Polymorphisms in Genes Encoding Tumor Necrosis Factor-α and HLA-DRB1 Are Not Associated with Response to Infliximab in Patients with Rheumatoid Arthritis

To the Editor:

Rheumatoid arthritis (RA) is a systemic, chronic inflammatory disease of unknown etiology, with a genetic predisposition[1]. Tumor necrosis factor-α (TNF-α) is known to play a pivotal role in the pathogenesis of RA[2]. Therefore, it is probable that any variation in the TNFA locus is inherited as part of individual haplotypes with MHC class I and II. In addition, several polymorphisms with possible functional significance have been identified in the promoter region of this gene[3]. Among these, the G to A polymorphism at position –308 generates G/G and G/A or A/A genotypes[4], and carriers of allele A are associated with high TNF-α production[5,6] and an increased susceptibility to and severity of the disease in patients with RA[3].

The G to A polymorphism at position -238 also generates G/G and G/A as the most common genotypes; the G/A form is associated with less erosion in patients with RA[3]. Anti-TNF therapy has shown high efficacy; however, only about 60% of RA patients respond effectively to infliximab[7]. To date, neither definitive biological nor clinical factors that allow us to predict the response to this treatment have been found[8]. Results from studies analyzing the role of TNFA polymorphisms and HLA-DRB1 in response to treatment with anti-TNF-α are controversial[9]. We investigated whether polymorphisms at positions –238 and -308 at the promoter region of the TNFA gene, and the presence of the DR3 and shared-epitope (SE) alleles, are able to predict response to longterm infliximab therapy (30 months).

Patients (n = 113) from 3 Spanish hospitals who fulfilled the American College of Rheumatology 1987 revised criteria for the classification of RA were included[10]. All patients were Spanish Caucasian. Patients with active RA, as defined by the Disease Activity Score in 28 joints (DAS28) > 3.2[11], despite treatment with disease modifying antirheumatic drugs for at least 6 months, were treated with infliximab (3 mg/kg/8 weeks) and methotrexate 10–15 mg/week. Blood samples were collected before treatment from all subjects, who authorized both HLA–DRB1 typing and TNFA polymorphism genotypes by Dynal Allset™ SSP DR and by real-time polymerase chain reaction (LightCycler 2.0), respectively. Assessment of response to treatment was performed by means of the DAS28 and Health Assessment Questionnaire (HAQ) at baseline and at 30 weeks. The clinical response was defined by EULAR criteria[12]. All calculations (chi-square test, Student 2-tailed t-test, and Fisher's exact test) were done using SPSS software, v. 12.0, and EPI-Info 6.

The baseline characteristics of the 113 subjects treated with infliximab showed that 77.9% were female, age 52.38 ± 12.9 yrs, and disease duration was 11.6 ± 8.0 years. The rheumatoid factor (RF) was positive in 73.5%. Tender and swollen joint counts were 13.5 ± 7.5 and 9.8 ± 5.9, respectively. The mean HAQ score was 1.45 ± 0.63. Erythrocyte sedimentation rate was 42.2 ± 23.2 mm/hour and serum C-reactive protein (CRP) level was 31.2 ± 33.1 mg/l. The mean DAS28 score was 6.06 ± 1.11 before beginning infliximab therapy. Among all subjects treated with infliximab, 58.4% were responders. The percentage of responders was not significantly higher in any genotype analyzed (Table 1). A comparison of the variation of DAS28 and HAQ scores in the TNFA group with A/A or A/G alleles with those in TNFA group with G/G alleles between Weeks 0 and 30 showed no significant differences (Table 2). However, analysis of the improvement in DAS28 and HAQ compared to the presence of the SE or DR3 alleles (at least one allele) showed a significant association between HAQ improvement and SE (Table 2).

Our study examined the possibility that functionally important allelic differences in genes, such as TNFA and DRB1, might be associated with

Table 1. Response to infliximab related to TNFA –238G>A and TNFA–308G>A polymorphism, shared epitope and HLA-DRB1 *03 in RA.

