REVIEW ARTICLE

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Benefit-Risk Assessment of Infliximab in the Treatment of Rheumatoid Arthritis

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Contents

Abstract

In the last decade, there have been substantial advances in the treatment of rheumatoid arthritis with the addition of several new disease-modifying agents to the therapeutic armamentarium. Biological agents targeting tumour necrosis factor (TNF) represent one such important addition. Infliximab, a chimeric anti-TNF monoclonal antibody, has shown remarkable promise in alleviating the signs and symptoms of rheumatoid arthritis in addition to retarding radiographic disease progression when used in combination with methotrexate. In its pivotal phase III trial, the addition of infliximab to patients with methotrexate-refractory disease was associated with substantial clinical benefit. Using American College of Rheumatology criteria for improvement, one-half of patients receiving infliximab (3 mg/kg every 8 weeks) plus methotrexate showed at least 20% improvement compared with only 20% of those receiving placebo plus methotrexate ($p < 0.001$) with over one-half of eventual responders obtaining criteria for improvement by the second week of observation. Although its use has been met with much deserved enthusiasm, recent reports have highlighted several potential serious adverse effects associated with infliximab (and other TNF antagonists), including infusion reactions, congestive heart failure, drug-induced lupus, and CNS demyelination. In addition, recent reports have cited the potential for reactivation of mycobacterial and fungal infection in patients receiving infliximab, mandating appropriate tuberculosis screening prior to drug initiation. Although

the frequency of serious drug-related toxicity (requiring discontinuation of the agent) appears to be quite low, these reports underscore the need for caution and close surveillance with the administration of TNF inhibitors, particularly given that strategies aimed at preventing toxicity remain unproven. Despite its potential for toxicity, infliximab remains a valuable alternative for patients with rheumatoid arthritis.

Rheumatoid arthritis (RA) affects approximately 0.5 to 1% of the population worldwide, exacting enormous societal costs through work-related disability and accelerated mortality. Over the last decade, there have been tremendous gains in our understanding of rheumatoid arthritis pathobiology, most notably the central role played by tumour necrosis factor (TNF)-α in the propagation of the synovial proliferation and inflammation that characterise the disease. In histological specimens, TNFα can be found in abundance at the pannus-cartilage junction,[1] the pathological hallmark of rheumatoid arthritis. Additionally, rheumatoid arthritis patients have significantly higher synovial fluid TNFα levels compared with otherwise healthy controls.[2]

A pro-inflammatory cytokine, TNFα is expressed on the cell surface of synovial macrophages where it is cleaved by TNFα-converting enzyme to form a soluble inflammatory signal. Soluble TNFα then binds to its cell surface receptors (p55 or p75 subtypes), an interaction that leads to a host of cellular immune responses including the induction of programmed cell death (apoptosis), the release of other pro-inflammatory cytokines (interleukin [IL]-6, IL-8, and IL-1β), the secretion of matrix metalloproteinases (MMPs) and the increased expression of endothelial adhesion molecules. IL-1β, MMPs, and endothelial adhesion molecules have all at one time or another been implicated in the pathogenesis of rheumatoid arthritis, suggesting that TNFα (acting as an upstream regulator of these molecules) represents an ideal target for therapeutic intervention.[3]

Data from clinical trials involving TNFα inhibitors perhaps provide the most compelling evidence to support the pivotal role of TNFα in rheumatoid arthritis pathogenesis. In the last 3 years, the US FDA and the European Union's (EU) Commission of the European Communities have approved two biological agents, etanercept and infliximab, that specifically target TNFα in the treatment of rheumatoid arthritis. As of March 2001, approximately 147 000 patients worldwide have been given infliximab including 45 000 rheumatoid arthritis patients in the US.[4] This review evaluates the therapeutic use of infliximab in rheumatoid arthritis, summarising efficacy and safety data from several clinical trials in addition to more recent observations arising from postmarketing surveillance.

1. Pharmacology, Administration and Monitoring Schedule

Infliximab, a chimeric monoclonal antibody composed of human constant and murine (mouse) variable regions (see figure 1), binds soluble TNFα rendering the molecule biologically inactive. Initially approved for use in refractory Crohn's disease, infliximab is approved for the treatment of rheumatoid arthritis in combination with low-dose,

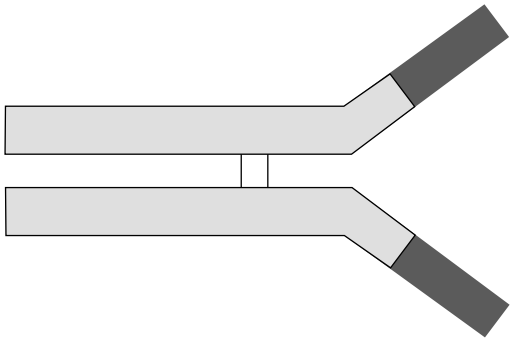

Fig. 1. Infliximab is an immunoglobulin G chimeric monoclonal antibody composed of a human constant region (grey) and murine (mouse) variable region (black).

