Scleritis: A Paradoxical Effect of Etanercept? Etanercept-associated Inflammatory Eye Disease

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ABSTRACT. ***Objective.*** To describe 3 cases of scleritis associated with etanercept use for rheumatoid arthritis (RA) and to review the literature related to inflammatory eye diseases associated with the use of etanercept.
Methods. Three cases of severe scleritis during etanercept therapy were analyzed. A systematic review of the literature in PubMed, Embase, and the Cochrane Library was performed, from 1962 to July 2010.
Results. Three patients with seropositive RA developed scleritis 7–28 months after initiation of etanercept, for the first time during their long-lasting disease. In all patients the underlying disease had responded well to anti-tumor necrosis factor therapy. Ocular inflammation went into remission after discontinuation of etanercept, and no other relapses were observed. One patient experienced a dechallenge-rechallenge phenomenon (improvement in symptoms following discontinuation of the agent, then reappearance or worsening of symptoms on reexposure to the agent). Forty-two cases of inflammatory eye diseases believed to be associated with the use of etanercept have been reported in the literature: 33 uveitis, 8 scleritis, 1 orbital myositis, concerning 16 patients with RA, 10 with juvenile idiopathic arthritis, 14 with ankylosing spondylitis, and 2 with psoriatic spondyloarthropathy. Dechallenge was performed in 28 patients, leading to resolution of symptoms. Rechallenge was done in 6 cases, with clear exacerbation.
Conclusion. Ocular inflammation is paradoxically a potential adverse effect of etanercept, even in previously uninvolved eyes. (First Release Dec 15 2011; J Rheumatol 2012;39:233–9; doi:10.3899/jrheum.110865)

Key Indexing Terms:
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The widespread use of tumor necrosis factor-α (TNF-α) blockers has led to the recognition of paradoxical adverse effects, defined as the onset or exacerbation of disorders that are usually improved by TNF-α antagonists. Cutaneous psoriasis, Crohn's disease, and uveitis exacerbations have been extensively reported. Scleritis, a serious and vision-threatening ocular disease, has recently been described as another possible paradoxical effect of anti-TNF-α agents and particularly of etanercept[1]. Scleritis is a destructive inflammatory eye disease characterized by scleral edema and inflammatory cell accumulation in the sclera. Untreated, the inflammatory process may extend to adjacent tissues, causing uveitis, glaucoma, retinal detachment, and perforation of the globe. About 50% of cases are idiopathic, with the majority of the others having an associated systemic connective tissue disorder. In about half of these patients, the systemic illness is a nodular seropositive RA. The overall prevalence of scleritis in patients with RA is reported to range from 0.67% to 6.3%[2,3].

We describe 3 cases of severe anterior scleritis following the administration of etanercept for RA. The scleritis was temporally related to etanercept injections. Drug discontinuation resulted in rapid resolution. We systematically reviewed the literature concerning inflammatory eye disease associated with the use of etanercept: 42 cases were identified and will be reviewed.

MATERIALS AND METHODS

Study selection. A systematic literature search was performed in PubMed Medline, Embase, and Cochrane Library databases from 1962 to July 2010 without a limit on years of publication or journal, using the following key words: "scleritis" (MeSH Terms) OR "scleritis" (All Fields) OR "uveitis" (MeSH Terms) OR "uveitis" (All Fields) OR "orbital myositis" (MeSH Terms) OR "orbital" (All Fields) AND "myositis" (All Fields) OR "orbital myositis" (All Fields) OR ocular (All Fields) AND "inflammation" (MeSH Terms) OR "inflammation" (All Fields) AND "TNFR-Fc fusion protein"

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(Substance Name) OR "TNFR-Fc fusion protein" (All Fields) OR "etanercept" (All Fields). The limits were English or French languages. In addition, reference lists of the reports initially found were hand-searched to identify additional relevant reports. We also included abstracts of the American College of Rheumatology (ACR) and European League Against Rheumatism meetings from 2006 to 2010. The inclusion criteria were all articles with case reports of inflammatory eye disease with etanercept therapy. The exclusion criterion was a prior eye episode except in flares with dechallenge-rechallenge phenomenon.

Data collection. Two investigators (CGV, CG) selected the articles and collected the data, using a predetermined form. For each case report, these data were collected: demographic characteristics (sex, age), rheumatic disease features and duration, extraarticular manifestation, duration and dose of etanercept treatment before onset of inflammatory eye disease, type of ocular disease, dechallenge-rechallenge, and concomitant treatments [disease-modifying antirheumatic drugs (DMARD), corticosteroids, nonsteroidal anti-inflammatory drugs (NSAID), and bisphosphonates].