	Responders[†], n (%)	OR (95% CI)	p
All patients	66/113 (58.4)		
TNFA genotypes			
308GG	50/86 (58.1)	0.95 (0.40, 2.25)	0.918
308AG or AA	16/27 (59.3)	1.04 (0.44, 2.44)	
238G	60/102 (58.8)	1.19 (0.36, 3.91)	0.785
238A or AA	6/11 (54.5)	0.84 (0.25, 2.76)	
SE-carriers*	43/69 (62.3)	1.51 (0.71, 3.21)	0.602
DR3+**	9/17 (52.9)	0.80 (0.29, 2.15)	0.621

[†] Improvement of at least 1.2 in Disease Activity Score 28 joints (DAS28) between the score before the first infliximab infusion and the score at week 30 or DAS28 < 3.2 at week 30. * SE-carriers: shared epitope in 1 or 2 from HLA-DRB1 alleles. ** DR3+: HLADRB1*03 positive (1 or 2 alleles). OR: odds ratio, CI: confidence interval.

Table 2. Improvements in Disesae Activity Score 28 joints (DAS28) and Health Assessment Questionnaire (HAQ) scores with infliximab and correlation with TNFA –238G > A and TNFA –308G > A polymorphism, Shared Epitope and HLA-DRB1*03 alleles. Values are the mean ± SD.

	–308AG/AA (n = 27)	–308GG (n = 86)	p	–238AG/AA (n = 11)	–238G (n = 102)	p	SE+[a] (n = 69)	SE–[b] (n = 22)	p	DR3+[c] (n = 17)	DR3–[d] (n = 76)	p
DAS28												
Week 0	6.11 ± 1.09	6.05 ± 1.12	0.796	6.06 ± 0.90	6.06 ± 1.13	0.987	6.15 ± 1.08	6.10 ± 1.15	0.861	6.26 ± 0.84	6.06 ± 1.17	0.516
Week 30	4.53 ± 1.84	4.63 ± 1.49	0.790	4.85 ± 1.98	4.58 ± 1.53	0.592	4.57 ± 1.61	4.70 ± 1.68	0.734	4.74 ± 2.28	4.51 ± 1.46	0.615
Improvement in DAS28	1.58 ± 1.52	1.42 ± 1.36	0.611	1.21 ± 1.94	1.48 ± 1.33	0.536	1.58 ± 1.46	1.40 ± 1.46	0.610	1.52 ± 1.92	1.55 ± 1.33	0.947
HAQ												
Week 0	1.45 ± 0.69	1.45 ± 0.62	1.000	1.48 ± 0.43	1.45 ± 0.66	0.886	1.47 ± 0.67	1.70 ± 0.53	0.164	1.40 ± 0.51	1.53 ± 0.69	0.472
Week 30	0.96 ± 0.70	1.07 ± 0.61	0.449	1.09 ± 0.81	1.04 ± 0.62	0.774	1.14 ± 0.67	1.03 ± 0.54	0.453	0.86 ± 0.57	1.14 ± 0.65	0.112
Improvement in HAQ	0.49 ± 0.53	0.38 ± 0.58	0.400	0.38 ± 0.94	0.41 ± 0.52	0.873	0.33 ± 0.59	0.67 ± 0.56	0.026	0.54 ± 0.64	0.37 ± 0.59	0.298

[a] SE+: shared epitpoe carriers (1 or 2 alleles). [b]SE: not shared epitope carriers (0 allele). [c] DR3+: HLADRB1*03 positive (1 or 2 alleles). [d] DR3–: HLADRB1*03 negative (0 allele). p values by Student's 2-tailed t test.

response to infliximab. The data we obtained did not support the concept that a certain combination of allelic forms influencing TNF-α production was associated with response to infliximab. Further, the association of the TNFA genetic polymorphism in subgroups stratified for the duration of disease, RF positivity, serum CRP level, age, and sex did not show a significant variation depending on polymorphism (data not shown). Our results are in contrast to others reported recently[9]. Such conflicting results are likely to be due to a variety of factors such as the racial/ethnic differences in TNFA, single nucleotide polymorphism and HLA-DRB1 allele frequencies, severity of disease, outcome measures employed, design of the study, and measures employed to define responses to treatment. However, our results agree with the findings from a study of a Caucasian Spanish population[13]. Our statistical analysis showed an association between SE and improvement in HAQ score. However, this single positive finding could represent a false-positive result, and we are unable to draw any clinically relevant conclusions concerning this statistical correlation.

