

# Anti-tumour necrosis factor $\alpha$ therapy in rheumatoid arthritis: an update on safety

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Anti-TNF $\alpha$  therapy may have associated risks of serious infection, congestive heart failure, malignancy, and multiple sclerosis. The magnitude of these risks is difficult to assess. This article reviews publications on the current knowledge about the safety of these agents.

cohort studies, and case reports/series were included. In addition, the references of retrieved articles were reviewed for any additional reports of adverse events.

## INFECTION

An increased risk of serious infection is a concern after blockade of TNF $\alpha$ . A serious infection is defined as any infection resulting in death, disability, or congenital malformation, which requires or extends hospitalisation, or is otherwise deemed medically significant.<sup>4</sup> TNF $\alpha$  has a crucial role in the body's defence against both bacterial and viral invasion,<sup>5</sup> particularly in the recruitment of neutrophils, eosinophils, and macrophages to the sites of infection. Therefore, if the effects of TNF $\alpha$  are blocked, patients may be placed at a greater risk of infection. Despite this theoretical concern, the rates of infection seen during clinical trials of etanercept, infliximab, and adalimumab in RA were not significantly increased compared with those in the placebo arms.<sup>6–9</sup> Minor infections, such as upper respiratory tract infections, were seen frequently, but not at a rate greater than in the placebo group. By contrast, serious infections requiring admission to hospital were rare.

“Controlled trials suggest that infections do not increase when TNF $\alpha$  blockers are used”

As mentioned above, clinical trials may not be powered to detect an increased rate of serious infections. This is particularly true as strict inclusion and exclusion criteria may limit the study to patients at low risk of infection. Despite this, a recent phase IV study of adalimumab, which did not restrict the use of concomitant DMARDs or corticosteroids among the enrolled patients, did not detect an increase in serious infections among treated patients compared with placebo.<sup>10</sup>

In contrast with the absence of an increased rate of serious infections during clinical trials, case reports of serious infections after the use of anti-TNF $\alpha$  have been published. These include at least two cases of necrotising fasciitis, one after the use of etanercept<sup>11</sup> and a second after infliximab.<sup>12</sup>

**Abbreviations:** ANA, antinuclear antibody; CHF, congestive heart failure; DMARD, disease modifying antirheumatic drug; dsDNA, double stranded DNA; FDA, Federal Drug Administration; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TB, tuberculosis; TNF $\alpha$ , tumour necrosis factor  $\alpha$

Agents that block the action of tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) are established as effective agents in the treatment of rheumatoid arthritis (RA), especially in patients with disease unresponsive to standard disease modifying antirheumatic drugs (DMARDs).<sup>1</sup> Blockade of this cytokine is likely to have effects beyond the suppression of synovial inflammation and there is concern that such effects might be associated with severe adverse events.

Data on the frequency of adverse events come predominantly from three sources: follow up of subjects recruited to clinical trials, surveillance of patients treated in routine practice, and spontaneous reporting to national pharmacovigilance systems. The drawbacks of each of these approaches have been highlighted elsewhere.<sup>2–3</sup> In brief the first relies on small sample sizes of selected subjects followed up for short periods of time and thus cannot detect either rare or longer term effects. The second, in the absence of a comparison group, cannot distinguish between the influence of the drugs and the influence of the indications for their use, especially as severe active RA, with extensive exposure to standard DMARDs, is associated with an increase in several causes of comorbidity. The third, although having the advantage of covering a nationwide population and being useful for detecting very rare events, again ignores the issue of a comparison cohort and relies on physician recognition and reporting of a potentially linked event.

It is important in the interim for prescribing physicians to be aware of current concerns based on these imperfect reporting streams. In this review we have attempted to provide an exhaustive summary of English published reports available in the public domain by the end of 2003. Although it is clear that the number of these publications will continue to grow, our aim is to provide an appropriate source for reference fixed to this point in time. Reports were identified in Embase up to January 2004, using the subject headings etanercept, infliximab, adalimumab, and rheumatoid arthritis. The search was limited to the English language. Adverse events identified through clinical trials,