RESULTS

Case reports. We identified 3 patients, whose main characteristics were collected retrospectively. All patients had RA, fulfilling the 1989 ACR criteria and resistant to conventional treatment with DMARD.

Patient 1. A 71-year-old man with a 19-year history of positive rheumatoid factor (RF) and anticitrullinated protein antibodies had erosive RA at the time of introduction of etanercept in October 2006. He presented cutaneous nodules as an extraarticular manifestation. Etanercept was given at the dosage of 25 mg twice a week as monotherapy. The treatment was well tolerated and articular manifestations were in remission when unilateral scleritis with uveitis developed in February 2009. He was treated with topical applications of corticosteroids, without any improvement. In March 2009 etanercept was discontinued, with a rapid resolution of ocular symptoms. Three weeks later the sclero-uveitis had disappeared, but the underlying articular disease was in flare. Adalimumab (40 mg/2 weeks) was successful and no ocular relapse was observed at a 1-year followup.

Patient 2. A woman had a 20-year history of RF-positive RA associated with cutaneous nodules and a sicca syndrome. A history of cutaneous vasculitis was noted. She was successfully treated with etanercept 25 mg twice a week for 7 months before developing a bilateral necrotizing scleritis. Ocular manifestations were treated with topical corticosteroids, without success. Systemic corticotherapy was temporarily beneficial, with secondary relapses. Only discontinuation of etanercept allowed remission, after 1 year. She was subsequently treated with infliximab (5 mg/kg) for 4 years and adalimumab (40 mg/2 weeks) for 2 years, and is currently receiving rituximab. No new scleritis relapses were observed.

Patient 3. A 44-year-old woman had erosive RA with positive RF since 1994. She never had extraarticular manifestations. In August 2003, etanercept 25 mg subcutaneously (SC) twice weekly was started, resulting in a dramatic clinical improvement, and within 3 months she went into remission. In November 2005 she developed severe bilateral scleritis with moderate anterior uveitis. She noted a worsening of her eye pain temporally related to etanercept injections and an improvement after transitory (1 week) discontinuation. She was treated with oral indomethacin and topical corticosteroids without efficacy. In May 2006, etanercept was discontinued and her ocular symptoms markedly improved. Because the joint disease flared, she decided to restart etanercept. Within 24 hours she experienced a dramatic ocular inflammation. She was hospitalized and etanercept was withdrawn. Three months later she remained free of ocular inflammation, but the joint disease was still active, despite 2 infusions of 1000 mg rituximab.

Literature search results. Initially, 1056 potentially relevant articles were screened. Forty-two cases of inflammatory eye disease believed to be associated with the use of etanercept were identified. Figure 1 shows the selection process.

Patient characteristics. There were 16 patients with RA, 10 with juvenile idiopathic arthritis (JIA), 14 with ankylosing spondylitis, and 2 with psoriatic arthritis. The characteristics of the patients are given in Table 1. Eye involvement included 33 cases of uveitis, 8 of scleritis, and 1 case of orbital myositis (Table 2). Mean age of the patients was 43.4 ± 13.6 years, and 78% were women. The mean rheumatic disease duration was 11.6 ± 8.9 years.

Drug administration and causality assessment. Etanercept was given according to current dosing, e.g., 25 mg SC twice a week in adults and 0.4 mg/kg for JIA. In 16 patients the dosage was not reported. The average time between the beginning of etanercept therapy and the onset of symptoms was 12.8 ± 9.2 months, with exposure times ranging between 1 and 36 months. Dechallenge (discontinuation of the agent) was performed in 28 patients, leading to resolution of symptoms. Rechallenge (reexposure to the agent) was done in 8 cases, with clear worsening of symptoms in 6 cases. Bisphosphonate use, which can induce uveitis flares, was reported in 1 patient.

DISCUSSION

The potential of anti-TNF-α agents in ophthalmology has been the subject of increasing interest in recent years. All anti-TNF-α drugs currently in clinical use, namely the monoclonal antibodies infliximab and adalimumab, as well as the soluble TNF receptor etanercept, have shown efficacy in treating not only joint inflammation, but also extraarticular manifestations, including uveitis and scleritis.