Thus, our study does not support the view that patients with RA show a different response to infliximab treatment at 30 weeks according to –308 and –238 TNFA polymorphisms, or the presence of SE or DR3 genes.

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Clustering of Extraarticular Manifestations in Patients with Rheumatoid Arthritis

To the Editor:

Rheumatoid arthritis (RA) is a chronic, inflammatory disorder associated with a number of extraarticular manifestations. Extraarticular RA (ExRA) tends to be more frequent in patients with severe disease[1]. We previously reported from a study of a community based sample of patients with RA that ExRA manifestations of some kind occur in about 40% of all patients, and that 15% develop severe ExRA manifestations at some time[2]. Different manifestations may share different pathogenetic mechanisms, including vascular abnormalities[3], and it has been shown that rheumatoid nodules predict severe extraarticular disease[4]. Based on this, it would be expected that some extraarticular manifestations tend to occur together, but this has never been formally tested. Further, the preferential time periods for onset of various manifestations have not been studied systematically.

We analyzed data from a community based RA cohort, in which the occurrence of ExRA manifestations was thoroughly investigated[5]. Using the resources of the Rochester Epidemiology Project, all incident cases of RA residing in Rochester, Minnesota, USA, with disease onset between January 1, 1955, and December 31, 1994, were identified (n = 609)[6]. The date of RA diagnosis was defined as the date of fulfillment of the 1987 American College of Rheumatology (ACR) criteria for RA. A structured review of all medical records from all care providers in the area was performed as described[5]. ExRA manifestations were identified and classified according to predefined criteria[2,5]. The date of first onset was noted for each manifestation. Patients were followed from diagnosis of RA until death, loss to followup, or December 31, 2000. ExRA manifestations were classified into the following groups: serositis (pericarditis or pleuritis), vasculitis (major cutaneous lesions or internal organ vasculitis), neuropathy (mono- or polyneuropathy), rheumatoid lung disease (interstitial lung disease or bronchiolitis obliterans organizing pneumonia), severe eye manifestations (scleritis/episcleritis/retinal vasculitis), Felty's syndrome, rheumatoid nodules, and secondary Sjögren's syndrome. The observed frequency of coexisting ExRA manifestations was compared to the expected, based on the marginal frequency of each manifestation. P values are based on Fisher's exact tests. The median time from fulfillment of the ACR criteria for RA to first diagnosis of ExRA was calculated for each manifestation.

ExRA manifestations occurred in 260 patients (42.7%) during a median followup of 11.8 years. The most frequent manifestation diagnosed was occurrence of rheumatoid nodules. The median time from the diagnosis of RA to onset of ExRA manifestations varied from 3.3 years for nodules to 11.5 years for pericarditis (Table 1). Vasculitis occurred in 20 cases, and these patients were significantly more likely than expected to also have neuropathy (p < 0.001), rheumatoid lung disease (p = 0.008), and nodules (p < 0.001; Table 2). Patients with rheumatoid nodules were more likely to have vasculitis, serositis, severe eye manifestations (p < 0.001, respectively) and rheumatoid lung disease (p = 0.001; Table 2). About 90% of RA patients with vasculitis or severe eye disease also had rheumatoid nodules. In addition, rheumatoid nodules occurred more frequently than expected in patients with Felty's syndrome (p = 0.02), secondary Sjögren's syndrome (p = 0.007), and neuropathy (p = 0.10).

