on current case reports and postmarketing surveillance data, it is prudent to counsel patients about the risk of fungal infection prior to initiation of therapy and to closely follow them during the first 3 months after initiation of INF. If a patient on anti-TNF therapy develops a fever, fungal infections should be considered. In regard to histoplasmosis and cryptococcus, patients should be counseled to avoid high-risk exposures such as cave exploring and cleaning bird roosts. In areas endemic for coccidioides such as the Southwestern United States, patients can have c. immitus titers checked prior to initiation of anti-TNF therapy. If positive, empiric prophylaxis with fluconazole can be considered, although no consensus guidelines currently exist for this therapy.

Tuberculosis—Although pre-registration studies with anti-TNFα agents revealed 15 cases of TB among over 8000 treated RA patients, passive surveillance studies have suggested a higher incidence of TB in association with TNFα antagonists [88]. There have been several reviews of the FDA's AERS examining TB associated with TNFα antagonists. In the first review of the AERS database, conducted from 1998 to May 2001, the estimated rate of TB among RA patients treated with INF in the US was 24.4 cases per 100,000, compared to a background TB in RA patients of 6.2 cases per 100,000 per year in US [89].

A review of the AERS database from November 1998 to March 2002 identified 25 cases of TB occurring in association with ETA, with a median interval of 11.5 months [90]. The estimated reporting rate of TB in patients with RA treated with ETA was ~10 per 100,000 patient-years.

In global clinical trial data released by Abbott pharmaceuticals in >10,000 RA patients, all of whom were screened for latent TB, the event rate of TB per 100 patient-years was 0.24 in longstanding RA (>3 years) and 0.11 per 100 patient-years in early RA [91]. In an analysis of the US postmarketing safety of ADA from Abbott-supported trials from 2002 to 2004 of pre-screened patients with an estimated 55,384 patients years of exposure, 11 patients were reported to have TB, yielding a rate of 0.02 per 100 patient-years [91]. Three of the eleven (27%) had extra-pulmonary TB.

An analysis of the BIOBADASER (Spanish Society of Rheumatology Database on Biologic Products) database revealed 17 cases of TB reported in 1540 patients, all associated with INF [92]. The estimated relative risk in INF-treated patients versus control RA patients was 19.9 (95% CI 16.2–24.8) in the year 2000 and 11.7 (95% CI 9.5–14.6) in the year 2001. The authors concluded that INF therapy was associated with an increased risk of TB. These data, however, arose in an era when pre-screening for TB was just beginning and it would be difficult to extrapolate the data to the present.

A study from Sweden, where the risk of TB in the general population in Sweden was reported as 5 cases per 100,000 persons, reported 15 cases of TB in RA patients treated with anti-TNF therapy from 1999 to September 2004 [93], 11 with INF, 6 with ETA, and with 2 patients receiving both agents. The relative risk of TB in RA patients on anti-TNF therapy compared to a control RA group not treated with TNFα antagonists was 4.0 (95% CI: 1.3–12). The calculated relative risk of TB in the control RA population compared to the general Swedish population was 2.0 (95% CI 1.2–3.4). The authors concluded that Swedish patients with RA are at increased risk for TB and that treatment with TNFα antagonists further increased this risk.

Although passive surveillance data are often insufficient to prove a causal relation, all three reviews of the AERS database revealed an increased risk of TB in anti-TNF-treated patients when compared to the general population, although they precede TB pre-screening as standard of care. They also revealed a generally higher incidence of TB with INF over ETA, at greatest frequency within the first 12 weeks of INF treatment. Recent studies in TB post-screening era, however, suggest that all available TNF antagonists pose a similar risk of active TB [94].

Screening for TB is strongly recommended prior to initiating therapy with TNFα antagonists. Several consensus guidelines for screening and treatment have been proposed by different organizations in Spain, France, and the United States [92]. A Spanish study evaluated the effectiveness of recommendations set forth to prevent reactivation of latent TB in patients treated with TNFα antagonists [95]. Rates of active TB after implementation of the recommendations decreased by 78% (incidence risk ratio 0.22, 95% CI: 0.03–0.88, p=0.008), highlighting the effectiveness of their implemented strategies.