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Patients with RA are already at an increased risk of serious infections in comparison with the general population.<sup>13</sup> Recently, published cohort studies have attempted to compare the rates of serious infection in patients treated with anti-TNF $\alpha$  agents with historical data from cohorts of patients with RA who were not exposed to these agents. These, however, have shown conflicting results. The South Sweden Registry found no increase in the rates of serious infection among patients receiving infliximab or etanercept compared with those receiving leflunomide.<sup>14</sup> A second study, from the United States, also found no increase in the rates of infection in the year after the initiation of etanercept treatment, compared with the period before etanercept in the same patients.<sup>15</sup> However, a third cohort study, also using patients as their own pre-biological controls, did find a more than 20-fold increase in the infection rate among patients, rising from a rate of 0.008 serious infections/year in the years before anti-TNF $\alpha$  therapy to 0.181 serious infections/year after the start of treatment.<sup>16</sup>

Besides the development of serious bacterial infections, there is also a concern over the development of opportunistic infections in patients receiving anti-TNF $\alpha$  therapies<sup>17</sup> (table 1). There are reports of reactivated histoplasmosis,<sup>18</sup> listeriosis,<sup>19</sup> pulmonary aspergillosis,<sup>20</sup> and *Pneumocystis carinii* pneumonia.<sup>21</sup>

However, the infection causing the greatest concern is tuberculosis (TB). The number of reports of TB during the clinical trials was relatively low, with one case reported during a clinical trial of 340 patients treated with infliximab<sup>22</sup> and 13 cases among 2468 patients during the clinical development phases of adalimumab.<sup>17</sup> By contrast, there have been no cases reported during clinical trials of etanercept.

There are now numerous case reports of TB developing in patients who have received infliximab. In 2001, 70 cases of TB associated with exposure to infliximab, from an unknown denominator of those treated, were reported, of which 47 had received the drug for RA.<sup>23</sup> More than 50% of the cases were extrapulmonary infections. The majority (64%) of the cases occurred in Europe. Since that report, cases have continued to be reported in patients who have received infliximab,<sup>24–34</sup> etanercept,<sup>35–36</sup> and adalimumab.<sup>27</sup> Most of these infections

have occurred in patients with a known history of TB, suggesting a reactivated infection, but some have occurred in patients with no known previous history of the disease.

#### “Tuberculosis develops in many patients with infliximab treatment”

Animal studies have shown that TNF $\alpha$  has a key role in the clearance of mycobacterial infections such as TB, specifically by the formation and maintenance of granulomata which control the infection. Indeed numerous studies have shown that in animals infected with TB subsequent blockade of TNF $\alpha$  results in fatal reactivation.<sup>37–38</sup>

It is interesting that although etanercept blocks the same cytokine, there have been very few reports of TB after its use. Under the spontaneous pharmacovigilance system, only nine cases of TB among patients receiving etanercept had been reported to the Federal Drug Administration (FDA) compared with the 70 cases with infliximab.<sup>23</sup> Possible suggestions for this discrepancy include the different mechanisms by which the two agents block TNF $\alpha$ .<sup>39</sup>

Interpretation of these data requires knowledge of the underlying risk of TB among patients from the same geographic area receiving non-biological treatment for RA. Studies from the United States<sup>40</sup> and Korea<sup>41</sup> did not suggest any important increased risk, in contrast with a fourfold rise over the level in the general population in Spain.<sup>42</sup> A more recent study from Spain, based on 1540 patients treated with TNF $\alpha$  inhibitors, reported 17 cases of TB (all in patients treated with infliximab).<sup>43</sup> The relative risk of TB in patients with RA treated with infliximab compared with those not treated with anti-TNF $\alpha$  agents was 19.9. As most of the cases of TB after infliximab treatment are felt to represent reactivation rather than de novo disease, the effectiveness of screening patients before treatment will be an important predictor of incidence. Indeed in Spain the risk of TB after infliximab treatment has fallen since national guidelines on the detection and management of latent TB infection were introduced.<sup>43</sup>

## NEUROLOGICAL DISEASE

One unexpected serious adverse event which has been reported after treatment with the anti-TNF $\alpha$  agents, particularly etanercept, is demyelinating disease (table 2). A publication from the FDA Medwatch<sup>44</sup> system in December 2001 reported 20 cases of neurological disease: 18 after etanercept and two after infliximab.<sup>45</sup> All cases were temporally associated with the treatment and all cases had a partial or complete response when the treatment was stopped. Sixteen had changes on magnetic resonance imaging consistent with demyelination. These reported numbers are no greater than the expected number in the