Our findings support the concept that different ExRA manifestations often coexist in patients with severe RA. The clustering of vasculitis with neuropathy and rheumatoid lung disease suggests shared disease mechanisms. Studies of nerve biopsy specimens from patients with RA-associated neuropathy have revealed signs of necrotizing vasculitis[7]. Further, rheumatoid nodules are characterized by early vascular changes resembling vasculitis[8]. As we found rheumatoid nodules to cluster with virtually all other ExRA manifestations studied, and nodules often precede other manifestations, this may indicate that vascular pathogenetic mechanisms are important in all types of ExRA. Immunoglobulin deposition, high inflammatory load, and systemic endothelial activation[3] have been implicated in ExRA. The influence of inflammation on the vasculature in systemic RA is of particular interest, given the association between RA and cardiovascular comorbidity[9], with a particularly increased risk in patients with severe ExRA[10]. The mechanisms underlying these associations should be studied further.

The major strength of this study is the community based approach, which limits selection of severe RA cases and enables an estimate of the true burden of extraarticular disease in the community. One limitation is due to the retrospective method, which limits the analysis to case-record data collected by the managing physician. On the other hand, this means that the observations made reflect manifestations considered clinically relevant.

Table 1. Duration of RA at diagnosis of individual extraarticular manifestations in the RA cohort (n = 609).

Manifestation	N	Median Time to Diagnosis, yrs (IQR)
Pericarditis	22	11.5 (7.4–18.7)
Pleuritis	24	7.3 (1.2–14.8)
Felty's syndrome	9	9.8 (8.8–11.0)
Neuropathy	11	8.0 (1.4–13.0)
Vasculitis	20	4.5 (1.1–13.9)
Severe eye disease*	9	5.5 (3.7–7.1)
Rheumatoid lung disease**	41	7.7 (3.1–14.9)
Secondary Sjögren's syndrome	58	6.9 (2.4–12.9)
Rheumatoid nodules	183	3.3 (0.4–8.7)

* Scleritis, episcleritis, or retinal vasculitis. ** Interstitial lung disease or bronchiolitis obliterans organizing pneumonia. IQR: interquartile range.

Table 2. Clustering of extraarticular manifestations in the RA cohort (n = 609).

Cluster	Cooccurrence		
	Observed	Expected	p
Pericarditis/pleuritis* and rheumatoid lung disease**	11	2.69	< 0.001
Pericarditis/pleuritis and rheumatoid nodules	26	12.0	< 0.001
Vasculitis and neuropathy	4	0.36	< 0.001
Vasculitis and rheumatoid lung disease	5	1.35	0.008
Vasculitis and rheumatoid nodules	18	6.01	< 0.001
Severe eye disease*** and rheumatoid nodules	8	2.70	< 0.001
Rheumatoid lung disease and rheumatoid nodules	22	12.3	0.001

* Pericarditis, pleuritis, or both. ** Interstitial lung disease or bronchiolitis obliterans organizing pneumonia.
*** Scleritis, episcleritis, or retinal vasculitis.

We have demonstrated that severe ExRA manifestations cluster in patients with RA in a community based sample. Vasculitis is particularly associated with neuropathy, rheumatoid lung disease, and nodules. Rheumatoid nodules are associated with all other ExRA manifestations, and often precede the onset of severe ExRA. These findings suggest shared disease mechanisms in systemic manifestations of RA.

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Spinal Subarachnoid Hemorrhage in Necrotizing Vasculitis

To the Editor:

Necrotizing vasculitides affect the central nervous system (CNS) in 10%–50% of cases[1]. Spinal cord involvement is rarely reported. We describe a patient with necrotizing vasculitis with spinal subarachnoid hemorrhage (SAH) at onset.

