Unusual toxicities with TNF inhibition: Heart failure and drug-induced lupus

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Clin Exp Rheumatol 2004; 22 (Suppl. 35): S141-S147.

Key words: TNF inhibitors, congestive heart failure, drug-induced lupus, rheumatoid arthritis.

ABSTRACT

Serious and unexpected adverse events, such as heart failure and drug-induced lupus, have been reported in patients receiving TNF inhibitor therapy. These events generally are easily recognizable, although they cannot be predicted nor avoided, other than by drug avoidance altogether. Many patients have great benefit from anti-TNF therapies. Their intelligent use requires a firm understanding of these rare toxicities, so as to minimize the morbidity associated with their uncommon occurrence.

Introduction

The introduction of biologic agents to specifically inhibit the pro-inflammatory cytokine, tumor necrosis factor (TNF), has transformed traditional treatment paradigms for a wide range of inflammatory disorders. Many patients with rheumatoid arthritis (RA), Crohn's colitis, psoriasis and a variety of spondyloarthropathies have been afforded newfound disease control, especially when traditional agents have failed, were only partially effective, or were not tolerated. After 6 years of use, these drugs have been administered to nearly 700,000 patients worldwide, although only a minority of patients with inflammatory diseases have received them. The restrained growth of this class of therapy is affected by high costs, limited numbers of ideal candidates, lack of clear guidelines for use and a continued concern for their long-term safety (1, 2).

The most common toxicities seen with these agents were defined during controlled clinical trials and drug development (3-5). However, following FDA approval, post-marketing surveillance has disclosed a number of rare or unusual signals that underscore the need for further large, population-based studies concerning the safety of TNF inhibitors (6-9). These rare and unusual events include opportunistic infections, serious infections, possible lymphoma, demyelinating disease, cytopenias, autoimmune disorders, and heart failure. Other essays in this volume address the subject of infection (10), demyelination (11), and lymphoma (12). This review will focus on heart failure and lupus-like disease, which are rarely seen in association with TNF inhibitor therapy and are currently without explanation.

Sources of data

As a consequence of drug approval, manufacturers have a responsibility to collect safety data actively and report these data to the appropriate agencies. For example, in the USA a manufacturer must submit periodic safety reports to the FDA twice yearly (March and September). Moreover, other parties are also focused on the safety of TNF inhibitors. These include the drug manufacturer (each having its own global safety/pharmacovigilance office), regulatory agencies (e.g., FDA, EMEA [European Agency for the Evaluation of Medical Products]), external individuals, researchers, clinicians and patient advocacy groups which may report additional safety data or have access to publically available drug safety reports. When analyzing the safety of TNF inhibitors, data are collected from the FDA's Medwatch/AERS (Adverse Event Reporting System), specific freedom of information (FOI) requests for safety reports, review of the medical literature, and scientific abstracts and composite data derived from national and international patient registries (9).

Each of the manufacturers of TNF inhibitors have committed itself to multiple, large on-going open-label safety registries to further discern the true incidences of rare or unusual events. Often causality can be difficult to define, as many of these events could be ascribed to the disorder under treatment, rather than to the treatment alone. A prolonged period of at least 5-10 years is required to distinguish between two

Table I. Adverse outcomes in CHF treated with TNF inhibitors+ (8).

Study name	RENAISSANCE	RECOVER	ATTACH
TNF inhibitor	Etanercept	Etanercept	Infliximab
N (NYHA Class)	925 (NYHC 2-4)	1123 (NYHC 2-4)	150 (NYHC 3-4)
Regimens	Placebo, 25 mg BIW, TIW	Placebo 25 mg BIW	Placebo 5 mg/kg or 10 mg/kg @ weeks 0, 2 & 6
Study duration	Median 12.7 mos.	Median 5.7 mos	28 weeks
Death rates*	Placebo 14.2% ETAN BIW 17.9% ETAN TIW 19.8%	Placebo 8.8% ETAN QWK 5.9% ETAN BIW 7.2%	Placebo / 5 mg/kg / 10 mg/kg @wk 28: 0 / 2.0% / 5.9% @wk 54: 8.2% / 8.0% / 15.7%
CHF* hospitalization	NA	NA	Placebo / 5 mg/kg / 10 mg/kg @wk 28: 10.2% / 6.0% / 21.6%
Concerns ?	TIW dose group more problems. NYHA Class II are NOT at lower risk		10 mg/kg @ higher risk

+All studies were prematurely halted for futility or poor outcomes; *at the end of study.

large populations (>10,000) of treated and untreated patients, and these comparisons are confounded by the fact that patients who are treated with biologic agents are likely to have a more severe clinical status. Finally, when post-marketing analyses yielded unexpected or serious safety signals, the FDA has twice initiated public proceedings to examine the safety of TNF inhibitors in clinical practice. These proceedings have been published elsewhere as part of the American College of Rheumatology (ACR) Hotline series (6-9).