Table I. Adverse effects associated with infliximab use in the treatment of rheumatoid arthritis: estimated frequency of occurrence and potential preventative measures

Adverse effect	Approximate frequency	Potential preventative measures	References
Infusion reaction	Mild to moderate (6–17%)	Reduce infusion rate	7-9
	Severe (<1–4%)	Premedication (paracetamol [acetaminophen], antihistamines)	
		Careful monitoring during and immediately following infusions	
Congestive heart failure	Not well defined	Avoid use in patients with known congestive heart failure	10
		Discontinue in patients developing signs or symptoms of congestive heart failure	
		Reduce dose of concomitant nonsteroidal anti-inflammatory drugs/glucocorticoids	
Infection	Upper respiratory infection (10–40%)	Avoid use with active infection	4,11-13
	Requiring antimicrobial therapy (30–50%)	Use with caution in high-risk patients (i.e. patients with diabetes mellitus)	
	Tuberculosis (24.4 per 100 000 person-years)	Tuberculosis skin testing and chest x-ray prior to initiating therapy	
		Antimicrobial prophylaxis for latent tuberculosis infection	
		Hold in perioperative period	
		Reduce dose of infliximab and/or concomitant immunosuppressives	
Drug-induced lupus	Rare (<1%)	Avoid use in patients with features of systemic lupus erythematosus	11,14
		Discontinue in patient developing signs and symptoms of lupus	
Malignancy	Not well defined	Use with caution in patients with malignancy history	11-13
		Avoid use with concurrent malignancy	
CNS demyelination	Rare (approximates 4 per 100 000 person-years)	Avoid use in patients with multiple sclerosis	13,15,16

weekly methotrexate. Infliximab is administered intravenously (initial recommended dose of 3 mg/kg) with repeated administration after 2 and 6 weeks and then every 8 weeks thereafter. The drug is administered in either the inpatient or office setting over a period of 2 hours. Distributed primarily within the intravascular compartment, serial administration does not result in drug accumulation. The terminal half-life of infliximab has been estimated to be between 8 and 9.5 days.[5]

In contrast to traditional disease-modifying anti-rheumatic drugs (DMARDs),[6] there are no widely accepted guidelines for toxicity monitoring with infliximab. However, concomitant methotrexate administration (and other agents including glucocorticoids and nonsteroidal anti-inflammatory drugs) requires careful serial monitoring to avoid potential serious drug-related toxicities.[6] Potential adverse effects associated with infliximab use and strategies aimed at preventing these toxicities are summarised in table I.

2. Clinical Efficacy

Elliott et al.[17] reported on the first use of a biological agent, infliximab, in the treatment of rheumatoid arthritis. Although primarily designed to assess issues of tolerability and safety, this initial phase I investigation provided an early glimpse of the enormous therapeutic promise of TNFα inhibition. Rheumatoid arthritis patients studied (n = 20) had long-standing (median duration 10.5 years), treatment refractory disease having received a median of four DMARDs prior to enrolment (range 2–7). Study subjects were given a total

infliximab dose of 20 mg/kg, administered intravenously over the course of 12–14 days (15 patients were given 5 mg/kg on days 0, 4, 8, and 12 and 5 patients were given two infusions of 10 mg/kg on days 0 and 14).

All clinical parameters measured in the study showed significant improvement. The duration of morning stiffness decreased by several-fold, from a median baseline value of 3 hours to just 5 minutes by week 6 ($p < 0.001$). In the same time period, pain scores improved from a median of 7.1 to 1.9 ($p < 0.001$) and median swollen joint counts declined from 18 to 5 ($p < 0.001$). Functional disability, measured with a modified version of the Health Assessment Questionnaire,[18] improved from a median baseline value of 2 to 1.1 ($p < 0.002$). Moreover, there was a striking decline in acute phase reactants, particularly with C-reactive protein levels, which fell from a median of 39.5 mg/dl at week 0 to 8 mg/dl by week 6 of follow-up ($p < 0.001$).