The importance of TB prevention recommendations was highlighted in a recent report from the BIOBADASER registry, which evaluated new cases of active TB in 5198 patients treated with TNF antagonists after the dissemination of recommendations to prevent reactivation of latent TB infection [94]. Fifteen active TB cases were noted (rate 172 per 100,000 patient-years, 95% CI 103–285). The probability of developing active TB was 7 times higher when recommendations were not followed. Thus, new cases of active TB still occur in patients treated with all available TNF antagonists due to lack of compliance with recommendations to prevent reactivation of latent TB infection.

It is prudent to counsel all patients regarding the risk of TB when considering anti-TNF therapy. All patients should be screened for latent TB with history, physical examination, and purified protein derivative (PPD) skin tests. RA patients–PPDs may be affected by reduced cell-mediated immunity and/or RA treatment, both tending to increase the possibility of false negatives. Thus it may be appropriate to consider chest films in RA patients when there is a suspicion of a compromised skin test. Also, the FDA recently approved QuantiFERON-TB Gold test, which measures interferon-α production after 16–24 h incubation of whole blood with synthetic peptides [96]. The assay appears to be more sensitive for detecting latent tuberculosis in patients with impaired cell-mediated immunity and is not affected by prior BCG vaccination, which is particularly important for populations where BCG vaccination is routine and tuberculosis is endemic. Another interferon-α based assay, T-SPOT.TB (ELISPOT assay), not yet available in the US, appears even more promising in this regard. Ongoing studies are validating these tests in patients with RA.

Treatment of latent TB should be initiated prior to starting anti-TNF therapy. There is a paucity of data regarding when TNFα antagonists can be started, whether treatment with a single agent (i.e., INH) is sufficient, and how long the therapy should be continued. Most physicians use INH alone, but the duration of therapy before starting anti-TNF therapy has ranged from 1–2 weeks to 6 months. Likewise the duration of INH therapy that is considered sufficient has ranged from 6 to 9 months, and the insistence on observed treatment (observing each time tablets are taken) has been debated [97]. Clinicians must be aware of the preponderance of unusual TB case presentations in patients treated with TNFα antagonists. TNFα antagonists should be immediately discontinued in the setting of active TB infection. Whether to resume anti-TNF therapy after TB therapy is completed is still controversial.

Non-infectious adverse consequences of TNFα antagonists

Malignancy

Lymphoma: Several epidemiologic studies have demonstrated an increased risk of lymphomas in patients with RA, occurring well before the advent of TNFα antagonist therapy. It is debated whether the risk is attributable to disease activity and severity or medical treatment. No specific DMARD has been definitively linked to increased lymphoma risk.

Several reports have evaluated the risk of lymphoma in patients treated with TNFα blockers [91,98,99]. Standardized incidence ratio (SIR) values vary from 2.6 to 11.5 in anti-TNF-treated groups compared to the general population. One study that compared the rate of lymphoma in TNF-treated RA patients to a control RA group found no increased risk [100]. A recent cohort study of 1152 biologic users and 7306 MTX users from 2 US states and 1 Canadian province [99] demonstrated a propensity score-adjusted pooled hazard ratio was 1.37 (95% CI 0.71–2.65) for hematologic malignancies and 0.91 (95% CI 0.65–1.26) for solid tumors, which does not support the likelihood of increased risk of malignancies by the use of biologic agents compared to MTX.

A rare form of non-Hodgkin's lymphoma that affects the liver and spleen, hepatosplenic Tcell lymphoma (HSTCL), has been reported in children and young adults taking INF for CD [101]. Six young adults (5 males, 1 female, aged 12–31) were diagnosed with HSTCL after receiving at least 2 doses of INF treatment. All patients were receiving other immunosuppressive drugs. Other TNF inhibitors have been minimally used in pediatric Crohn's, hence their safety in this regard is unknown. No cases have been reported with any TNF inhibitor in RA or juvenile arthritis.