A 37-year-old woman presented with 2 days of fever, leg paresthesias, and weakness. Three months previously she had had polyarthritis, weight loss, and headaches. Intramuscular adrenocorticotropic hormone for presumed rheumatoid arthritis temporarily relieved her symptoms. She had no significant medical or family history. On admission, she was febrile (102.9°F), tachycardic (110/min), and hypertensive (150/72 mm Hg). Cervical lymphadenopathy, bibasilar rales, wrist synovitis, lower extremity hyperreflexia, muscle weakness, and nondermatomal sensory loss were noted. Laboratory screening showed hemoglobin 8.6 g/dl, white blood cell (WBC) count 23,900/mm^3, neutrophils 87.3%, lymphocytes 6.3%, platelets 871,000/mm^3, erythrocyte sedimentation rate 134 mm/hour, C-reactive protein 27.5 mg/dl. Urinalysis showed 2+ proteinuria, WBC 10–25/high power field with no casts. Rheumatoid factor was positive (281 IU/ml). Serum cryoglobulin was elevated (31.3 mg/dl). The following tests were normal/negative: liver, kidney function tests, CK antinuclear antibodies, anti-dsDNA, C3, C4, anti-extractable nuclear antigen, RPR, anticardiolipin antibodies, lupus anticoagulant, anti-hepatitis C virus antibodies, hepatitis B surface antigen, and PPD skin test. Prothrombin and partial thromboplastin time, HCV-RNA testing, urine, and serum electrophoresis were not done. Brain magnetic resonance imaging (MRI) revealed multiple deep white-matter frontal lesions. Cervical and lumbosacral spine radiographs and MRI were normal. Broad antimicrobial coverage was started. Five days later, she developed urinary and fecal retention, upper extremity weakness, hyporeflexia, and decreased sensation involving the right second and third fingers and left first and second fingers. Serum creatinine rose to 2.5 mg/dl. Urinalysis showed coarse and fine granular casts and hematuria. Urinary protein excretion was 2.12 g/24 hours. Renal ultrasound revealed diffuse parenchymal disease. Cerebrospinal fluid (CSF) was bloody with red blood cell count 5879, WBC 9, neutrophils 80%, lymphocytes 16%, glucose 37 md/dl (normal 50–80), protein 57 mg/dl (normal 20–50); no malignant cells were noted. Blood, CSF, urine and stool samples were negative for pathogenic microorganisms. MRI showed increased signal intensity at T5 to T10 and conus levels on T2-weighted images with adjacent extramedullary intradural abnormal signal intensity consistent with subacute SAH (Figures 1A, 1B). Computed tomography (CT) myelogram confirmed cord compression. Spinal angiography revealed no arteriovenous malformation or vasculitic changes. Perinuclear antineutrophil cytoplasm antibodies (pANCA) and antimyeloperoxidase (anti-MPO) were positive. Abdominal CT revealed bilateral striated nephrograms, pericardial effusion, and mesenteric lymphadenopathy. Abdominal magnetic resonance angiography revealed renal contour infarcts, left renal subcapsular hematoma, and renal aneurysms at the right upper pole (1.5 cm) and left mid-pole (3–4 mm). A diagnosis of possible polyarteritis nodosa (PAN) was made. Parenteral methylprednisolone and oral cyclophosphamide were started. MRI 2 weeks later showed regression of the thoracic intradural lesion. Seven months later, she had normal neurologic findings and renal function.

This case fulfilled American College of Rheumatology classification criteria for PAN (weight loss, polyneuropathy, hypertension, azotemia, and arteriographic abnormalities), but also has features suggestive of microscopic polyangiitis (MPA: possible lung disease, positive pANCA and anti-MPO antibodies). This case is notable because of the presence of central and peripheral nervous system features at onset; and because of the spinal SAH, which is reported rarely in association with vasculitis in general. Less than 1% of SAH is spinal in origin[2].

Spinal cord complications, especially SAH, are rarely reported in association with necrotizing vasculitides. Given the predominance of features of PAN and MPA in our patient, we reviewed the literature for spinal cord involvement in PAN or MPA. We found 11 reports of PAN with spinal cord

Figure 1. Sagittal T1 (A) and T2 MRI (B) images of the spine show dependent blood (bright on T1, dark on T2, intracellular methe-moglobin; black arrows). The T2 sagittal view also shows intramedullary increased signal (white arrows).

involvement with sufficient clinical data for review. A wide spectrum of manifestations including myelopathy[3] and subdural hematoma[4] have been described. It was among the presenting features in 5 cases[2,5-7], in contrast to previous observations that CNS manifestations usually occur in the late stages of PAN. In other cases, spinal involvement occurred 4–96 months after onset of PAN[3,4,8-10]. SAH was noted in 5 cases, with manifestations including back pain[2,4,5] and sphincter paralysis[5]. Myelography showed filling defects in 4 cases[2,4,5,11]. Angiography was done in one case[2], revealing a spinal artery aneurysm. Vasculitis involving blood vessels and other major organs was confirmed by biopsy or autopsy. Complete data on CSF analysis, ANCA testing, and hepatitis B testing were unavailable in most cases.