**Table 1** Reports of opportunistic infection among patients receiving anti-TNF $\alpha$  treatment for RA

Citation	Description of event(s)
<i>Infliximab</i>	
De Rosa <sup>20</sup>	<i>Aspergillus fumigatus</i> pneumonia
Cursiefen <sup>68</sup>	Bilateral eyelid molluscum contagiosum
True <sup>69</sup>	Disseminated cryptococcal infection
Maini <sup>22</sup>	Coccidiomycosis
Sawalha <sup>70</sup>	<i>Histoplasma capsulatum</i> panniculitis
Nakelchik <sup>71</sup>	Histoplasmosis
Lee <sup>18</sup>	Histoplasmosis (5)
Wood <sup>72</sup>	Histoplasmosis (2)
Gluck <sup>73</sup>	Listeriosis (2)
Slifman <sup>19</sup>	Listeriosis (8)
Harney <sup>74</sup>	Peptostreptococcal pericarditis
Tai <sup>21</sup>	<i>Pneumocystis carinii</i> pneumonia
Hage <sup>75</sup>	Pulmonary cryptococcosis
<i>Etanercept</i>	
Lee <sup>18</sup>	Histoplasmosis
Wood <sup>72</sup>	Histoplasmosis
Slifman <sup>19</sup>	Listeriosis
Phillips <sup>15</sup>	<i>Mycobacterium avium</i> intracellulare psoas abscess
Chopra <sup>76</sup>	<i>Mycobacterium marinum</i> tenosynovitis
Benz <sup>77</sup>	Necrotising herpetic retinopathy
Smith <sup>78</sup>	Parainfluenza virus type 3 pneumonia
Carter <sup>79</sup>	Soft tissue infection neck— <i>Streptococcus constellatus</i>

**Table 2** Reports of neurological disease among patients receiving anti-TNF $\alpha$  treatment for RA

Citation	Description of event(s)
<i>Etanercept</i>	
Mohan <sup>45</sup>	Demyelinating disease (18)
Sicotte <sup>49</sup>	Multiple sclerosis
van der Laken <sup>80</sup>	Transverse myelitis
<i>Infliximab</i>	
Mohan <sup>45</sup>	Demyelinating disease (2)
Marotte <sup>81</sup>	Aseptic meningitis
ten Tusscher <sup>82</sup>	Bilateral anterior toxic optic neuropathy
Hrycaj <sup>83</sup>	Parkinson's disease

**Table 3** Reports of autoimmune disease after the use of anti-TNF $\alpha$  treatment for rheumatoid arthritis

Citation	Description of event(s)
<i>Infliximab</i> Saleem <sup>84</sup>	Acute hepatic injury with interface inflammation in association with ANA/IgG dsDNA (+)
Kent <sup>85</sup>	Bullous skin eruption
McCain <sup>86</sup>	Cutaneous vasculitis
Jarrett <sup>87</sup>	Cutaneous vasculitis (5)
	Mononeuritis multiplex
	CNS vasculitis
Geborek <sup>14</sup>	Leucocytoclastic vasculitis
Fitzcharles <sup>88</sup>	Leucocytoclastic vasculitis (2)
Musial <sup>89</sup>	Polymyositis
Favalli <sup>90</sup>	Systemic lupus erythematosus
Debandt <sup>91</sup>	Systemic lupus erythematosus
<i>Etanercept</i>	
Galaric <sup>92</sup>	Cutaneous vasculitis
McCain <sup>86</sup>	Cutaneous vasculitis*
Cunnane <sup>93</sup>	Cutaneous vasculitis
	Pulmonary vasculitis
Misery <sup>94</sup>	Discoid lupus
	Cutaneous necrotising vasculitis
Brion <sup>95</sup>	Discoid lupus
	Necrotising vasculitis
Soliotis <sup>96</sup>	Erythema multiforme
Berthelot <sup>97</sup>	Lethal medium vessel vasculitis
Jarrett <sup>87</sup>	Leucocytoclastic vasculitis
Caramaschi <sup>98</sup>	Orbital myositis
Andres <sup>99</sup>	Silent thyroiditis
Bleumink <sup>100</sup>	Subacute cutaneous lupus erythematosus (2)
	Discoid lupus (2)
Shakoor <sup>101</sup>	Systemic lupus erythematosus
Cairns <sup>102</sup>	Systemic lupus erythematosus
Swale <sup>103</sup>	Systemic lupus erythematosus
Debandt <sup>91</sup>	Systemic lupus erythematosus (2)
Geborek <sup>14</sup>	Systemic lupus erythematosus
	Discoid lupus*

\*Recurred in same patient after subsequent treatment with infliximab.

general population based on the estimated number of patients treated with etanercept.<sup>45</sup>

