Safety of biologic therapies--an update.

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J Rheumatol 2005;74;8-12
http://www.jrheum.org/content/74/8

Safety of Biologic Therapies – An Update

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ABSTRACT. Tumor necrosis factor (TNF) antagonists have set a new therapeutic standard for rheumatoid arthritis (RA). Agents including infliximab, etanercept, and adalimumab have demonstrated substantial improvement in signs and symptoms, disability, and quality of life, while significantly inhibiting joint damage in early and long-standing RA. Safety issues in concert with efficacy determine risk/benefit ratio and hence a position in the therapeutic algorithm. This brief review focuses on infection, congestive heart, and malignancy. (J Rheumatol 2005;32 Suppl 74:8-12)

Key Indexing Terms:
BIOLOGIC THERAPIES
RHEUMATOID ARTHRITIS
SAFETY
CLINICAL TRIALS

Tumor necrosis factor (TNF) antagonists have set a new therapeutic standard for rheumatoid arthritis (RA). Agents including infliximab (Remicade®), etanercept (Enbrel®), and adalimumab (Humira®) have demonstrated substantial improvement in signs and symptoms, disability, and quality of life, while significantly inhibiting joint damage in early and long-standing RA. As with any agent, safety issues in concert with efficacy determine a risk/benefit ratio and hence a position in the therapeutic algorithm. With TNF antagonists key safety considerations include (1) infection, both common and opportunistic, (2) cytopenias, (3) demyelinating disease, (4) lupus-like syndromes, (5) congestive heart failure, and (6) malignancies, particularly lymphomas. This review, which focuses on infection, congestive heart failure, and malignancy, is an update to a presentation at the Fifth International Symposium on Advances in Targeted Therapies, April 2003[1]. Much of the information was obtained from the US Food and Drug Administration, AAC Consulting Group, The National Databank for Rheumatic Disease (NDRD) of Dr. Fred Wolfe, Wichita, Kansas, and from data on file with Abbott Pharmaceuticals, Amgen Inc., and Centocor, Inc.

Safety data can be obtained from a variety of sources including (1) placebo-controlled randomized clinical trials, (2) postapproval databases, particularly the FDA MedWatch spontaneous reporting program, and longterm registries such as the NDRD, as well as (3) registries in Sweden, Germany, and England.

A number of factors influence interpretation of adverse event data. Within clinical trials, ascertainment bias in enrolling patients into trials, population homogeneity, short trial duration, and a relatively small sample size may substantially influence the safety profile. Restricted entry into clinical trials based on comorbidities, i.e., no significant and potentially life-threatening medical conditions, as well as restricted concomitant medications, implies a unique population with lower risks of adverse events than in the general population. On this basis, comparison of adverse events in patients in clinical trials and in postapproval observation databases is difficult.

Although postapproval adverse event reporting is influenced to a far lesser extent by population homogeneity, comorbidities, restricted concomitant medications, duration of followup, and sample size, this approach still has significant limitations. Postapproval data are limited by substantial underreporting, incomplete and unverifiable data acquisition, and ascertainment bias. It has been estimated that less than 1% of serious adverse events are reported to the FDA on the MedWatch Program[2-5]. The propensity for reporting is influenced by the seriousness of the event as well as how long the drug has been approved, since most events reported occur early, particularly within the first 2 years. Unanticipated adverse events are also more likely to be reported.

Interpretation of postapproval adverse event data also depends on how the data are ascertained and reported. For example, data on drug exposure for etanercept is readily obtained through the number of prescriptions, while difficulty arises in ascertainment of infliximab as a consequence of bulk shipments to providers and weight-based dosing. As a consequence, patient-year exposure to etanercept is expressed as time on drug, while infliximab exposure is expressed as elapsed time since initiation of drug regardless of whether it is continued.

Constituents of the database also influence reporting rates. Thus, patients with juvenile arthritis and psoriatic arthritis are often included in etanercept data, while patients with Crohn's disease are often included with infliximab data (Table 1). Since the rate of *Mycobacterium tuberculosis* (MTB) reporting is considerably lower in Crohn's disease as a consequence of the periodic infliximab

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Table 1. Available data from clinical trials, postapproval surveillance, and RA safety database.

	Etanercept	Infliximab	Adalimumab***
RA trials, number of patients	3839*	1298**	9460
RA trials, patient-years exposure	8336	2468	9894
Postapproval, number of patients	230,000	277,000	NA
Postapproval patient-years exposure	423,000	466,000	NA

*Includes PsA, JRA (as of Dec 2003). **Includes Aspire Trial (as of Oct 2003). ***Includes pivotal extension studies, ACT and REACT (as of Dec 2003).