Presence of spinal cord involvement along with other major organ involvement seems to be associated with significant mortality, as among the reported cases, clinical recovery occurred in only 3 cases[2,3,8]. A regimen of combination corticosteroids and cyclophosphamide, which is what our patient received, has been reported to improve survival rates up to 80%.

There are limited data on the pathogenesis of aneurysms and SAH in vasculitis in general, although inflammatory processes and hemodynamic factors leading to blood vessel wall weakening have been generally recognized as a major factor[2]. These vascular phenomena, given their rarity, present a challenge for further study in regard to their pathogenesis and treatment.

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Peripheral Mononeuropathy with Etanercept Use: Case Report

To the Editor:

Tumor necrosis factor-α (TNF-α) antagonist therapy has been associated with central and peripheral polyneuropathy demyelinating syndromes such as multiple sclerosis, Guillain-Barre syndrome, Miller-Fischer syndrome, and chronic inflammatory demyelinating polyneuropathy (CIDP)[1]. This is the first report of a patient with inflammatory arthritis who developed peripheral mononeuropathy taking etanercept.

A 43-year-old Caucasian man was initially diagnosed with psoriatic arthritis (PsA) in 1997. His past course of treatment had been challenged by intolerance and inefficacy of different therapeutic modalities. He was initially treated with methotrexate (MTX) with a good response. However, he experienced adverse effects including headaches, nausea, vomiting, and diarrhea and he discontinued MTX therapy.

Two years later, during a severe flare of the psoriasis and arthritis, cyclosporine was used as monotherapy and later in combination with leflunomide, with good disease control. However, he developed hypertension on cyclosporine therapy and it had to be discontinued. Biologic agents including alefacept, infliximab, and etanercept were also used. They either controlled the arthritis but not the psoriasis or they were not efficacious at all.

The patient was evaluated in our rheumatology clinic in October 2005 for management of recalcitrant PsA. Etanercept in combination with leflunomide was initiated, which controlled his arthritis and psoriasis. However, he discontinued the etanercept after 12 weeks due to lack of insurance coverage. Thereafter, etanercept treatment was resumed on 3 more occasions over the course of a year based on his insurance coverage.

Eight weeks after reinitiating etanercept and leflunomide therapy for the fourth time, he presented with acute-onset numbness in the ulnar aspect of his left hand, fourth and fifth digits. His neurological examination showed mildly decreased left hand intrinsic motor strength (4/5) and diminished pinprick sensation on his left fifth digit. His mental status, ambulation, cranial nerves II-XII, coordination, deep tendon reflexes, motor strength, and sensation were intact. Given the distribution of find-

ings, he was diagnosed with ulnar neuropathy. He denied any precipitating factors, including trauma or prolonged positioning of the arm. Etanercept was suspected to be the culprit and it was discontinued. Electromyography (EMG) was performed, which revealed left demyelinating ulnar mononeuropathy with evidence of approximately 80% conduction block localized to the segment between the elbow and the axilla (in the arm). There was no evidence of left cervical motor radiculopathy. Peripheral demyelinating mononeuropathy secondary to etanercept was the entertaining diagnosis. After etanercept was discontinued, no other medications were started until he reported improvement of his neuropathy 6 weeks later. During this time, he continued taking leflunomide, which had been started 6 months before. However, leflunomide as monotherapy did not control his inflammatory arthritis activity. Therefore, 9 weeks after discontinuation of his etanercept, he was started on cyclosporine in addition to leflunomide, but this regimen also failed to control his PsA. He was also offered a followup with neurology, but since his neuropathy was markedly improving off etanercept he declined it, and followup EMG/nerve conduction studies were not obtained.