In a follow-up study, eight patients from the initial open-label investigation were given up to four repeated infliximab doses (an initial dose of 20 mg/kg followed by 10 mg/kg on subsequent cycles).[19] Treatment intervals varied based on objective evidence of disease flare. Although repeated drug infusions were generally effective in ameliorating the signs and symptoms of rheumatoid arthritis, the elapsed time between treatments became gradually shorter with more extended follow-up. Four of the eight patients developed human antichimeric antibodies (HACAs) to infliximab, suggesting that drug-related antigenicity may limit long-term use.

Similar to the results of the initial open-label study, the first placebo-controlled study of infliximab in rheumatoid arthritis underscored the therapeutic potential of TNFα inhibition[20] (table II). In this study, patients with refractory disease were given a single infliximab infusion (1 mg/kg or 10 mg/kg) or placebo. After 4 weeks of follow-up, 79% of patients in the 10 mg/kg group showed at least 20% improvement as measured by Paulus criteria[21] compared with only 8% receiving placebo ($p < 0.0001$).

In addition to addressing issues of efficacy and safety, subsequent phase II and III clinical trials were designed to examine the durability of the clinical response with repeated infliximab administration (table II). In the first such study, patients with methotrexate-refractory disease were given serial infusions of infliximab (1, 3, or 10 mg/kg at weeks 0, 2, 6, 10, and 14) with or without concomitant low-dose methotrexate (7.5 mg/week) or intravenous placebo infusions plus methotrexate.[7] Consistent with prior results, infliximab was associated with significant clinical improvement compared with placebo. Approximately 60% of patients receiving infliximab experienced at least 20% improvement using Paulus criteria compared with only 15% of those receiving placebo plus methotrexate ($p <$

Table II. Placebo-controlled trials of infliximab in the treatment of rheumatoid arthritis (RA)

Trial	Study duration (weeks)	No. enrolled	Active treatment	Control treatment	Clinical response: Paulus criteria for 20% improvement		Clinical response: ACR criteria for 20% improvement	
					active (% pts)	control (% pts)	active (% pts)	control (% pts)
Phase II (Elliott et al.[20])	4	73	10 mg/kg IV, single infusion	Placebo	79	8		
Phase II (Maini et al.[7])	26	101	3 and 10 mg/kg IV at weeks 0, 2, 6, 10, and 14 wks	Placebo[a]	60	15		
Phase Ib (Kavanaugh et al.[22])	12	28	5, 10, 20 mg/kg IV, single infusion	Placebo[a]			81	14
Phase III (Maini et al.[11])	30	428	3 mg/kg IV every 8 wks	Placebo[a]			50	20

a All patients (placebo and infliximab groups) given concomitant weekly methotrexate.

ACR = American College of Rheumatology; **IV** = intravenous.

0.001). Moreover, the coadministration of methotrexate with low-dose infliximab (1 mg/kg) was associated with a substantial increase in both the magnitude and duration of clinical response.

In a 12-week trial, patients (n = 28) with treatment refractory rheumatoid arthritis were randomised to receive a single infusion of infliximab (5, 10, or 20 mg/kg) or placebo in addition to weekly methotrexate (table II).[22] Patients given infliximab were substantially more likely than those receiving placebo to obtain at least 20% improvement as measured using the American College of Rheumatology (ACR)[23] criteria for improvement at some point during follow-up (81 vs 14%, p = 0.003). Clinical improvement was noted to be evident in the infliximab-treated patients during the first week of follow-up. In an open-label extension of the trial, patients were given repeated infliximab infusions (10 mg/kg) at weeks 12, 20, and 28; of 19 patients who received active therapy in the blinded portion of the trial, 53% maintained at least 20% improvement through 40 weeks of follow-up.

In the more recent pivotal, phase III Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) trial, 428 rheumatoid arthritis patients with methotrexate-refractory disease were given infliximab (3 or 10 mg/kg) or placebo every 4 to 8 weeks in addition to stable dose methotrexate (median dose 15 mg/week).[11] Using ACR criteria for improvement one-half of patients receiving infliximab plus methotrexate (3 mg/kg every 8 weeks) showed at least 20% improvement compared with only 20% of those receiving placebo plus methotrexate ($p < 0.001$). In contrast to experience with standard DMARDs, the clinical response observed with infliximab was rapid, with over one-half of eventual responders obtaining criteria for improvement by the second week of observation.