More long-term data are needed to develop a consensus on the estimated risk of lymphoma with anti-TNF therapy. Continued surveillance of patients is warranted until the relationship of lymphoma development with TNFα antagonists is fully characterized.

Solid tumors—Studies of TNFα antagonist therapy in RA reveal no increased risk of solid tumors compared to the general population [99,102], corroborating results reported by the FDA. In contrast, a recent meta-analysis [82] reported higher rates of malignancies in RA patients treated with anti-TNF agents (29 of 3493 or 0.8%) compared to those on either placebo or active controls (3 of 1512 or 0.2%). However, malignancy remained rare overall. Studies in specific populations, however, have suggested some increased risk. For example, a study of ETA in patients with Wegener's granulomatosis, all of whom had previously received treatment with cyclophosphamide, reported an excess of solid tumors [103].

Congestive heart failure (CHF)—Randomized controlled clinical trials of anti-TNF agents in CHF showed dose-dependent trends toward worse prognosis [75,76]. Other studies did not indicate an increased risk of CHF from TNFα antagonist use [91,104]. These studies have led to following recommendations regarding anti-TNF therapy: (a) RA patients with no history of CHF do not need a baseline echocardiogram to screen for heart failure; (b) patients with well-compensated, mild CHF (NYHA classes I and II) should have a baseline echocardiogram done. Patients with a normal ejection fraction can receive therapy after a fully informed discussion with the patient, but close monitoring is required. Anti-TNF therapy should be avoided in patients with a decreased ejection fraction. This recommendation implies, but does not require, use of echocardiography in patients with a history of CHF; (c) anti-TNF therapy should be avoided in patients with NYHA class III or IV heart failure; (d) patients who develop heart failure while on anti-TNF therapy should be discontinued and be evaluated for other causes of heart failure. We currently recommend against the reinstitution of anti-TNF therapy in such patients.

Hemocytopenias—Although extremely rare, hematological dyscrasias such as aplastic anemia and pancytopenia have been described in association with TNFα antagonists. There are no current recommendations for regular monitoring of blood counts, but physicians should educate patients to seek medical attention if they develop signs and symptoms of pallor, gum bleeding, easy bruisability, generalized bleeding, persistent fever, or infection. If a patient develops aplastic anemia or pancytopenia while on anti-TNF therapy, the agent should be stopped and the patient should be evaluated for evidence of other underlying disease.

Neurological—Demyelinating disorders have been described in postmarketing surveillance and published case reports with all three TNFα antagonists. However, it is difficult to make any causal association given the limitations of postmarketing data collection. The incidence of demyelinating disease does not appear to be increased in patients on anti-TNF therapy when compared to the general population. Until more data are available, these agents should be avoided in patients with pre-existing demyelinating conditions such as multiple sclerosis. TNFα antagonists should be stopped if a patient develops a new-onset demyelinating disorder. Data on seizures following anti-TNF therapy are anecdotal, and a pre-existing seizure disorder does not seem to be a contra-indication to anti-TNF therapy.

Autoimmune and inflammatory conditions—Several studies have documented the occurrence of ANA and anti-dsDNA antibodies with anti-TNF use [105,106]. Across various cohorts, the prevalence of ANA in RA patients rose from 28% (range 24 to 40%) before INF to up to 80% (range 69 to 95%) after 30 to 104 weeks of INF treatment. As expected, the occurrence of positive ANA in the seronegative spondy-loarthropathies at baseline was much lower, 8% (range 4 to 12%); it increased up to 46% (range 29% to 62%). As per the INF package insert, 15% of INF-treated patients developed anti-dsDNA antibodies compared with none in the placebo arms. As per the ETA package insert, 11% of 323 patients treated with ETA in clinical trials developed a positive ANA compared with 5% of the placebo group. In 549 patients from a Scandinavian registry, anti-DNA increased from 0.4% to 3% after treatment with ETA [107]. In a small study of 20 patients with seronegative spondyloarthropathy treated with ETA, the ANA rose from 15% to 30% and the anti-dsDNA rose from 0 to 15% after 2 years [108].