Saurenmann, *et al*[4] and Tynjala, *et al*[5] analyzed the effects of infliximab and etanercept in cases of childhood uveitis and found that although both agents seemed beneficial, infliximab was associated with better clinical responses in a larger percentage of patients. Braun, *et al*, using data from recently performed trials, found that reduction of the number of anterior uveitis flares by agents directed against TNF-α was slightly more marked among patients treated with infliximab, but this

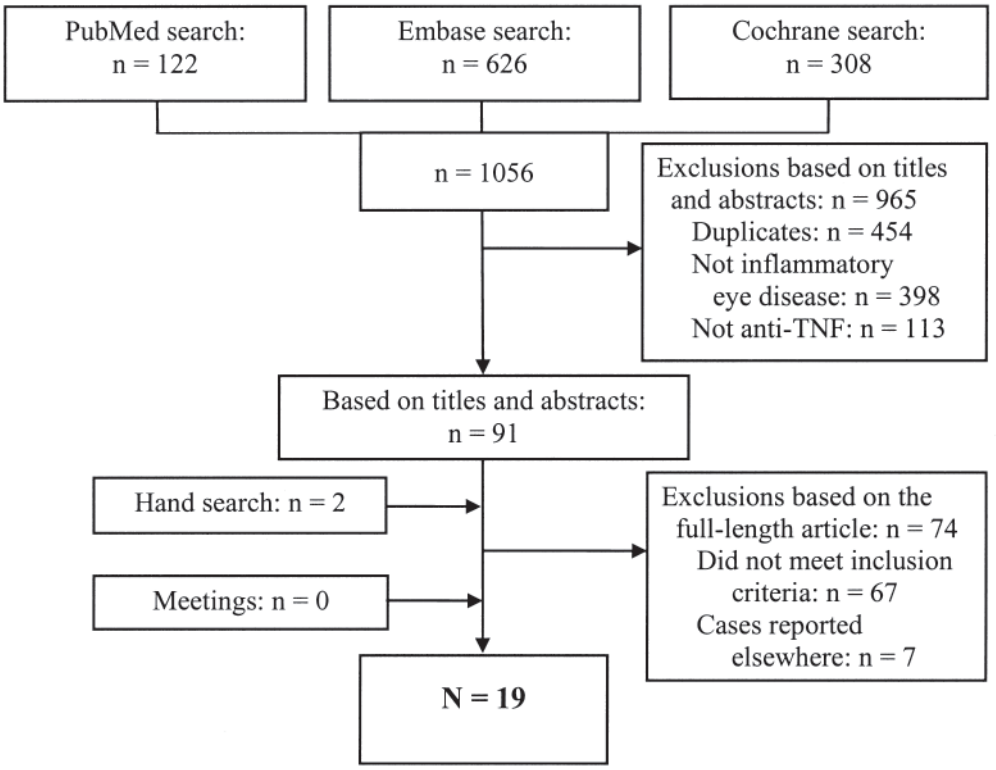

Figure 1. The process of the literature search. TNF: tumor necrosis factor.

difference was not significant[6]. Guignard, *et al*[7], in a retrospective study, and Cobo-Ibanez, *et al*[8], in a prospective study, suggested that anti-TNF antibodies lowered the rate of uveitis flares in patients with spondyloarthropathy, whereas soluble receptor did not seem to lower this rate. Galor, *et al*[9] found a statistically significant superiority of infliximab in the control of ocular inflammation in cases of refractory uveitis. Moreover, in a recent registry-based study, Lim, *et al*[10] reported a significantly greater number of cases of uveitis with etanercept in comparison with infliximab and adalimumab. Based on the results derived from 16 patients with rheumatic diseases, Smith, *et al* suggested that etanercept has limited efficacy for ocular inflammation even when it has efficacy for systemic disease[11]. The information on adalimumab for ocular disease is still very limited, although recently Restrepo and Molina reported a successful treatment of severe nodular scleritis with this agent[12].

The first hypothesis that we can formulate to explain ocular involvement despite articular improvement with etanercept is that antibody-based TNF-α inhibition is superior to receptor decoy therapy for the treatment of ocular inflammation occurring in the course of rheumatic disease.