In a separate report from the ATTRACT study group, investigators examined the impact of infliximab plus methotrexate (vs placebo plus methotrexate) on radiological outcomes over a 1-year period of follow-up.[12] While radiographic disease progression was observed in those given methotrexate alone, patients receiving additional infliximab showed no evidence of disease progression. For the first time, a DMARD (or DMARD combination in this case) arrested the rheumatoid arthritis erosive process, an effect that appeared to be independent of other measures of clinical response. Importantly, this phase III investigation showed no evidence of a 'tapering' response with repeat infliximab infusions after 12 months of therapy. However, the issue of drug antigenicity was not fully addressed in this trial because the presence of infliximab in serum samples limited the ability to measure HACAs. Of the 60 patients who withdrew prior to the study's termination, five patients (8%) developed HACAs, all at low titre. Given the small number of patients in whom HACAs were ascertained, it is unclear whether the development of antibodies against infliximab was associated with a reduced clinical response to the drug.

3. Adverse Effects: Incidence, Risk Factors, and Prevention

3.1 Infusion Reactions

Mild to moderate infusion reactions (such as urticaria, pruritus, flushing, and chills) may occur with infliximab administration with an observed cumulative risk as high as 6[7] to 17%.[8] Although severe reactions (including both delayed and immediate hypersensitivity reactions) have been reported,[24,25] such reactions are a relatively rare complication of infliximab administration and are an uncommon cause of treatment discontinuation in published trials. Of the 342 rheumatoid arthritis patients randomised to receive infliximab (plus methotrexate) in the ATTRACT trial, none had serious infusion reactions. In contrast to the ATTRACT results, the frequency of serious infusion reactions associated with infliximab use has been reported to be as high as 4% among a community-based cohort of rheumatoid arthritis patients.[9] The pathogenesis of infliximab-related infusion reactions has not been precisely defined. Moreover, the effectiveness of potential interventions (including pretreatment with histamine-

blocking agents and/or paracetamol [acetaminophen] or slowing the drug infusion rate) remains unproven.

3.2 Infection

In the multicentre ATTRACT trial,[11,12] the number of patients with infections requiring antimicrobial administration were reported to be similar for those who received methotrexate alone (35%) and for those receiving the combination of infliximab plus methotrexate (44%). Rates of serious infection were also similar in the two treatment groups (8 vs 6%, respectively). Although not reaching statistical significance, patients receiving infliximab had slightly higher rates of upper respiratory infection (34 vs 22%), sinusitis (17 vs 6%), and pharyngitis (11 vs 6%).

It is notable that there were two infection-related deaths in the ATTRACT trial, one from disseminated coccideomycosis and one from tuberculosis. Recently published results from post-marketing surveillance have also suggested a potential association between infliximab therapy and the incidence of opportunistic infections, particularly those arising from the reactivation of *Mycobacterium tuberculosis*.[4] Results from *in vitro* and animal studies suggest that TNFα may play an important role in localising infection and thus preventing reactivation of tuberculosis.[26-28] As of March 2001, passive surveillance data from the US FDA revealed 70 cases of tuberculosis associated with infliximab use, two-thirds of which received the agent for the treatment of rheumatoid arthritis.[4] Of note, there appeared to be a temporal relationship between the time of drug initiation and the development of infection with a median elapsed time between first dose and tuberculosis diagnosis of 12 weeks (range 1 to 52 weeks). Alarmingly, over one-half of cases showed evidence of extrapulmonary involvement and one-fourth had disseminated disease at the time of diagnosis.

Results from passive surveillance suggest that infliximab use is associated with an approximate 4-fold increase in tuberculosis incidence among rheumatoid arthritis patients compared with similar patients not receiving infliximab (24.4 vs 6.2 cases per 100 000, respectively).[4] However, given the number of potential confounding variables, establishing a causal association between infliximab use and increased tuberculosis risk in rheumatoid arthritis remains difficult. A significant proportion of these patients (almost 80%) were receiving concomitant immunosuppressive agents including glucocorticoids, methotrexate, and/or azathioprine. Despite the imprecision of risk assignment, post-marketing observations have led the manufacturer to place a boxed warning on the packaging insert for the drug, identifying the need to evaluate for and treat latent tuberculosis infections prior to initiating infliximab.