So far, there is no correlation between the incidence of anti-dsDNA antibodies in patients taking anti-TNF agents and SLE. However, there is a very low incidence of SLE that occurs with the use of TNF blocking agents. In Centocor postmarketing surveillance data, SLE occurred in 2 of 2292 patients (0.22%). A retrospective review of all TNFα inhibitor use in French hospitals [109] documented an incidence of 0.19% for INF and 0.18% for ETA.

Anti-cardiolipin antibodies (ACL) increased from about 16% to about 26% after 6 months in 121 RA patients [110]. ACL-negative patients had a better ACR20 response to INF than ACL positive patients; no such correlation was found for ETA. One study found an increase of up to 15% in ACL among patients using ETA over 5 years while others showed no change [107,108].

Anti-histone antibodies increased from 18% to 79% in 59 RA patients on INF or ETA in one report [111]. In contrast, DeRycke et al. showed no increase in anti-histone antibodies for either INF or ETA-treated patients with RA or seronegative spondyloarthropathy [108].

A different form of antibodies that should be considered is anti-ETA or anti-ADA antibodies (HAHA: human anti-human antibodies) or anti-INF antibodies (HACA: human anti-chimera antibodies). HACA developed more commonly in patients who were nonresponders to INF (6 of 10 patients at three months) or in patients who had infusion reactions (3 of 11 patients) than in patients who responded to therapy (0 of 10 patients) or controls (0 of 11) [112]. Limited data

with respect to ADA show that 8% of 71 RA patients developed HAHA and this correlated inversely with the ACR20 response [113]. No such correlation was found for ETA, although 5% of the patients developed antibodies among 549 patients [107].

In summary, ETA and INF are associated with the formation of autoantibodies (especially ANA, anti-dsDNA and anti-cardiolipin antibodies). The formation of these antibodies is not associated with any specific clinical syndrome. On the other hand, a clinical syndrome of SLE occurs rarely (approximately 0.2%) and seems to be associated with both ETA and INF. Little is published about the formation of antibodies after ADA.

Vasculitis: The rare reports of vasculitis in patients receiving TNFα antagonists are puzzling. The causal association is based upon one or more of the following: temporal association between drug and onset of vasculitis, development of new serological abnormalities suggesting drug-induced autoimmunity such as a positive ANA or anti-dsDNA, improvement or resolution of vasculitis after drug discontinuation, or recurrence of vasculitis upon reintroduction of the drug. One theory is that TNFα antagonists and TNFα form immune complexes that are deposited in small capillaries, triggering a type III hypersensitivity reaction. Another is that anti-TNF agents induce a lupus-like reaction, which results in vasculitis. Cutaneous vasculitis represents the most cases of vasculitis described after anti-TNFα therapy. The largest case series was obtained from the FDA AERS [114]. Thirty-five cases of leukocytoclastic vasculitis (LCV) were identified –20 with ETA and 15 with INF. In 22 of the 35 cases, patients had marked improvement or complete resolution of LCV after discontinuation of the TNFα antagonist. Six patients experienced recurrence of LCV after reinitiating anti-TNF therapy. Vasculitis appears to be a very rare but potentially serious complication that likely represents a type III hypersensitivity reaction. In patients who develop this reaction, it is safest to stop the TNFα antagonist and treat with a regimen of steroids and antihistamines with or without immunosuppressive agents.

Glomerulonephritis and other inflammatory conditions: We found 11 cases of biopsy proven glomerulonephritis occurring after anti-TNF therapy in the literature: 8 with ETA, 2 with ADA, and 1 with INF. In three of these patients, discontinuation of the TNFα antagonist along with treatment with steroids and immunosuppressives resulted in improved renal function. The one patient in whom ETA was continued developed alveolar hemorrhage with pauci-immune pulmonary vasculitis on lung biopsy.