Levels of TNF $\alpha$  are increased both in the cerebrospinal fluid and in the circulation in patients with active multiple sclerosis (MS),<sup>46, 47</sup> and thus it might be expected that anti-TNF $\alpha$  therapy might be beneficial in this group of disorders. However, the results of two studies of anti-TNF $\alpha$  therapy, one of infliximab and another with lenercept (a soluble TNF $\alpha$  p55 receptor), actually found a worsening of clinical disease in patients with known MS.<sup>48</sup> The reasons for this are not understood.<sup>47</sup> It is of concern, however, that there are reports of MS developing in patients treated with anti-TNF $\alpha$  with no known history of neurological disease.<sup>49</sup> Although the coincidental onset of both diseases in the same patient is entirely possible, it is also feasible that the drug has triggered latent demyelination or, in fact, has caused the disease.

## AUTOIMMUNE DISEASE

The development of autoantibodies, including antinuclear antibody (ANA) and anti-double stranded DNA antibodies (anti-dsDNA), after the use of anti-TNF $\alpha$  therapies was well documented during the clinical trials of these agents. About 60% of patients enrolled in the ATTRACT study developed a new ANA and 10% developed new anti-dsDNA at some point during treatment with infliximab.<sup>50</sup> The pathological significance of these observations is uncertain. Only one patient developed a lupus-like syndrome during the study.<sup>22, 50</sup> The development of new ANA and anti-dsDNA has also been reported in about 10% of patients receiving either adalimumab or etanercept during phase III clinical trials,<sup>6, 7, 9</sup> but with no cases of systemic lupus erythematosus (SLE).

By contrast, post-marketing surveillance of these agents has disclosed numerous case reports of autoimmune disease, particularly leucocytoclastic vasculitis and SLE (table 3). Most of these developed after starting anti-TNF $\alpha$  therapy, improved when it was discontinued, and were not life threatening. In some cases, patients were known to have a positive ANA before the start of anti-TNF $\alpha$  therapy. In interpreting these case reports it is noted that patients with one autoimmune disease, such as RA, do have an increased frequency of a second autoimmune disease, particularly SLE,<sup>51, 52</sup> and the reports of these reactions may simply represent coincidental disease. However, drug-induced lupus is not an uncommon phenomenon. The development of new autoantibodies with the use of anti-TNF $\alpha$  therapy suggests these drugs may, in some patients, have a causative role.

## CARDIAC DISEASE

Another major area of concern has been in relation to cardiac disease, particularly the possibility that anti-TNF $\alpha$  therapy may lead to worsening of congestive heart failure (CHF). As with MS, this concern is initially counterintuitive as serum levels of TNF $\alpha$  are raised in patients with CHF and indeed correlate with the severity of CHF.<sup>53</sup> Early reports suggested that treatment with a single dose of intravenous etanercept in patients with severe CHF might improve symptoms without significant side effects.<sup>54</sup> Two large randomised, placebo controlled trials of anti-TNF $\alpha$  agents in patients with CHF were undertaken. The first study, RENAISSANCE/RECOVER, compared etanercept with placebo in patients with advanced heart failure.<sup>55</sup> It failed to detect any improvement in either CHF symptoms or mortality after etanercept treatment. The second study, ATTACH, compared infliximab with placebo in patients with advanced heart failure.<sup>56</sup> This study observed an increased rate of death and admission to hospital in the infliximab group. It is not clear why treatment with infliximab should exacerbate CHF, but the increased mortality was only seen in the group receiving 10 mg/kg infliximab. For most patients, this exceeds the dose recommended for RA.<sup>57</sup> No increased mortality was seen at the lower dose of 5 mg/kg.

“Congestive heart failure may be exacerbated when high dose infliximab is used”

An analysis from the FDA Medwatch system has now reported the development of CHF in 47 patients who had received anti-TNF $\alpha$  therapy, the majority for RA<sup>38</sup> with a lesser number for Crohn's disease,<sup>6</sup> psoriatic arthritis,<sup>1</sup> juvenile idiopathic arthritis,<sup>1</sup> and one unknown underlying diagnosis.<sup>58</sup> Forty per cent had new onset CHF without documented risk factors (15 patients with RA, 4 other), 40% developed new onset CHF but with documented risk factors (14 patients with RA, 5 other), and in 9 exacerbation of known CHF occurred (all patients with RA). Of those with new onset CHF, 68% had received etanercept and 32% had received infliximab. Of the patients with an exacerbation of known CHF, 33% had received etanercept and 66% infliximab. The median time to onset of CHF was 2.5–4 months. The majority of patients were aged 50 years or older. Of concern, however, are the 10 patients aged less than 50 (five with RA) with new onset of CHF. Only three of these patients reported an underlying risk factor for CHF. In most patients symptoms of CHF have resolved or improved with treatment. Three patients had died at the time of the report.