In addition to infections secondary to *M. tuberculosis* and coccideomycosis, there have been reports of infliximab-associated histoplasmosis, listeriosis, and *Pneumocystis carinii* pneumonia.[13,29] Given the role that TNFα plays in keeping infection localised, time is of the essence. It is essential that TNFα inhibitors are discontinued at the first sign of infection and only restarted after complete resolution of the superimposed infection. To that end, both physicians and patients alike should be acutely aware of the risk of serious infection with infliximab. TNFα inhibitors should not be used in rheumatoid arthritis patients with ongoing active infection and should be used with caution in those at high risk for infection (i.e. patients with diabetes mellitus, splenectomised patients). In addition to close surveillance and patient education, we advocate the routine use of age-appropriate preventive healthcare that includes pneumococcal and influenza vaccinations.

3.3 Demyelinating Disease

In contrast to data from animal studies that suggested a beneficial effect of TNFα inhibition in the treatment of disorders characterised by CNS demyelination,[30,31] human studies have shown a deleterious effect of anti-TNFα therapy. In a study involving two patients with rapidly progressive multiple sclerosis, infliximab therapy was associ-

ated with an increase in the number of gadolinium-enhancing lesions observed on magnetic resonance imaging (MRI).[32] Although investigators observed no deterioration in the patients' overall clinical status, they did note significant increases in cerebrospinal fluid (CSF) immunoglobulin (Ig) G index and CSF lymphocyte counts following each drug infusion. In a randomised, double-blind study, patients with multiple sclerosis given lenercept (a soluble p55 TNF-receptor-Ig fusion protein) were significantly more likely to experience disease exacerbations than patients with multiple sclerosis given placebo.[33]

Results of passive surveillance from the US FDA's Adverse Events Reporting System suggest that in addition to exacerbating the signs and symptoms of pre-existing multiple sclerosis anti-TNFα therapy may actually be associated with multiple sclerosis incidence. In December of 2001, Mohan and colleagues[15] reported the occurrence of 19 cases of suggestive CNS demyelination in the setting of TNFα inhibition (17 following etanercept therapy; two following infliximab infusions). As with infection risk, the investigators site a temporal relationship between the initiation of therapy and the onset of neurological symptoms (mean 5 months; range 1 week to 15 months). Drug discontinuation led to improvement or resolution of neurological signs and symptoms in all cases. In one case, re-exposure to etanercept led to worsening status on MRI examination. Although a majority represented incident cases, 4 of the 19 patients had previous diagnoses of either multiple sclerosis or other multiple sclerosis-related conditions and experienced flares of their previous symptoms.

As with tuberculosis risk, investigators are limited in their ability to conclude a causal association between anti-TNFα therapy and CNS demyelination. The incidence of neurological events in patients receiving anti-TNFα agents does not appear to be higher than the background incidence of multiple sclerosis in the general population.[15] Clearly, the precise role that TNFα plays in mediating CNS demyelination remains incompletely defined and further investigation in this area is warranted.[16] In the meantime, healthcare providers should not use TNFα inhibitors in patients with known multiple sclerosis or multiple sclerosis-related conditions. Additionally, an appropriate diagnostic evaluation should be undertaken for patients developing neurological symptoms and/or signs suggestive of CNS demyelination in the context of anti-TNF therapy.[15]

3.4 Congestive Heart Failure

Results from experimental studies have suggested that TNFα may play an important role in the pathogenesis of congestive heart failure (CHF).[34,35] While results of initial randomised, double-blind studies suggested that etanercept may be beneficial in CHF treatment,[36,37] subsequent phase III studies of the drug were halted when it appeared that statistical significance for primary efficacy outcomes would not be reached.[38] Clinical studies of infliximab in CHF have been similarly disappointing. In October of 2001, the manufacturers of infliximab released a warning regarding the use of this drug in the setting of CHF.[10] In an ongoing phase II study, patients with moderate to severe CHF experienced higher mortality and hospitalisation rates; 7 of 101 patients treated with infliximab died compared with no deaths among the 49 patients with CHF given placebo. As a result, the manufacturer has cautioned that healthcare providers should avoid initiating infliximab in patients with CHF; that treatment should be discontinued in patients with worsening signs or symptoms of CHF; and that infliximab discontinuation should be considered in patients with stable, concomitant CHF (particularly for those who have not had a significant clinical response to the drug).

3.5 Autoimmunity

Autoantibody formation to double-stranded DNA (dsDNA) has been well described in association with infliximab administration.[11,14] In the phase III ATTRACT trial, 16% of infliximab-treated patients developed anti-dsDNA antibodies compared with none in the placebo-treated group.[11] Charles et al.[14] recently pooled data

from a single open-label trial and two randomised trials involving a total of 153 rheumatoid arthritis patients treated with infliximab. The incidence of anti-dsDNA antibody development was dependent on the measurement technique employed and varied from as low as 7% to as high as 14%. In the same report, the incidence of antinuclear antibody formation in the infliximab-treated patients increased from 29% prior to treatment to 53% following treatment.