Ulnar neuropathy is commonly seen with traumatic nerve injuries[2,3] and with nerve entrapment at the elbow, which can occur without any obvious inciting factor or anatomical predisposition[4]. While PsA has been associated with entrapment neuropathies[5], as a consequence of local inflammation, psoriasis has not been associated with peripheral neuropathies. This patient's neurological symptoms started 8 weeks after etanercept use, which is earlier than the reported average time for demyelinating conditions associated with anti-TNF-α. His symptoms improved after the drug was discontinued, which supports an association between the use of the TNF-α antagonist and his neurological symptoms. This is in accord with the findings of Mohan, *et al*, who reported partial or complete resolution of symptoms after discontinuation of anti-TNF-α therapy[6].

Drug-induced peripheral neuropathy seems like the most plausible diagnosis based on symptom improvement after drug discontinuation and lack of other possible causes such as trauma, metabolic abnormalities, and other underlying disease process[7]. In addition, the EMG was not consistent with nerve entrapment at the elbow. At the onset of his symptoms, the patient was also taking amlodipine and hydroxyzine and using triamcinolone acetonide ointment. He had also previously taken MTX, leflunomide, and cyclosporine. Among these medications at the doses used by this patient, leflunomide has been associated with peripheral neuropathy[11], most commonly in patients with rheumatoid arthritis[8]. It usually manifests as paresthesias with normal NCS[9]. In some patients, nerve conduction studies and EMG may show sensorimotor axonal neuropathy, but not demyelinating neuropathy as in this case[10]. Our patient's neuropathy improved 6 weeks after etanercept was withdrawn, although he continued taking leflunomide, which had been started 6 months before the neuropathy. This timeframe, the demyelinating expression of his neuropathy, and the improvement of his symptoms after withdrawal of etanercept, while he continued taking leflunomide, make etanercept more likely to have caused the neuropathy as compared to leflunomide.

Different outcomes have been reported when patients are rechallenged with the offending drug, with either worsening of neurological status on magnetic resonance imaging[6] or no symptom recurrence on reexposure. The outcome of some of the cases who were rechallenged was confounded by the underlying disease and it was difficult to draw any conclusion[12]. Rechallenge with anti-TNF-α was not attempted in our case.

Initially, TNF-α inhibitors were thought to be neuroprotective by counteracting with TNF-α, since the latter has been shown to cause axonal myelin degeneration and oligodendrocyte necrosis in central nervous system explants[13]. This notion was further compounded by studies in a well established murine model for human multiple sclerosis (MS) in which anti-TNF antibody was shown to prevent autoimmune demyelination from occurring[14]. But further murine studies were conflicting and a TNF-knockout mouse model revealed that these mice suffered from severe neurologic impairment and high mortality, with histological evidence of extensive demyelination and monocytic cell infiltration. The severity of the neurologic disease in TNF-α-deficient mice[15] markedly improved after reinsti-

tution of TNF-α, which is thought to promote remyelination through its influence in the proliferation of oligodendrocyte progenitors[16].

In subsequent human studies, patients with MS treated with TNF-α inhibitors also had an unexpected increase in the number of gadolinium-enhancing lesions[17] and in the number of MS exacerbations[18]. This led to the theory that TNF-α has a protective role in limiting the extent of immune-mediated inflammation and demyelination.

TNF-α inhibitors are being widely used in the treatment of rheumatic and inflammatory bowel diseases. They represent a major breakthrough in the treatment of these diseases, but they have also been associated with some potentially serious adverse effects, one of which is demyelination. For this reason, TNF-α inhibitors are contraindicated in patients with central demyelinating disorders. Individual susceptibility must account for the variable responses to TNF-α inhibitors and to the onset of demyelinating diseases in some people, but these mechanisms are still not completely understood. Although the occurrence of demyelinating syndromes associated with TNF-α inhibitors seems rare, the true incidence is unknown and it may be underreported. Nevertheless, TNF-α inhibitors are still promising drugs in the treatment of autoimmune inflammatory disorders, and their use is becoming more widespread. By reporting a new adverse effect associated with etanercept treatment, we aim to increase public awareness and patient safety.

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