The alternative hypothesis, supported by the dechallenge-rechallenge phenomenon observed, is that scleritis can be a paradoxical effect of etanercept. Attribution analysis proposed by Miller, *et al*[13] is a method to evaluate the likelihood of an association between an environmental exposure and an adverse event in rheumatic-related disease. According to the criteria of Miller, the specified primary attribution elements include temporal association, lack of likely alternative explanations, dechallenge (improvement in symptoms following discontinuation of the agent), rechallenge (reappearance or worsening of symptoms on reexposure to the agent) and biological plausibility (the likelihood of the agent causing the signs and symptoms, based on its known *in vivo* and/or *in vitro* effects).

The 5 primary elements of the attribution analysis suggest a relationship between etanercept and scleritis. Regarding the temporal relationship, the average time between the beginning of therapy and the onset of symptoms was 12.8 months, with exposure times ranging between 1 and 36 months. Patient 3 developed notable worsening of scleritis the day following the administration of etanercept. No likely alternative explanations could be elicited, except RA. A critical attribution element was the dechallenge-rechallenge phenomenon. A rechallenge effect was noted in scleritis for the first time in Patient 3 as well as in the 6 cases of uveitis reported by Taban, *et al*[14], Reddy and Backhouse[15], Coates, *et al*[16], Lim, *et al*[10], and Galor, *et al*[9]. In our 3 patients and in 28 patients from the literature, withdrawal with or without other measures resulted in either complete or partial improvement of eye symptoms.

Concerning biological plausibility, difficulties in explaining the underlying pathogenetic mechanism of etanercept-induced scleritis arise from a limited knowledge of the phys-

Table 1. Characteristics of patients with inflammatory eye disease associated with etanercept reported in the literature.

Case	Study	Age, yrs/ sex	Rheumatic Disease	Disease Duration, yrs	Extraarticular Manifestations	HLA-B27	Duration of Etanercept Treatment*, mo	Dosage	Inflammatory Eye Disease	Dechallenge/ rechallenge	Concomitant DMARD	Comment
1	Schmeling[20]	17 F	JIA polyarticular	10.5	0	—	10	0.4 mg/ kg twice weekly	Uveitis	Dechallenge	MTX, pred, NSAID	Dechallenge was present in 2 of 12 cases of uveitis
2	Schmeling	10 F	JIA oligoarticular	5	0	—	12	0.4 mg/ kg twice weekly	Uveitis	Dechallenge	MTX, pred, NSAID	Dechallenge was present in 2 of 12 cases of uveitis
3	Saurenmann[4]	NA	Psoriatic JIA	4.1	NA	NA	NA	NA	Uveitis	NA	NA	
4	Saurenmann	NA	JIA oligoarticular	6.4	NA	NA	NA	NA	Uveitis	NA	NA	
5	Kaipiainen-Seppänen[21]	31 F	Juvenile spondyloarthropathy	21	0	+	8	25 mg twice weekly	Acute anterior uveitis	Dechallenge	MTX	One relapse 2 yrs after etanercept discontinuation
6	Reddy[15]	44 F	AS	23	0	+	3	25 mg twice weekly	Anterior uveitis	Dechallenge-rechallenge	MTX	
7	Quartier[22]	NA	JIA polyarticular	NA	NA	NA	12	0.4 mg/ kg twice weekly	Uveitis	Dechallenge	No MTX	Prior inflammatory eye disease unclear
8	Quartier	NA	JIA oligoarticular	NA	NA	NA	12.5	0.4 mg/ kg twice weekly	Uveitis	Dechallenge	No MTX	Prior inflammatory eye disease unclear
9	Tiliakos[23]	48 F	RA	6	0	—	18	25 mg twice weekly	Scleritis	0	0	
10	Tiliakos	58 F	RA	20	Nodules	—	20	25 mg twice weekly	Anterior uveitis	0	MTX	
11	Smith[11]	61 F	RA	NA	NA	NA	1	25 mg twice weekly	Bilateral scleritis	NA	MTX, pred	
12	Smith	45 F	RA	NA	NA	NA	2	25 mg twice weekly	Bilateral scleritis	NA	Pred	
13	Smith	56 M	RA	NA	NA	NA	6	25 mg twice weekly	Bilateral scleritis	NA	MTX	
14	Smith	51 F	RA	NA	NA	NA	30	25 mg twice weekly	Chronic anterior uveitis	NA	MTX, pred	
15	Smith	46 M	PSA	NA	NA	NA	7	25 mg twice weekly	Acute anterior uveitis	NA	0	
16	Taban[14]	52 F	AS	NA	Recurrent bilateral anterior uveitis	—	11	25 mg twice weekly	Bilateral anterior	Dechallenge-rechallenge	0	
17	Lim[10]	NA	RA	NA	NA	NA	NA	NA	Uveitis	Dechallenge-rechallenge	NA	Incomplete reporting of the dechallenge-rechallenge
18	Lim	NA	RA	NA	NA	NA	NA	NA	Uveitis	Dechallenge-rechallenge	NA	Incomplete reporting of the dechallenge-rechallenge

Table 1. Continued.