Other inflammatory conditions: There are now more than 20 reports on anti-TNF treatment-associated psoriasis, emphasizing the importance of postmarketing experience vs. clinical trials. There are also reports of rare cases of discoid lupus and cerebral thrombophlebitis described with anti-TNF therapy.

Injection/Infusion site reactions: Injection site reactions are common with ETA and ADA, usually in the first month of treatment and decreasing with time. INF is associated with mild infusion reactions requiring a decrease in infusion rate or pretreatment with a histamine H1 receptor antagonist with or without low-dose parenteral glucocorticoids. If a patient develops a serious infusion reaction or anaphylactic reaction to INF, therapy should be stopped and supportive care administered until the patient is stabilized. The patient should not receive another dose of INF.

Safety in pregnancy: The currently approved TNFα inhibitors are classified by the FDA as pregnancy risk category B, i.e., no adverse pregnancy effects in animal studies and insufficient controlled human studies. There is a limited experience with TNFα inhibition during pregnancy [115]. From the INF Safety Database, where pregnancy outcome was available for 96 women with CD or RA directly exposed to INF before or during confirmed pregnancy, there was no

increased risk of adverse pregnancy outcome [116]. An interim analysis by the Organization of Teratology Information Services did not find increased rates of miscarriage and fetal malformation in RA patients exposed to ETA or INF as compared to RA controls, but there was an increase in preterm delivery and low birth weight infants in all RA patients The British Society for Rheumatology Biologics Register in patients with rheumatic diseases exposed to TNFα inhibitors did not find an increased rate of toxicity to the fetus or mother [117]. Thus, data available so far suggest that TNFα inhibitors may be safe during early pregnancy. Larger prospective studies are needed.

Data are even more scant on the safety of TNFα inhibitors during the second and third trimesters when placental transport of IgG is generally more efficient than in the first trimester. In 14 women with CD or RA exposed to TNFα inhibitors beyond the first trimester, all pregnancies yielded live births with no congenital anomalies. Three infants were premature, one had low birth weight, and two had perinatal complications [54,115,117]. A case report in a 33-year-old woman with CD suggested that the INF antibody crossed from the mother's placenta to the fetus, with the prolonged half life of INF in the infant [54]. A long-term follow-up of this and similar cases will be critical to gauge the effects of TNFα blockade in early life.

Complications associated with anti-TNF agents are summarized in Table 5.

Synthesis

It is hoped that the three currently approved TNFα antagonists are just the beginning of disease mechanism-based therapies in IMID. Such new treatments may also provide an opportunity to dissect disease mechanisms. It would be critical to identify biomarker and genetic profiles of patients who are likely to respond to anti-TNF agents. Industry leaders and federal agencies must take these opportunities to fund studies using human materials from trials to identify disease and drug mechanisms. While relocation of record number of basic and clinical investigators to industry in recent years is likely to speed new drug development, universities and federal funding agencies must do their part to produce and retain investigators to fuel uninhibited basic and clinical research. Finally, as these highly effective drugs are bringing revenues to industry, some of this must be devoted to develop newer drugs or processes to bring these effective therapies to the masses, thus reducing the suffering, improving the workforce and socioeconomic well-being of the world.

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Table 1

TNFα antagonists licensed for clinical use

Drug	Form	Disease indications[a]	Dosage and administration
Infliximab (INF)	Chimeric humanized IgG1 anti-TNF antibody	RA	Intravenous infusion 3 to10 mg/kg every 8 weeks
		AS CD UC PsA Plaque Ps (chronic severe) Pediatric Crohn's	
Etanercept (ETA)	Soluble TNFRII-human Fc fusion protein	RA	Subcutaneous injection 25 mg twice a week; 50 mg per week; or 50 mg twice weekly followed by reduction to maintenance dose of 50 mg weekly
		JCA (polyarticular) PsA AS Ps (chronic moderate to severe)	
Adalimumab (ADA)	Recombinant human IgG1 anti-TNF monoclonal antibody	RA	Subcutaneous injection
		PsA AS CD	40 mg every other week 40 mg weekly

AS, ankylosing spondylitis; CD, Crohn's disease; JCA, juvenile chronic arthritis; Ps, psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis.