Table 2. Characteristics of TNF antagonists.

	Infliximab	Etanercept	Adalimumab
Structure	Chimeric mAb	TNF IgG1 fusion protein	Human mAb
Binding target	TNF	TNF, lymphotoxin	TNF
Binding affinity	1.8×10^9	10^{10}	2.3×10^{10}
Half-life, days	8–9.5	4–5	12–14
In vitro complement mediated cell lysis	+	–	+
Dose	q 60 days	q 3–4 days	q 7–14 days
Efficacy in Crohn's disease	+	–	+

mAb: monoclonal antibody.

treatment regimen, inclusion of RA and Crohn's patients together in a *M. tuberculosis* database will affect the reporting rate.

Intensity of surveillance will also influence numbers of events reported. Thus, a facilitated reporting system was utilized to track etanercept with outbound calls to patients regarding their health status. As a consequence, an increased number of reports of adverse events would be expected. Similarly, periodic visits to infusion centers for infliximab infusions may also improve adverse event reporting. Finally, the availability of drug also has an effect on the adverse event profile. Only infliximab is approved for government funding in the US for patients over 65 years of age, resulting in an older population being treated with infliximab compared with etanercept. However, the mean age of infliximab treated patients was less than 65 years of age.

The characteristics of the TNF antagonists currently approved are different, particularly in terms of structure, binding target, half-life, capability of *in vitro* cell lysis, dosing, and efficacy in Crohn's disease (Table 2). In Crohn's disease it remains unclear whether *in vitro* cell lysis accounts for differential efficacy of TNF-producing cells and incidence of granulomatous infections such as MTB. Recent data suggest that lymphocyte apoptosis in the lamina propria of patients with Crohn's influences its efficacy[6-8]. More recent preliminary data from Catrina and colleagues[9] have shown that in RA etanercept and infliximab both induce apoptosis *in vivo* and *in vitro*. These results suggest that TNF blockade-induced apoptosis is less likely to account for differences in the safety profile of TNF antagonists with respect to activation of latent MTB. Given the conflicting data in RA and Crohn's disease, more information is required to clarify the role of apoptosis in activation of MTB.

INFECTION

One of the most important safety issues confronting TNF antagonists is infection. A higher rate of upper respiratory infections has been observed with TNF antagonists compared with placebo in clinical trials, although the rate of serious infections was comparable (Table 3). MTB has been the most common granulomatous infection observed with TNF antagonists. Its incidence is influenced by age, low socioeconomic status, and particularly geography. Geography has influenced the rate of MTB observed in early clinical trials with adalimumab. All of the initial 542 patients treated with adalimumab who developed MTB were from Germany. Only 5 cases were observed in 1900 patients treated subsequently, of which 2 were MTB-positive on screening (Table 4). The substantial reduction in MTB reflects screening and likely dose reduction. A similar reduction in MTB reporting was observed with an MTB education/screening program with infliximab. Despite extensive education MTB reports continue, albeit at a lower level. Support for the value of screening comes from Gomez-Reino, *et al*, who observed a substantial reduction in MTB reports with screening[10].

In a recent review of MTB in patients receiving infliximab in the National Databank for Rheumatic Diseases (NDRD), an increased rate of MTB was observed with infliximab relative to patients with RA, patients not receiving infliximab, and a healthy US population[11]. However, patients receiving infliximab were not screened for MTB.

The prevalence of MTB from postapproval surveillance reflects to a large extent the country of exposure/origin of the patients (Table 4). This issue has considerable relevance, since 38% of infliximab use postapproval compared with 10% of etanercept use occurred in Europe/Norway, where the prevalence of MTB is considerably higher than in the US. The onset of MTB post-exposure differs significantly, with the median time of onset of 11.2 months with etanercept, while 61% of patients treated with infliximab who developed MTB did so within the first 3 infusions (6 weeks). All TNF antagonists have been associated with extrapulmonary MTB, reflecting the potency of these agents to modulate the immune system. This finding suggests that MTB

Table 3. M. tuberculosis in patients treated with TNF antagonists in clinical trials.

	Etanercept*	Infliximab**	Adalimumab***	
			Pre-screen	Post-screen
No. of patients treated	3839	1298	9460	
Exposure, patient-years	8336	2458	534	9360
No. of TB cases	—	5	7	14
Geography				
USA	—	NA	—	3
Outside USA	—	NA	7	11
Characteristics				
Time to onset, mo	—	—	3–8	
Extrapulmonary	—	—	NA	

*Includes PsA, JRA (as of Dec 2003). **Includes Aspire Trial (as of Oct 2003). ***Includes pivotal extension studies, ACT and REACT (as of Dec 2003). NA: not available.