Although autoantibody production appears to be a relatively frequent phenomenon in the setting of infliximab therapy, drug-induced lupus appears to be substantially less common, occurring in less than 1% of those studied. In the ATTRACT trial (which involved >300 infliximab-treated rheumatoid arthritis patients), one patient developed drug-induced lupus in the absence of autoantibody production.[11] The patient's symptoms resolved with the cessation of infliximab. Similarly, Charles et al.[14] reported a single case of drug-induced lupus associated with infliximab therapy in rheumatoid arthritis. The patient's symptoms and anti-dsDNA antibodies resolved within 8 weeks of infliximab discontinuation and the initiation of glucocorticoid therapy. Given these reports, it is our practice to avoid the use of TNFα-antagonists in arthritis patients with clinical features suggestive of systemic lupus erythematosus. For patients developing signs and symptoms of lupus while receiving infliximab treatment, infliximab therapy should be held and a thorough evaluation (including the measurement of anti-dsDNA antibodies) should be undertaken.

3.6 Malignancy

There has been significant speculation regarding the potential impact of TNF antagonism on malignancy risk. In the ATTRACT trial, five infliximab-treated patients developed a malignancy (two were recurrences and three were newly diagnosed).[11,12] Malignancies diagnosed during the study included basal cell carcinoma (n = 1), rectal carcinoma (1), recurrent breast cancer (n = 1), squamous cell carcinoma and melanoma (1), and B-cell lymphoma (1). Notably, all five patients developing malignancy were receiving high dose infliximab (10 mg/kg).

Ten cases of lymphoma involving infliximab-treated patients were reported to the US FDA between March of 1999 and December of 2000;[13] six of these patients were being treated for active Crohn's disease. Based on these data, the lymphoma incidence rate for patients receiving anti-TNFα agents approximates that of the general population.[13] However, these data must be interpreted with caution given the limitations of passive surveillance, particularly in regards to problems of under-reporting.[13]

As with other potential adverse effects, establishing a causal association between TNFα antagonism and the occurrence of malignancy is difficult. Rheumatoid arthritis patients have been estimated to have a 2- to 20-fold increase in risk of non-Hodgkin's lymphoma in the absence of anti-TNFα therapy.[39] Additionally, patients taking infliximab are frequently given concomitant immunosuppressive agents (i.e. methotrexate) that have been independently implicated in lymphoma incidence and, thus, may confound any potential association between TNFα inhibition and malignancy risk. Continued follow-up of infliximab-treated rheumatoid arthritis patients will be needed to more clearly define the malignancy risk associated with its long-term use. Until such time, it seems prudent to use anti-TNFα agents with caution in patients with a history of malignancy, particularly lymphoproliferative malignancy. The onset of new constitutional symptoms or those out of proportion to disease activity (e.g. fevers, chills, night sweats, anorexia) in the absence of infection or significant rheumatoid arthritis disease flare should raise suspicion for the existence of a neoplasm and prompt an appropriate diagnostic evaluation.

4. Conclusion

The availability of anti-TNFα agents, including infliximab, has dramatically changed the treatment landscape in rheumatoid arthritis. With the addition of biologicals to the rheumatoid arthritis armamentarium, the major task facing physicians is

finding ways to accurately predict response and/or toxicity to these agents as well as that to other standard DMARDs and DMARD combinations. The unique mechanism of action of infliximab makes it a potentially attractive agent in combination regimens. Additionally, its rapid onset of action may make it an ideal 'induction' therapy.[40] Trials comparing infliximab-methotrexate with other DMARD combinations and trials assessing the use of TNFα inhibitors as induction therapies would be of great interest.

As the rheumatology community awaits the results of such trials, healthcare providers must continue to exercise caution with the use of these agents. A growing awareness of potentially life-threatening complications of infliximab administration mandates that both patients and physicians prescribing these agents are aware of these risks. Other than judicious patient selection, strategies aimed at preventing infliximab-associated toxicity (table I) remain untested and require investigation in a randomised prospective fashion. With an improved understanding of how to optimise TNFα antagonism for the individual patient, infliximab and other TNFα inhibitors are likely to become increasingly important in the effective management of rheumatoid arthritis.

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