TNF and heart failure

TNF has been presumed to play a crucial role in the pathogenesis of heart failure and cardiac cachexia (2, 13). Systemic effects of TNF, IL-1 and other proinflammatory cytokines are well known causes of anorexia, cardiac cachexia, endotoxic shock, etc. These cytokines may also have untoward vascular effects by promoting the expression of adhesion molecules and alterations in blood flow (13). TNF has been shown to have negative inotropic effects on the myocardium and may further contribute to left ventricular dysfunction and cardiomyopathy. TNF also causes myocyte dysfunction and death, and may cause myocardial fibrosis and alteration of myocardial matrix proteins to contribute further to the myocardial failure. Several studies have shown increased circulating levels of TNF in patients with congestive heart failure (CHF), especially in those with NYHA class III and IV disease that is associated with severity and higher mortality risk. Transgenic mice which overexpress TNF have dilated cardiomyopathy and premature death. These data led many investigators to an *a priori* assumption that TNF inhibition would improve cardiac function and survival in patients with CHF (11).

Clinical trials with both etanercept and infliximab were initiated in patients with heart failure who did not have arthritis or inflammatory diseases (14-16). After 6-12 months of study these trials were halted prematurely due to the absence of effect and/or poorer outcomes (8, 9). Reasons for the absence of anticipated benefit with either drug, or for the paradoxical outcomes seen in patients on higher doses of etanercept or infliximab, are not understood.

Table I summarizes the clinical trials that were reviewed at a March 2003 FDA conference concerning the safety of TNF inhibitors (8, 9). Etanercept was studied in two randomized controlled trials (RENNAISSANCE and RECOVER trials) involving 2,048 patients with NYHA class 2-4 heart failure (14, 15). These patients had a history of CHF for a mean of 4.6 to 5.6 years, were predominantly male (78%), Caucasian (84-99%), 62-65 yrs old, and had entry ejection fractions of 22-24%. Most were NYHA Class 3 (70-72%), with some being NYHA Class 2 (24-27%) These studies were discontinued after 12 and 5.7 months respectively for "futility"; defined as less than 10% benefit in morbidity or mortality endpoints (CHF hospitalizations, death rates, improvement in NHYA class, patient global assessment).

While no benefit was seen, several patients did experience adverse cardiac outcomes, even those with NYHA class 2 disease. The multi-national RECOVER trial did not show benefit or worsening using conventional dosing of 25 mg weekly or twice weekly. The North American RENNAISSANCE trial showed a non-signifcant trend toward more flares of CHF and hospitalization in those treated with higher doses of etanercept, 25 mg thrice weekly. It is not known if the premature cessation of these trials may have masked further cardiac risks associated with etanercept therapy.

Infliximab was also studied in a pilot, phase II trial of 150 RA patients (8, 9, 16). This North American, placebo-controlled trial involved NYHA class 3 and 4 CHF patients. Patients were randomized to receive 3 infusions of placebo or 5 mg/kg or 10 mg/kg infliximab over 6 weeks and were then followed. This study was discontinued after an interim analysis at week 28 (Table I) indi-

cated that CHF hospitalizations and deaths were higher in the 10 mg/kg infliximab treated group (21.6% hospitalizations, 5.9% deaths), compared with the placebo treated group (10.2% hospitalizations, no deaths). When these patients were followed for 54 weeks, 4 deaths were noted in the placebo and 5 mg/kg groups, while 8 deaths were seen in the 10 mg/kg treatment group. These results prompted a change in product label and an October 2001 "Dear Doctor" letter warning clinicians of this association.

Heart failure in RA patients

Over the last few years it has become increasingly clear that the increased mortality rates seen in RA are partly due to augmented rates of cardiovascular events stemming from the damaging vascular effects of systemic inflammation (2, 13). These data affirm that RA patients are at increased risk for developing cardiac disease. Analysis of TNF inhibitor-treated RA patients, especially those without a prior history of CHF, recent myocardial infarction or uncontrolled hypertension, may clarify further the risk of heart failure when using these agents.

