Laboratory monitoring of biologic therapies

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ABSTRACT

The purpose of this report is to provide suggested guidance concerning the monitoring of TNF blocker therapy. Since the completion of randomized trials, several new long-term safety concerns have arisen, involving mycobacterial and opportunistic infections, cytopenias, lymphoma, demyelinating disease, drug-induced lupus, congestive heart failure and hepatotoxicity. Since these serious events are rare, widespread post-marketing use and prolonged follow-up have been required to analyze their prevalence. Monitoring of TNF inhibitors is necessary to reassure physicians and patients of the continued efficacy and safety of these drugs.

No published recommendations on monitoring are available The clinician must weigh the potential clinical benefits of TNF inhibition against potential adverse effects. Patients should be evaluated carefully for the risk or presence of infection, tuberculosis and other serious adverse events by regular visits, careful clinical assessments, and an assiduous, high index of suspicion for these rare events. Tuberculin skin testing using PPD is recommended before starting treatment with any TNF inhibitor.

Introduction

The use of biologic response modifiers has steadily grown since their introduction in 1998. Marketing surveys estimates that more than 10% of rheumatoid arthritis (RA) patients in the USA are taking or have taken a drug targeting tumor necrosis factor (TNF). Worldwide sales of such agents has grown to nearly 4 billion US dollars per annum. Despite their increasing popularity, surveys indicate that the vast majority of the biologic use rests with a minority of rheumatologists. Hence, many rheumatologists use such advanced therapies sparingly or not at all.

A conservative approach to prescribing biologic agents may emerge over concerns regarding costs, drug safety, limited experience, limited long term use and/or the absence of clear guidelines concerning monitoring and strategies to avoid adverse events. While these agents have been available for 3-7 years and been used in more than 1,000,000 patients worldwide, considerable uncertainty remains regarding how best to monitor the safety of these agents. This uncertainty may be based largely on rare reports of serious adverse events (that may have been prevented by laboratory monitoring), and the absence of clear guidelines to monitor therapy in the product label.

The purpose of this report is to provide suggested guidance concerning monitoring of TNF blocker therapy. These suggestions are based on manufacturers prescribing information, expert opinion, and a medical literature search of "safety" and "monitoring" and "TNF inhibitors", as well as the individual agents; etanercept, infliximab and adalimumab.

Safety monitoring and product labeling

Safety concerns for TNF inhibitors have been repeatedly reviewed and examined by investigators and regulatory agencies (1-3). Since completion of randomized trials to introduce these agents, several new long term safety concerns have arisen. These include mycobacterial and opportunistic infections, cytopenias, lymphoma, demyelinating disease, drug-induced lupus, congestive heart failure and hepatotoxicity. Since these serious events are rare, widespread post-marketing use and prolonged follow-up has been required to analyze their prevalence. Therefore the product labeling for all 3 currently marketed TNF inhibitors have undergone several revisions to address these issues.

The frequencies of rare adverse events are listed in Table I. These data were compiled from a variety of sources, in-

cluding the product label and prescribing guidelines, publicly released safety information (4,5) (from the FDA and manufacturer) and a recent survey of 1,021 rheumatologists (6). In the latter survey, respondents were asked to estimate the frequency of these safety concerns amongst their patients receiving TNF inhibitors over the last 5 years. Despite disparate origins, the data are remarkably consistent in suggesting that many of these serious events are quite rare. Other than serious infections like pneumonia and transaminitis, most of these adverse events occur in fewer than 1% of patients receiving a TNF inhibitor. The seriousness of these events must be weighed against their rarity when devising any monitoring strategy meant to limit such toxicities.

Table I. Frequency of serious adverse events with TNF inhibitors.

	Infliximab*	Etanercept	Adalimumab	All TNF inhibitors[$]
Pneumonia	1.7%*	< 1%*	0.92%[@]	2.26%
Tuberculosis	0.4%*	0.03%[+]	0.23%[@]	0.36%
Cytopenia[†]	0.9-1.4%@	ND	0.08/100 pt-yr[@]	1.10%
Lymphoma	0.31%[+]	0.26%[+]	0.41%[+]	0.36%
Demyelinating disorders	ND	ND	0.08%[@]	0.39%
Drug-induced lupus	0.2%(7)		0.05%[@]	0.87%
Congestive heart failure	0.2%[+]	0.06%[+]	0.1%[+]	0.71%
Transaminitis (≤ 3-fold)	34%[@]	ND	ND	0.51%
Hepatic failure	0.006[@]	ND	ND	0.05%

* Package insert data from pivotal randomized clinical trial results 9/1/05.
[+] Data from 2003 FDAArthritis Advisory Committee review of TNF safety (5).
[@] 2004 Post marketing data reported (data provided by manufacturer).
[$] Based on a survey of 1021 rheumatologists (6).
[†] Cytopenia includes leucopenia, neutropenia, thrombocytopenia.
(7) De Bant *et al*. estimates the frequency to be 0.19%.

Table II. What do rheumatologists monitor in RAstarting on a TNF inhibitor ? Results of a survey of 1,021 rheumatologists conducted in April 2005.

Measure	Positive respondents (n=892)
Physician overall assessment	83%
CBC	81.5%
ESR	79..8%
C-reactive protein	68.3%
Tuberculin skin test (PPD)	59.1%
Rheumatoid factor	16.4%
CCPantibody	12.2%
HAQ (scored)*	16.3%
Pregnancy test	5.2%
Disease activity score (DAS)[+]	6.5%
ACR20 or ACR-N	2.8%

PPD: purified protein derivative; CCP: cyclic citrullinated peptide; HAQ: health assessment questionnaire.
* includes any version of the HAQ (mHAQ, MD-HAQ, Clin-HAQ, etc.)
[+] includes any version of the DAS (DAS28, DAS44, DAS-CRP, etc.)
Source: Reference 6

Table III. Tests ordered for monitoring of biologic agents (ordered by % rheumatologists).