Table 4. M.tuberculosis (MTB) in patients with RA treated with TNF antagonists after approval of drug.

	Etanercept*	Infliximab**
No. of patients treated	230,000	277,000
Exposure	423,000	466,000
Use		
USA	90%	64%
EU/Norway	10%	36%
MTB reports	38	242
Geography		
USA	26	90
Outside USA	12	152
Time to onset	Median 11.20 mo	By 3 infusions: 60% By 7 months: 97%
Characteristics		
Extrapulmonary	34%	30–45%
Miliary	16%	—

*As of Dec 2003. **As of Oct 2003. EU: European Union.

screening is prudent with all TNF antagonists. One caveat regarding skin testing is the incidence of anergy in RA. Several studies have suggested that up to one-third of patients with RA demonstrate anergy[12]. Moreover, it is not uncommon for the MTB skin test to be placed or read inappropriately, particularly by untrained personnel. For this reason, screening has reduced but not completely eliminated MTB with TNF antagonists. On this account there must be a high index of suspicion for MTB and other granulomatous diseases.

Through the fourth quarter of 2003, 38 postmarketing MTB reports (26 US, 12 non-US) have been received of 230,000 etanercept treated patients (95% treated in US), to yield a worldwide rate of ~17 reports per 100,000 patients exposed, and a US reporting rate of ~13 per 100,000 patients. This contrasts with infliximab where, as of October 2003, 441 MTB reports have been received, yielding a reporting rate worldwide for Crohn's disease and RA of ~88 patients per 100,000 treated. Two hundred forty-two cases of MTB have been reported in RA patients — 90 US and 152 non-US of 277,000 RA patients treated. Assuming that 64% of the 277,000 RA patients treated with infliximab reside in the US, the reporting rate in the 177,000 RA patients in the US is ~50 MTB cases per 100,000 patients treated. Of note, 57% of cases involved the pulmonary site, while 18% were miliary, 20% lymph nodes, 5% pleural, and 30% in other sites. Similar sites of involvement have been observed with etanercept. Postmarketing reports of MTB in ~10,000 adalimumab treated patients has revealed a reporting rate in the US of ~20 patients per 100,000 treated (pers. comm.).

A number of opportunistic infections have been reported with TNF antagonists both within clinical trials and postapproval. The most common of these relatively rare infections include histoplasmosis, *Pneumocystitis carinii*, listeriosis, and aspergillosis. Geography has relevance here, since opportunistic infections are observed more frequently in Europe than the US. The clinical trial data showed more MTB and other opportunistic infections compared with etanercept. Consistent with the concept of TNF antagonists increasing the risk of opportunist infections, Bergstrom, *et al* demonstrated that patients in a region endemic for coccidioidomycosis in the US who underwent treatment with infliximab appeared to have a higher risk (5.23, confidence interval 1.54-17.71; $p < 0.01$) for developing symptomatic coccidioidomycosis as compared to those not receiving infliximab[13].

CONGESTIVE HEART FAILURE

Preliminary data suggested that inhibition of TNF ameliorated congestive heart failure (CHF). However, studies of both etanercept and infliximab failed to show such a benefit. Two clinical trials of etanercept in 2000 patients with CHF without RA with New York Heart Association (NYHA) classification functional class 2 to 4 revealed the possibility of increased mortality of etanercept in CHF, particularly at a 3 times per week dose, in patients with less severe heart disease[14,15]. Despite these data, it is unclear whether etanercept is associated with increased

Table 5. Standardized incidence rates of cancers and lymphomas in patients treated with TNF antagonists.

Study	Country	No. of RA patients	Years of Followup	SIR for Cancer	SIR for Lymphomas
Gridley, 1993[22]	Sweden	11,683	20	1.0	2.4
Mellemkjaer, 1996[23]	Denmark	20,699	14	1.1	2.4
Isomaki, 1978[24]	Finland	46,101	7	1.1	2.7
Matteson, 1991[25]	Canada	530	7	1.5	8.0
Baecklund, 1998[19]	Sweden	11,683	18	—	1.0 (L act)
					5.4 (M act)
					25.8 (H act)
Ekstrom, 2003[26]	Sweden	76,527	<1–20+	1.09	2.0

SIR: standardized incidence rate. L/M/H act: low/medium/high disease activity.