RA patients without a history of significant cardiovascular disease were studied during pivotal phase II and III clinical trials for all three TNF inhibitors (3-5, 9) (Table II). With each drug there was no increase in the number of CHF flares or *de novo* cases. In the etanercept RA clinical trials involving 3,389 patients, new-onset CHF occurred in only 2 placebo-treated and 2 etanercept-treated patients. Analysis of more than 1,600 RA patients treated in controlled clinical trials indicated that new onset CHF occurred in 0.2% of infliximab and 2.1% of placebo-treated RA and Crohn's disease patients. During the adalimumab clinical trials, the incidence of new onset CHF was 0.1% for adalimumab treated patients (N = 1362) and 0.5% in placebo-treated patients (N = 683). Therefore, in the randomized controlled trials of all 3 TNF inhibitors involving more than 7,300 patients, a total of 18 new onset CHF reports have emerged; 7 occurring with use of TNF inhibitors (< 0.2%) and 11 with the use of placebo (0.7 – 2.1%). Thus, review of these clinical trial data suggests that the risk of TNF inhibitor-associated heart failure in RA patients without background heart disease is substantially different than when these drugs are given to patients who have heart failure alone.

CHF post-marketing safety reports

The FDA has reviewed spontaneous reports from the Medwatch (AERS) system and disclosed 158 spontaneous reports of CHF associated with the use of TNF inhibitors (8, 9). A more extensive analysis of 51 of these patients was performed. The study group comprised 30 patients treated with etanercept, 21 with infliximab, and none on adalimumab, (the analysis was performed prior to drug approval). There were 9 exacerbations of pre-existing CHF, and 42 cases of new onset CHF. Among the new onset cases, half had no prior risk factors. The mean age was 64 years and the median time to onset was 3.5 months (range 1 day to 2 yrs). Three deaths occurred. Ten of the 51 patients who developed CHF (4 etanercept, 6 infliximab) were less than 50 years of age. Three had known risk factors. The median ejection fraction was 20%. All stopped anti-TNF therapy: 3 resolved, 6 partially improved and 1 patient died. Following this FDA review, several publications have addressed the incidence of heart failure among RA patients treated with TNF inhibitors. For example, Michaud and Wolfe have reported the results of a National Data Bank for Rheumatic Disease study that identified incident cases of heart failure in 13,171 RA patients receiving TNF inhibitors and other DMARDs (17). In their study, heart failure was more common in RA patients (3.9%) than in those with osteoarthritis (2.3%). Among RA patients, those who received TNF inhibitors had fewer episodes of heart failure (3.1%) than those receiving other DMARDs (3.8%). Moreover, those RA patients without evidence of prior heart disease were at very low risk for CHF, regardless of whether they had received TNF inhibitors or not. Similarly, Lenart *et al.* has reported an analysis of a South Swedish Registry that compared 412 TNF inhibitor-treated RA registry patients with 580 RA patients (control group) and showed a lower incidence of cardiovascular events among TNF-treated patients (14 events in 667 person-years or 2.1%) than controls (123 events in 2303 person-years or 5.3%) (18). The age-adjusted incidence rates per 1000 person-years were 28.5 for controls, but only 0.57 in TNF inhibitor-treated RA patients. They concluded that the effective control of inflammation may in fact lower the risk of cardiovascular disease in RA (18).

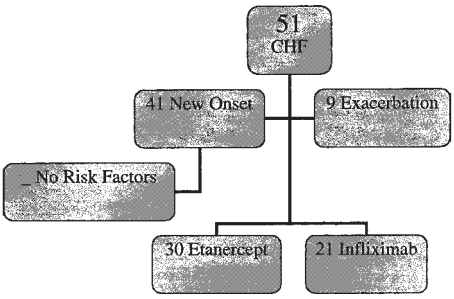
Practical considerations concerning the use of TNF inhibitors with CHF

It appears that a rare and unknown association may exist between TNF inhibitor use and new onset CHF. While data from the CHF trials suggest not only no cardiac benefit, but also potential hazardous consequences of TNF inhibitor use, especially with higher doses, use of anti-TNF in patients with RA does not appear to contribute to incident CHF. Whether TNF inhibitors can safely be used in patients with RA and other inflammatory disorders who have pre-existing CHF has not been objectively studied. Until further studies become available, it may be prudent to avoid initiation of TNF inhibitors in patients with pre-existing NYHA Class III or IV disease or unstable heart failure. RA patients whose heart failure is well controlled and those who are currently receiving TNF inhibitors should be told of these risks and have their cardiac status monitored closely.