[a] Indications approved by the Food and Drug Administration (FDA) and European Union EMEA.

Table 2

Clinical trials of TNFα antagonists in psoriatic arthritis (PsA) and psoriasis (Pso)

Reference	Agent	Protocol	Disease duration (mo) at entry (median)	Previous treatment	Endpoints
A. PsA					
[18]	ETA	25 mg BIW, 12 weeks study	PsA: 9.5 (placebo), 9.0 (ETA); Pso: 17.5 (placebo), 19 (ETA)	Allow MTX and steroid Previous use of DMARDs	At week 12, PsARC response in 87% vs. 23% in ETA vs. placebo; ACR20 in 73% vs. 13%
[19]	ETA	25 mg BIW, 24 weeks, then open-label up to 48 weeks	PsA: 9.2 (placebo), 9.0 (ETA); Pso: 19.7 (placebo), 18.3 (ETA)	Allow MTX and steroid	At 12, 24, and 48 weeks, 59% on ETA vs. 15% on placebo achieved ACR20. PASI significant at 24 weeks. Radiographic progression inhibited
[118]	INF	5 mg/kg, 16 week then open-label up to 50 weeks study	PsA: 11 (placebo), 11.7 (INF) Pso: 19.4 (placebo), 16.9 (INF)	DMARDs, NSAIDs, steroid	At 16 weeks, ACR20 response in 65% INF vs. 10% placebo. 29% vs. 0% ACR70. Benefit sustained through week 50
[22]	INF	5 mg/kg, 24 weeks study	7.5 (placebo) 8.4 (ADA)	DMARDs, NSAIDs, allow MTX, and steroid	At 14 weeks, ACR20 in 58% on INF and 11% on placebo. PsARC 77% vs. 27%. PASI 75 in 64% vs. 2%
[23]	ADA	40 mg every other week, 24 weeks study, 299 completed the study	9.2 (placebo) 9.8 (ADA)	MTX	At weeks 12 and 24, ACR20 in 58% ADA vs. 14% placebo. Sharp score -0.2 vs. 1. PASI 75 in 59% vs. 1%. Disability and quality of life improved.
[24]	ADA	Patients who completed the ADEPT trial elected to receive open-label ADA 40 mg sc BIW after 24 weeks, 48 weeks study		MTX (some patients)	At 48 weeks, 56%, 44%, and 30% patients achieved ACR20, ACR50, and ACR70 response rates, respectively. 33% achieved PASI 100. Reduced disability index
B. Pso					
[119]	INF	5 or 10 mg/kg or placebo at 0, 2 and 6 weeks (11 in each group); 10-week study	6 mo or more	Topical corticosteroid failure	9 in 5 mg group and 10 in 10 mg group vs. 2 in placebo responded
[120]	ETA	Placebo, 25 mg wkly, 25 mg twice wkly, or 50 mg twice wkly; 24-week	18.4 to 19.3 years (mean)	Topical steroids (88%), systemic or phototherapy (76%)	At 12 weeks, 4, 14, 34, and 49% achieved PASI 75 in placebo, 25 mg wkly, 25 mg twice wkly, and 50 mg wkly groups
[121]	INF	3 or 5 mg/kg (99 in each group) or placebo (n=55) at 0, 2 and 6 weeks; 10-week study	17; minimum 6 mo; PASI ≥12	Psoralen-UVA or systemic treatment	≥75% reduction in PASI in 72%, 88%, and 6% in 3 mg, 5 mg and placebo groups, respectively
[122]	ETA	50 mg or 25 mg, or placebo sc BIW×12 weeks	19 years; minimum 0.8 years; PASI ≥10	Phototherapy or systemic therapy or candidate for it	At week 12, 49%, 34%, and 3% achieved PASI 75 in 50 mg, 25 mg, and placebo groups, respectively
[59]	INF	5 mg/kg or placebo at weeks 0, 2, and 6, then every 8 weeks to week 46. At week 24, placebo-treated patients crossed over to INF	18.7 (mean); minimum 6 mo; PASI ≥12	Phototherapy or systemic therapy	At week 24, PASI 75 (82% vs. 4%) and PASI 90 (58% vs. 1%) in INF vs. placebo
[123]	ETA	Placebo or 50 mg twice-wkly	20.1 and 19.7 years (mean); PASI ≥10	Systemic or phototherapy (or a candidate for it).	47% vs. 5% achieved PASI 75 at week 12. ≥50% improvement in depression and fatigue
[61]	ADA	40 mg wkly or every other week) vs. placebo; 12-week; 48-week extension	18, 21, and 19 years (mean); minimum 1 year	Topical therapies	At week 12, 80%, 53%, and 4% patients on wkly, every other week or placebo achieved PASI 75 improvement. Responses were sustained for 60 weeks
[124]	INF	Induction (weeks 0, 2, and 6) with 3 or 5 mg/kg or placebo. INF patients randomized again at week 14 to continuous or intermittent maintenance at their induction dose	15.1–17.9	Phototherapy or systemic therapy	At week 10, PASI 90 in 37–45% (vs 0.5% for placebo). Through week 50, continuous better than intermittent within each dose, and 5 mg/kg better than 3 mg/kg continuous
[125]	ADA	40 mg wkly or every other week) vs. placebo; 12-week	18, 21 and 19 years (mean); minimum 1 years		Greater improvements with either dosage vs. placebo in disability index and SF-36 mental component scores. SF-36 physical component scores improved with 40 mg dose