Table 6. Recent data on lymphoma in patients treated with TNF antagonists.

	Etanercept	Infliximab	Adalimumab
Treated/Exposure			
No. of patients	3389	1298*	9460
Patient-years	8336	2458	9894
Total no. of cases	6–9	4	15
Hodgkin's	3/6	1/3	2/3
non-Hodgkin's**			
Mean time to onset,	21	10–19	18
mo (range)	(0.1–4.6)	(6.4)	(2.0–42.0)
SIR lymphoma	2.31–3.47	6.4	4.35
(95% CI)	(1.59–6.59)	(1.7–16.3)	(2.3-7.4)

*Rheumatoid arthritis only; ** majority diffuse large B cells.

mortality or morbidity in patients with CHF. Given a relative risk of increased morbidity of 1.2 with etanercept, caution should be used in patients with a history of CHF. Infliximab was evaluated in a 52 week study of 15 patients with NYHA functional class 3 to 4. An increased rate of hospitalization and mortality was observed in patients receiving infliximab at a dose of 10 mg/kg given initially at 2 and 6 weeks[16]. No clinical trials of adalimumab in CHF have been carried out. In a review of CHF and TNF antagonists in the NDRD, etanercept and infliximab revealed no increase in CHF relative to controls[17]. More recently, evidence has accumulated suggesting that treatment with anti-TNF-α antibody may improve endothelial function in RA[18].

MALIGNANCY

The development of malignancy is an issue given the immunosuppressive nature of the TNF antagonists. For solid tumors, data with etanercept and infliximab showed that the number of tumors observed during followup of patients treated in clinical trials was comparable to the age, sex, and race matched cohort obtained from the Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute of the USA.

The risk of lymphoma, however, is more complex, given that the incidence of lymphomas is increased in patients with RA. The standardized incidence rate (SIR), i.e., ratio of the observed to expected number of lymphomas within the SEER database, has been reported as high as 8.0 (Table 5)[19]. The average SIR within a number of large database studies is about 2.0–2.5. This risk has been shown to correlate with activity and severity of disease as well as exposure to immunosuppressive agents. In clinical trials, SIR observed for lymphomas with TNF antagonists is within the range of prior reports (Table 6). Most of the lymphomas associated with the use of TNF antagonists are non-Hodgkin's lymphomas, with a mean time to onset averaging 1021 months. Data from the NDRD showed modest increases in the SIR relative to patients receiving methotrexate alone and those not receiving disease modifying drugs, with wide and overlapping 95% confidence intervals[20]. Postapproval surveillance reports of lymphoma with TNF antagonists revealed reporting rates of 10–30 events per 100,000 patient-years, while the expected rate of lymphomas in a normal population aged 65 within the SEER database is 70 events per 100,000 patient-years. The spontaneous lymphoma reporting rate for RA with infliximab was 24 per 100,000 patient-years, while the US rate with adalimumab was 10 per 100,000 patient-years as of October 2003 (pers. comm.). The spontaneous lymphoma reporting rate for RA with etanercept therapy (all cases reported and/or confirmed by healthcare professionals) as of April 2004 was 22 per 100,000 patient-years. The actual incidence postapproval is unclear, since the degree of underreporting of lymphomas is difficult to ascertain. A recent editorial by Deborah Symmons and Alan Silman addressed the use of anti-TNF therapy and risk of lymphoma in RA. They concluded that the data on lymphoproliferative malignancies risk are reassuring, but no clear answer is available at present[21].

Taken together, current data suggest a higher rate of lymphomas in patients receiving TNF antagonists relative to normals. Whether the risk of lymphomas is high-

er with TNF antagonists than in patients receiving conventional disease modifying drugs remains unclear.

CONCLUSION

As with any immunosuppressive agent, safety considerations remain an issue. For the most part, serious adverse events are uncommon and the risks appear manageable. Despite the risks inherent in therapy with TNF antagonists, the risk/benefit ratio to date is extremely good. However, only prolonged observational studies will address issues longterm regarding the frequency of known adverse events, as well as early ascertainment of rare events.

ACKNOWLEDGMENT

The author thanks Jeannette Henderson, Nancy Restiva, and Rosemary Dale for their excellent secretarial assistance. Thanks also to Abbott, Inc., Amgen, Inc., and Centocor, Inc. for assistance in providing their data on file; and to Drs. A. Kavanaugh and J. Cush for assistance in the preparation of this report. The author is also grateful to Dr. Leo van de Putte for enabling an update of the Advances in Targeted Therapy publication 2003.

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