Table II. New onset heart failure during clinical trials of TNF inhibitors in RA.

	Etanercept (n = 3,389)	Infliximab (n > 1,600)	Adalimumab (n = 2,045)
Active drug	2	0.2%	0.1%
Placebo	2	2.1%	0.5%

Table III. Analysis of 51 patients with new onset CHF in RA.



Mean age = 64 yrs
Median onset from TNF to CHF = 3.5 mos (24 h – 2 yrs)
3 deaths
20% (10) CHF pts < 50 yrs
6 infliximab & 4 etanercept
Ejection fraction = 20%
3 with CHF risk factors
all d/c TNF @ CHF Dx
3 resolved
6 improved
1 death

Table IV. Frequency of autoantibodies and drug-induced lupus during TNF inhibitor clinical trials[+].

	ANA(+)	dsDNA(+)	Drug-induced lupus
Rheumatoid arthritis	30-40%	0-4%	NA
Lenercept	13%	3%	NA
Infliximab	52%	17%	3/1678
Etanercept	11%	15%	0/
Adalimumab	12.9%	5.6%	1/2334

[+] Frequencies derived from package insert for each agent; data from phase II and III clinical trials prior to drug approval. In each instance, autoantibody frequency was greater than placebo control patients (from refs 3-5).

TNF inhibitors, autoantibodies and drug-induced lupus

The occurrence of autoimmunity in patients receiving TNF inhibition was first described during clinical trials with lenercept, a soluble p55 receptor construct that bound TNFα (19). ANA positivity (13%) and dsDNA antibodies (3%) were observed in a 247 patient trial wherein lenercept was effective, but was not shown to be more effective than MTX alone. Subsequent development of other TNF inhibitors has indicated variable percentages of autoantibodies (Table IV). While ANA and dsDNA antibody positivity was not uncommon, overt drug-induced lupus was rarely observed (2-5).

During clinical trials, these autoantibodies were commonly recorded and seroconversion from negative to positive ANA tests (and vice versa) was seen more commonly in those receiving TNF inhibitors than in the control patients. The incidence of new ANA positivity was 26-62% with infliximab, 11% with etanercept and 12% with adalimumab. The incidence of new dsDNA antibodies was 15% for infliximab and etanercept and 5.9% for adalimumab. In a study of 156 infliximab treated patients, Charles *et al.* found low titers of predominantly IgM anti-dsDNA antibodies in 7% of patients (20). Only one patient (0.64%) developed drug-induced lupus with fever, rash, pleuropericarditis and arthritis flare; this patient also had IgG and IgA anti-dsDNA antibodies.

Pathogenesis of TNF-induced autoimmunity

The etiology of the development of ANA positivity or drug-induced lupus are unknown (20-24), and the pathogenesis of autoimmunity in the context of a TNF-deficient state remains unknown. In addition to its proinflammatory effects, TNF functions as an immunoregulatory B cell growth factor. It also affects multiple cell types, including dentritic cells that may alter B cell activity (23). TNF serum levels are increased in patients with lupus, as are tissue concentrations in the kidneys (24). While it appears that TNF may play a contributory role in human lupus, data from murine models of lupus indicated that TNF may contribute to disease progression in NZB/NZW mice, while a paradoxical beneficial effect is observed in the MRL mouse (23, 25). Moreover, TNF may play paradoxical roles at different time points in maturation.

Extrapolation of these data to humans with RA or systemic lupus is further confounded since a weak TNF inhibitor, thalidomide, has been reported to improve joint disease in RA and skin disease in SLE, without autoimmune flares or new serologic abnormalities. Nonetheless, some investigators have suggested that levels of TNFα expression may favor the development of autoreactivity in susceptible individuals. It has been shown that following infliximab infusion, there may be a paradoxical rise in IL-10 levels (26). While IL-10 exhibits anti-inflammatory effects, it is also well known to stimulate humoral activity, and may promote the enhanced autoantibody production seen with therapeutic TNF inhibition.

How common is drug-induced lupus?