Reference	Agent	Protocol	Disease duration (mo) at entry (median)	Previous treatment	Endpoints

BIW, biweekly; wkly, weekly; DMARDs, disease-modifying anti-rheumatoid drugs; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 3

Clinical trials of TNFα antagonists in AS

Reference	Agent	Protocol	Disease duration at entry (mean) years	Previous treatment	BASDAI 50 D/P, % patient	ASAS 20 D/P, % patient
[26]	INF	5 mg/kg, 12 weeks study [26], open-label extension 1 year [27], 2 years [28], and 3 years [29]	16.4 (placebo)	No DMARDs	53/9	73/27
[27]			14.9 (INF)			
[28]						
[29]						
[30]	INF	5 mg/kg, 24 weeks study (ASSERT)	13.2 (placebo) 7.7 (INF)	Yes DMARDs	51/10.7	61.2/19.2
[31]	ETA	25 mg biweekly, 16 weeks, open-label extension 40 weeks	12 (placebo) 15 (ETA)	Yes DMARDs 38%		
[32]	ETA	25 mg biweekly, 12 weeks Open-label, crossover up to 30 weeks for the initial placebo group and 24 weeks for the eta group	11 (placebo) 15 (ETA)	Yes, previous DMARDs, steroid Allow concomitant NSAIDs	57/6	78.6/25
[33]	ETA	25 mg biweekly, 24 weeks	10.5 (placebo) 10.1 (ETA)	43–44% concomitant DMARDs, steroid		59/28
[34]	ETA	25 mg biweekly, 12 weeks	9.7 (placebo) 15 (ETA)	Yes prior DMARDs, allow concomitant DMARDs, steroid, NSAIDs	71.1/25.6	60/23
[35]	ADA	40 mg every other week, 24 weeks, open-label up to 80 weeks (ATLAS)	10 (placebo) 11.3 (ADA)	Yes prior DMARDs Allow concomitant DMARDs, steroid, NSAIDs	45.2/15.9 (12 weeks) 42.3/15 (24 weeks)	58.2/20.6 (12 weeks) 51/19 (24 weeks)