Test	MTX BL– F/U	ETA BL– F/U	IFX BL– F/U	ANK BL– F/U
CBC	100 - 95	98 – 93	97 – 91	80 – 78
AST	96 - 90	79 – 54	81 – 57	66 – 50
ALT	97 - 89	79 – 55	80 – 59	65 – 52
Creatinine	100 - 66	89 – 55	88 – 61	70 – 53
Hepatitis panel	52- 2	31 – 2	33 – 1	26 – 2
Albumin	83 - 61	72 – 36	69 – 41	52 – 34
Chest x-ray	47 - 2	43 – 1	50 – 1	28 – 1
PPD	*	73 – 1	83 – 1	39 - 1

Source: Reference 8
BL: baseline; F/U: Follow-up; MTX: methotrexate; ETA: etanercept; IFX: infliximab; ANK: anakinra.
*not asked

How do rheumatologists monitor biologic agents?

Monitoring of TNF inhibitors is necessary to reassure physicians and patients of the continued efficacy and safety of these drugs. No published recommendations on monitoring are available. Two surveys of rheumatologists have provided similar information (6, 8).

The most recent survey (6) queried 2,880 practicing US rheumatologists, who were asked to participate in an online survey of "the indications/use for biologics and TNF inhibitors, safety monitoring and safety concerns." Nearly 35% (1,021) responded to this survey that included 33 questions about use of TNF inhibitors, safety monitoring and safety concerns (6).

When assessing safety of TNF inhibitors, US rheumatologists rely primarily on clinical assessments (history, physical examination) (92%), hepatic enzymes (69%), and CBC (77%). Although 20% stated they never order cancer screens or serologies such as ANA or double-stranded DNA, most acknowledged performing serologies (78%), cancer screens (82%) and chest radiographs (76%) when clinical signs or symptoms warranted such investigations. When asked how often serologies (ANA, dsDNA) are performed in patients receiving TNF inhibitors, most (57%) perform these either with signs of lupus (58%), with fewer doing these

before drug initiation (14%), or yearly (9%) or every 6 months (9%). Twelve percent reported that they never do serologic testing. Although repeated questions using different formats often gave different results, the most prevalent choice persisted.

The most common laboratory tests used to monitor patients treated with TNF inhibitors (Table II) included complete blood counts (82%), sedimentation rates (80%), C-reactive protein (68%), and tuberculin skin tests (i.e., PPD) (59%). Uncommon measures included serum rheumatoid factor (16%) and anti-CCP antibodies (12%), health assessment questionnaire (12%), DAS (6%), or an ACR20 (or ACR-N) outcome (2%).

A similar survey regarding monitoring of adverse events associated with biologic agents and methotrexate was conducted among 310 rheumatologists in 2003, with 123 responses (40%) (8) Responses were similar to the more recent survey (Table III), with the majority of physicians indicating that monitoring CBC and liver function tests; 83% placed a PPD and 50% ordered a chest x-ray if it was positive. Most rheumatologists reported monitoring patients less than every 4 months. A similar pattern was observed for monitoring practices of rheumatologists for biologic agents to those used for methotrexate monitoring, possibly indicating adoption of methotrexate monitoring guidelines in the absence of specific biologic agent monitoring guidelines.

It appears that US rheumatologists rely heavily upon qualitative assessments (physician overall assessment, symptom review, morning stiffness, and complaint focused joint exams) and laboratory measures (CBC, ESR, CRP, hepatitis screens, ANA) when assessing and treating their RA patients. Less commonly employed are quantitative clinical measures, including (28 joint tender and swollen joint counts, functional measures) and patient questionnaire measures.

Suggested monitoring guidelines

The clinician must weigh the potential clinical benefits of TNF inhibition against potential adverse effects. Although specific laboratory monitoring is not currently mandated, the frequency and chronology of cytopenias and hepatotoxicity warrants that a complete blood count and liver function tests be performed every 3 months for first 12 months in those begun on TNF inhibitors. In many cases, patients will be taking methotrexate, for which this monitoring is also indicated.

While autoimmune disorders (eg, drug-induced lupus, multiple sclerosis) have been reported sporadically with use of all three anti-TNF agents, serologic testing done during the pivotal randomized clinical trials strongly suggest there is no value to pre-treatment or periodic serologic testing, as these have no predictive value. By contrast, serologic testing of ANAand double stranded DNAantibodies should be performed in patients who show signs of autoimmune disease to help establish a diagnosis.

There are no useful or tested tools to help avoid the low incidence of demyelinating disease, congestive heart failure or lymphoma. There is no research available concerning the role of CSF studies, cancer screens, BNP levels or echocardiography in assessing longitudinal risk in these patients. Rather, it may be more prudent to avoid TNF inhibitors in patients with such a prior history of these events, until further longitudinal research delineates the safety in this instance. However, in certain cases, after careful discussion between doctor and patient, a patient may decide that a TNF inhibitor may be taken cautiously in view of the “risks” of RA. More importantly, patients should be evaluated carefully for the risk or presence of infection, tuberculosis and other serious adverse events by recurrent visits, careful clinical assessments, and an assiduous high index of suspicion for these rare events. Tuberculin skin testing using PPD is recommended before starting treatment with all TNF inhibitors.

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