Drug-induced lupus is defined as the new occurrence of a lupus-specific feature (e.g., serositis, cytopenia, arthritis) in the context of ANA positivity, and with the resolution of symptoms upon withdrawal of the offending agent. Although the time to clinical improvement is often rapid and related to the half-life of the drug, the time to become ANA negative generally is more prolonged and may require up to 12 months to fully resolve (27).

Overall, the risk of developing drug-induced lupus from TNF inhibitor use

Table V. New drug-induced lupus associated with TNF inhibitors in Dallas, Texas.

Patient	1	2	3	4
Age/Sex	35F	26F	44F	63F
Indication	RA	RA	Crohn's	RA
TNF inhibitor	Infliximab	Infliximab	Infliximab	Etanercept
Lag time (months)	23	14	3	1.8
1st Symptom	Pericarditis	Fever, rash	Arthritis	Pleuritis
Arthritis	0	Poly	Poly	0
Serositis	++	+	0	+
Cytopenia	Lymphopenia	0	0	Lymphopenia
ACR criteria	4	5	2	4
Resolved ?	Yes, 4 wks	Yes, 4 wks	Yes, 6 wks	Yes, 6 mos

Table VI. Manifestations of anti-TNF associated drug-induced lupus (27).

	Cush 2004	DeBandt 2004	Dallas (unpublished)
No.	22	12	4
Female	> 80%	100%	100%
Inflix/Etan/Ada	I-9 E-9 A-1	I-9 E-3	I-3 E-1
No. of SLE criteria	ND	All > 4	4, 5, 2, 4
Prior ANA(+)	50%	3/12	1/4
Onset lag time	2 wks – 17mos	Mean = 8 mos.	1.8 – 23 mos
Arthritis	5/19	5/12	2/4
Serositis	5/19	3/12	2/4
Fever	2/13	9/12 constitutional	2/4
Cutaneous	12/19	11/12	1/4
Cytopenias	3/19	12/12	2/4
ANA +	100%	100%	100%
Anti-dsDNA	~80%	11/12	2/4
Low complement	5/19	ND	2/4
Mean time to resolution	3-8%	8 weeks	4-6 weeks
Negative rechallenge*	ND	3 Etanercept	1 Adalimumab

*Patients were rechallenged with the offending TNF inhibitor without recurrence of lupus-like disease.

appears to be quite low, with only 4 reports among 1,897 infliximab-treated patients (0.2%) (28). Although there were no reports of drug-induced lupus in etanercept clinical trial patients, there have subsequently been several reports in the post-marketing era (29). Rare cases of lupus-like disease were also noted with adalimumab (9). A recent review of this problem disclosed 22 reports in the medical literature (30). Table V details 4 new patients recently identified in Dallas (unpublished observation, S. Cohen, G.A. Quiceno, J. Cush).

A recent EULAR abstract identified 22 new cases of drug-induced lupus after treatment with TNF inhibitors among a cohort of RA patients (31). Ten of these patients met only 3 lupus criteria while the remaining 12 met 4 or more criteria. These investigators estimated the prevalence of lupus associated with TNF inhibitors to be 1.7 events per 1000 patients – a rate similar to that reported above in the infliximab trials. Finally, a review by Callegari *et al.* of FDA safety data accumulated up to March 2002 identified 59 infliximab- and 16 etanercept-treated patients with drug-induced lupus. The calculated incidence rates were 0.13 and 0.29 per 1000 patients, respectively (32).

Lupus-like manifestations

While there may be some duplicate reporting of the same patients, there appear to be more than 100 cases of drug-induced lupus associated with TNF inhibitor therapy (28-32). The profile of patients developing a lupus-like disease is described in Table VI. Most patients appear to have an acute onset of mild to moderate lupus manifestations that may include constitutional features, fever, polyarthritis, serositis, rashes or cytopenias. While arthalgias and myalgias were common, the new onset of both large and small joint polysynovitis was seen in roughly one-third of drug-induced cases. The occurrence of an acute flare of polyarthritis in a patient with RA who is well controlled on a TNF inhibitor should raise suspicion for drug-induced lupus and prompt appropriate evaluation and testing.