Case	Study	Age, yrs/ sex	Rheumatic Disease	Disease Duration, yrs	Extraarticular Manifestations	HLA-B27	Duration of Etanercept Treatment*, mo	Dosage	Inflammatory Eye Disease	Dechallenge/ rechallenge	Concomitant DMARD	Comment
19	Lim	NA	RA	NA	NA	NA	NA	NA	Uveitis	Dechallenge	NA	
20	Lim	NA	RA	NA	NA	NA	NA	NA	Uveitis	Dechallenge	NA	
21	Monnet[24]	36 M	AS	13	0	+	5	25 mg twice weekly	Bilateral anterior uveitis	Dechallenge	NA	
22	Coates[16]	42 F	AS	15	0	+	2	NA	Bilateral anterior uveitis	Dechallenge-rechallenge	MTX	
23	Coates	41 F	AS	26	0	—	5	NA	Bilateral anterior uveitis	Dechallenge	0	Infliximab with good response
24	Coates	37 F	AS	20	0	+	36	NA	Bilateral anterior uveitis	0	0	About to start adalimumab
25	Coates	48 M	AS	2	0	—	2	NA	Bilateral anterior uveitis	0	MTX	Continues etanercept, uveitis controlled with topical treatment
26	Botsios[25]	63 F	RA	11	0	—	15	25 mg twice weekly	Diffuse anterior scleritis	Dechallenge	MTX	Failure infliximab 5 mg/kg. Successfully treated with anakinra 100 mg daily + MTX
27	Caramaschi[26]	42 F	RA	5	0	NA	5	25 mg twice weekly	Orbital myositis	NA	MTX, pred	
28	Scrivo[27]	32 F	AS	3	No uveitis	NA	23 (first episode) 30 (second)	NA	Uveitis	Dechallenge	0	Switch to adalimumab after second episode
29	Scrivo	31 F	PSA	13	Uveitis 6 years before	NA	18 (first) 40 (second)	NA	Uveitis	Dechallenge	0	Switch to adalimumab after second episode
30	Scrivo	16 F	JIA	8	No uveitis	NA	28	NA	Uveitis	Dechallenge	0	Switch to adalimumab
31	Galor[9]	57 F	RA	NA	No uveitis	—	31	25 mg twice weekly	Bilateral anterior uveitis	Dechallenge	MTX	Switch to infliximab
32	Galor	55 F	RA	NA	0	—	8	25 mg twice weekly	Left anterior necrotizing scleritis	Dechallenge	MTX	
33	Galor	53 F	AS	NA	Uveitis	+	NA	25 mg twice weekly	Bilateral anterior uveitis	Dechallenge-rechallenge	MTX	
34	Wang[28]	27 F	AS	0.3	0	+	1.5	25 mg twice weekly	Acute uveitis	Dechallenge	0	No relapse after etanercept discontinuation during the 9 mo followup
35	Le Garrec[1]	69 F	RA	33	0	NA	16	NA	Anterior nodular scleritis	Dechallenge	Lefl SSZ Pred	Rechallenge with adalimumab and new flare after 4 mo
36	Le Garrec	49 F	RA	8	Sicca sd	NA	12	NA	Anterior nodular scleritis	Dechallenge	Pred	Relapse after discontinuation Concomitant use of bisphosphonate
37	Le Garrec	49 F	AS	2	0	+	14	NA	Acute anterior uveitis	Dechallenge	Pred	
38	Fouache[29]	41 M	AS	NA	0	NA	14-18 months	25 mg twice weekly	Acute anterior uveitis	Dechallenge	0	

Table 1. Continued.