Case reports have also appeared of other cardiac conditions in patients with RA receiving anti-TNF $\alpha$  drugs. These include a case of sudden death, without organic cause on necropsy, in a 64 year old man with no known underlying cardiac disease

**Table 4** Reports of haematological disease after the use of anti-TNF $\alpha$  treatment for RA

Citation	Description of event(s)
<i>Infliximab</i>	
Kavanaugh <sup>8</sup>	B cell lymphoma
Brown <sup>104</sup>	Lymphoproliferative malignancy (15)
Geborek <sup>14</sup>	Non-Hodgkin's lymphoma (1)
Aouba <sup>105</sup>	Hodgkin's disease (1)
Marchesoni <sup>65</sup>	Haemophagocytic syndrome
	Bone marrow hypoplasia
<i>Etanercept</i>	
Brown <sup>104</sup>	Lymphoproliferative malignancy (3)
Kremer <sup>106</sup>	Non-Hodgkin's lymphoma
Bathon <sup>107</sup>	Hodgkin's disease
Geborek <sup>14</sup>	Immunocytoma of breast (1)
	Acute myeloid leukaemia (1)
Kuruville <sup>66</sup>	Aplastic anaemia
<i>Adalimumab</i>	
Ziakas <sup>108</sup>	Mantle cell lymphoma

who was receiving infliximab.<sup>59</sup> There has also been a case report of new onset atrial fibrillation in a 57 year old man receiving etanercept.<sup>60</sup>

Care should be taken when interpreting the onset of CHF in patients with RA receiving anti-TNF $\alpha$  therapy. Cardiovascular disease is the leading cause of death among patients with RA, with increased standardised mortality ratios, compared with the general population.<sup>61–63</sup> These increased ratios suggest that patients with RA are already dying from cardiovascular disease in excess of the level expected for people in the general population of the same age and sex.

#### HAEMATOLOGICAL DISEASE (INCLUDING MALIGNANCY)

Finally, concern has been raised about haematological abnormalities after the use of anti-TNF $\alpha$  therapies in RA (table 4). These include lymphoproliferative malignancies and cytopenia. We have recently reviewed the former.<sup>64</sup>

There has also been the concern about bone marrow suppression with the use of anti-TNF $\alpha$  agents in RA. These include a report of pancytopenia after the use of infliximab<sup>65</sup> and a report of aplastic anaemia after treatment with etanercept.<sup>66</sup> An FDA briefing has also reported two additional cases of aplastic anaemia and seven cases of pancytopenia after the use of etanercept for RA.<sup>67</sup> Caution must be used in interpreting the role of anti-TNF $\alpha$  therapy in each of these cases. All cases developed in patients with chronic RA receiving multiple drugs. The exact part played by the anti-TNF $\alpha$  drug is unknown.

#### SUMMARY

The advent of anti-TNF $\alpha$  therapy is an important advance in the management of RA. However, reports about the safety of anti-TNF $\alpha$  therapy, including a risk of serious infection, congestive heart failure, malignancy, and MS, have been accumulating in the literature. However, it is difficult to interpret the importance of these events, because of both underreporting and uncertainty about the actual number of patients treated. The results also do not account for the baseline risk of serious adverse events associated with RA and its conventional treatment.

This review emphasises the need for systematic follow up and registries of patients receiving these drugs. The biggest challenge will be to find an appropriate comparison group of patients with RA not receiving anti-TNF $\alpha$  therapies. It is important when calculating risk that the comparison cohort

has similar duration and severity of disease, such that the expected event rate will accurately reflect that of an anti-TNF $\alpha$  treated cohort. However, as the anti-TNF $\alpha$  therapies become more widely available, it will become more difficult to collect this comparison cohort prospectively. To deal with these methodological issues, several countries within Europe (including the United Kingdom, Sweden, Germany, and Spain), as well as the National Databank for Rheumatic Diseases in the United States, have established registries, which will include a comparison cohort of patients with RA receiving non-biological antirheumatic treatments. However, it is likely to be some years before robust answers are available on the magnitude of any risk associated with exposure to anti-TNF $\alpha$  agents.

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