Early reports suggested that discoid or subacute cutaneous lupus or purpuric lesions (hypersensitivity vasculitis) were common cutaneous presentations. However, a wider spectrum of findings has been described, including facial and malar rashes, an acute "sunburn" intense erythema over the face, trunk or extremities, and urticaria. Alopecia and new onset Raynaud's phenomenon have not been described. Serositis, involving the pleural or pericardial membranes, has been seen in up to one-third of patients. Fever and elevated acute phase reactants are seen in a minority of patients, and appear to correlate with serositis, acute inflammatory arthritis, and autoantibodies. There have been no clinical reports of the nephritis, cerebritis, or the antiphospholipid syndrome.

While ANA positivity is required for diagnosis, many patients also exhibit other autoantibodies including rheumatoid factor, anti-dsDNA antibodies, and other antibodies directed against Sm, RNP, histone and cardiolipin. Hypocomplementemia has been observed less frequently. Confirmation of the diagnosis rests with the resolution of lupus-like manifestations upon with withdrawal of the offending TNF inhibitor. The time to resolve symptoms ranges from 3-8 weeks in most patients, and may to be related to the half-life of the agent. Monitoring of autoantibodies in clinical practice is not recommended in current prescribing guidelines, although their identification

may be necessary in anti-TNF-treated patients who exhibit a flare of their arthritis, unexplained rashes, serositis, fever, or other clinical signs which suggest drug-induced lupus

Management of drug-induced lupus

Baseline testing and ongoing monitoring of ANA, native DNA or other autoantibodies in patients who are receiving anti-TNF therapy is not advised and not required by prescribing guidelines (2, 13, 30). Some patients reported to develop a lupus-like syndrome while receiving a TNF inhibitor had a history of a lupus-like feature, ANA positivity, lymphopenia, DLE, Sjögrens syndrome etc., Clinical trials have shown that ANA (and even DNA) serologic findings changed frequently from positive to negative and were not predictive of response, toxicity or autoimmune toxicities. It also appears that RA patients who are ANA-positive may safely receive TNF inhibitors without a substantial risk of further autoimmune disease. Anecdotally, TNF inhibitors have been used in lupus patients who had problematic inflammatory synovitis, with improvement in synovitis and without worsening of other lupus features (see below). The author is aware of 4 patients who developed TNF inhibitor-associated drug-induced lupus who were later rechallenged with the same or a different agent without recurrence (Table VI). Nonetheless, a cautionary report indicates that 2 patients who had RNP + MCTD received either etanercept or infliximab and later flared with arthralgias, myalgias, rash, fevers (33).

Can TNF inhibitor therapy be used in lupus?

Lupus, multiple sclerosis (MS) and demyelinating disorders are currently regarded as relative contraindications for the use of these agents. However the rationale for such exclusion is based on little objective evidence of risk. Concerns regarding autoimmune worsening with the use of a TNF inhibitor stem from: 1) rare occurrences (less than 200 total cases amongst > 600,000 patients treated worldwide) of lupus or MS in those receiving TNF inhibitors; 2) the prevalence of ANA positivity (12-62%) and DNA positivity (5-15%) (Table IV); 3) murine models that implicate TNF inhibition with poorer outcomes; and 4) rare suggestion (without proof) of *de novo* SLE following TNF inhibition.

These observations are countered by other data which nullify their impact. First, up to 40% of RA patients are ANA-positive, and that such a finding has no known influence on disease expression or toxicity risk. Second, in several thousand patients who were treated in double-blind clinical trials, use of a TNF inhibitor in ANA + RA patients did not lead to greater serologic positivity, more autoimmune events, or cases of drug-induced lupus. Although drugs like procainamide, quinidine, or minocycline may induce serologic changes or (rarely) drug-induced lupus, they are not contraindicated in patients with lupus or other autoimmune diseases. Finally, lupus patients have antecdotally been treated with TNF inhibitors without compromise and often with great benefit. The author has treated 2 SLE patients with problematic synovitis with TNF inhibitors, with good results and no flare of their lupus. At the 2004 EULAR meeting, Aringer and Smolen reported that lupus activity, measured by SLEDAI, and arthritis improved in all of 6 lupus patients treated with intravenous infliximab 300 mg at weeks 0, 2, 6, and 10 (34). Four patients with nephrotic syndrome showed significant improvement in proteinuria. Although dsDNA antibodies were found in 4 patients, all demonstrated elevated or normal complement levels. No flare of lupus activity and no serious adverse events or infusion reactions were seen Although this pilot trial lends support to the possibility that ant-TNF therapy may be safe and effective in lupus, further controlled clinical trials are required before such an approach can be advocated.

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