Case	Study	Age, yrs/ sex	Rheumatic Disease	Disease Duration, yrs	Extraarticular Manifestations	HLA-B27	Duration of Etanercept Treatment*, mo	Dosage	Inflammatory Eye Disease	Dechallenge/ rechallenge	Concomitant DMARD	Comment
39	Fouache	41 M	AS	NA	0	NA	14-18 months	25 mg twice weekly	Acute anterior uveitis	Dechallenge	0	
40	Fouache	42M	AS	NA	0	NA	14-18 months	25 mg twice weekly	Acute anterior uveitis	Dechallenge	0	
41	Martin-Mola[30]	NA	JIA	NA	No uveitis	NA	NA	25 mg twice weekly	Uveitis	0	0	
42	Martin-Mola	NA	JIA	NA	No uveitis	NA	NA	25 mg twice weekly	Uveitis	0	0	

* Before onset of inflammatory eye disease. NA: not available; JIA: juvenile idiopathic arthritis; AS: ankylosing spondylitis; RA: rheumatoid arthritis; PSA: psoriatic arthritis; MTX: methotrexate; Pred: prednisone; Lefl: leflunomide; SSZ: sulfasalazine.

Table 2. Subtypes of inflammatory eye diseases associated with etanercept. Results are expressed as mean ± SD.

Inflammatory Eye Disease	N	Age, yrs, sex	Rheumatic Disease	Disease Duration, yrs	Extraarticular Manifestations	Duration of Etanercept Treatment, mo	Dechallenge/ rechallenge
Scleritis	11	56.1 ± 9.7 10F/1M	RA	15.4 ± 9.4	2 cutaneous nodules	12.8 ± 9.3	7 dechallenge 1 dechallenge-rechallenge
Uveitis	33	39.2 ± 12.9 17F/6M	14 AS 10 JIA 2 PSA 7 RA	11.3 ± 8.3	3 prior uveitis 1 cutaneous nodules	14.1 ± 9.8	18 dechallenge 6 dechallenge-rechallenge 4 not available
Orbital myositis	1	42/F	RA	5	0	5	Not available

RA: rheumatoid arthritis; AS: ankylosing spondylitis; JIA: juvenile idiopathic arthritis; PSA: psoriatic arthritis.

iopathology of scleritis. A study showed that ocular infiltrating T cells from patients with active uveitis stimulated *in vitro* with soluble TNF-α receptors began to synthesize TNF-α[17]. Soluble receptors influence TNF-α activity *in vitro* and *in vivo* and maintain the balance between active, free TNF-α and the inactive form bound to its soluble receptors. The soluble forms in high concentrations act as inhibitors by competing with TNF-α cell-surface receptors. However, in lower concentrations, soluble receptors can prolong the biologic half-life of TNF-α by functioning as a carrier protein, protecting TNF-α from degradation and therefore stabilizing its activity[18].

Another explanation is that TNF-R p55 is the most biologically active of the 2 receptors but that TNF-R p75 has a 5-fold higher affinity for TNF-α. When TNF-α levels are low, p75 TNF-R facilitates p55 TNF-R activity possibly by a ligand-passing mechanism or as a result of intracellular kinase activation[19]. Increasing levels of soluble p75 TNF-R by administering etanercept (p75 receptor fusion protein), or decreasing levels of circulating TNF-α by administering infliximab, may interfere with immune homeostasis and disease pathogenesis by as-yet undefined mechanisms, to potentially exacerbate a patient's underlying tendency to develop inflammatory ocular disease.

These case reports and review raise the possibility that etanercept may precipitate an inflammatory reaction in predisposed individuals. However, this review had some limitations, including the retrospective design, the small number of reports, multiple observers, variable followup intervals, heterogeneity of the form of ocular inflammation, the type of systemic association, the population characteristics, and the difficulty in distinguishing an ocular inflammation related to a joint disease and an adverse event.

Ocular inflammation is paradoxically a potential adverse effect of etanercept even in previously uninvolved eyes. Patients being treated with TNF-α soluble receptors should be closely monitored for the development of ocular signs and symptoms in order to detect flares secondary to etanercept therapy.

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Correction

Scleritis: A Paradoxical Effect of Etanercept? Etanercept-associated Inflammatory Eye Disease

Gaujoux-Viala C, Giampietro C, Gaujoux T, Ea H-K, Prati C, Orcel P, Wendling D, Lioté F. Scleritis: A paradoxical effect of etanercept? Etanercept-associated inflammatory eye disease. J Rheumatol 2012;39:233-9. The affiliation for Dr. Gaujoux-Viala should be given as follows: C. Gaujoux-Viala, MD, Pierre et Marie Curie University, and AP-HP, Department of Rheumatology, Pitié-Salpêtrière Hospital, Paris, France. We regret the error.

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