Table 4

Clinical trials of TNF antagonists in juvenile idiopathic arthritis (JIA)

References	Agent	Protocol	Previous Rx	Response –% patient
[39]	ETA	0.4 mg/kg up to 25 mg BIW	NSAIDs, DMARDs steroid	74 (30% response)
[40]		3-mo open-label then 4-mo randomized double-blind		64 (50% response)
		2 years follow-up		36 (70% response)
				81 (30% response)
				79 (50% response)
				67 (70% response)
[44]	ETA	0.4 mg/kg BIW	Failed previous DMARDs	6 month
		1–48 mo (median 12 mo)	Concomitant MTX 80%	83 (30% response)
			Steroid 68%	72 (50% response)
				52 (70% response)
[42]	ETA	Open-label, 13 mo; an intent-to-treat analysis; n=61	MTX-resistant or intolerant patients treated with ETA	3 mo: 73 (≥30% response)
				12 mo: 39 (≥30% response)[a]

BIW, biweekly; wkly, weekly; DMARDs, disease-modifying anti-rheumatoid drugs; mo, month; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs.

[a]Response dwindles with time. A higher rate of treatment failure in patients with systemic-onset JIA. 12 of 60 patients had a wide spectrum of severe side effects.

Table 5

Overall summary of complications associated with TNFα antagonist therapy

a.	TNFα antagonists should be avoided in patients with advanced congestive heart failure (NYHA class III–IV) and in patients with a depressed ejection fraction.
b.	TNFα antagonists should be avoided in patients with a pre-existing demyelinating disease.
c.	The presence of various antibodies (i.e., ANA, anti-dsDNA, anti-cardiolipin) should not modify the use of anti-TNF therapy, but therapy should be discontinued if clinical symptoms do occur.
d.	Injection/Infusion reactions are the most common adverse event reported with anti-TNF therapy. They generally decrease in intensity over time and rarely result in drug discontinuation.
e.	Anti-TNF treatment is associated with a slightly increased incidence of bacterial infections (relative risk of about 2), but serious infection risk does not appear to be increased. As with any DMARD, patients should be aware of the increased risk of infections, and physicians should remain vigilant.
f.	Given the concern of reactivation of tuberculosis with anti-TNF therapy, all patients should be screened for TB with history, physical examination, PPD ±chest radiography. If positive for latent TB, patients are strongly recommended to begin treatment prior to initiation of anti-TNF therapy.
g.	Patients should be screened for HIV and hepatitis C and B prior to initiating anti-TNF therapy. Preliminary data suggest that TNFα antagonists may be safe in chronic hepatitis C. TNFα antagonists should be used in concert with antiviral therapy to prevent HBV reactivation.
h.	The data in regard to the safety of TNFα antagonists in HIV is extremely limited and if used, patients should be thoroughly counseled and great caution must be taken given the risk of infection in this immunocompromised population.
i.	The overall incidence of fungal infections associated with anti-TNF therapy is extremely low. However, if a patient on TNFα antagonists develops a fever, fungal infections should be considered.
j.	The relationship between TNFα inhibitors and lymphoma is unclear. In RA patients, anti-TNF therapy does not seem to increase the risk of lymphoma and solid malignancies over a control RA population. A continued vigilance with structured surveillance of patients is warranted until more data are available.
k.	Pancytopenia, aplastic anemia, psoriasis, and vasculitis are rarely reported with anti-TNF therapy, but if they develop, the TNFα antagonist should be discontinued.
l.	Pregnancy: limited data available so far suggest that exposure to TNFα inhibitors during early pregnancy does not increase the risk of adverse outcomes to mother or fetus. However, until more data are available, it is sensible to recommend contraception for women taking TNFα inhibitors during their childbearing years and stopping these drugs prior to planned conception. Data are even more scant on the safety of TNFα inhibitors during the second or third trimester and lactation.