Who might be predisposed to the development of serious side effects when treated with TNF-alpha antagonist?

Sirs,

We read with great interest the letter of Boyer and colleagues (1) concerning the development of serious heart side effects in patients treated with infliximab. Treatment with TNF-alpha blockers is absolutely contraindicated in patients with heart failure and that was believed to prevent serious complications in the past. Boyer's letter shows us that this process is not restricted to patients with the compromised left ventricular function but occurred randomly in apparently healthy subjects in a wide spectrum of rheumatologic diseases. Moreover, those facts suggest that it is impossible to identify patients who are prone to develop serious cardiovascular side effects. In this letter we would like to share our personal experience with infliximab and cardiac function in patients with rheumatoid arthritis. We observed a group of 30 patients with rheumatoid arthritis treated with infliximab at a dosage 3mg/kg/infusion. In one year's observation we failed to show that treatment with infliximab in patients with rheumatoid arthritis results in the deterioration of the left ventricular function (2). Moreover, we showed a small, but statistically non-significant increase in ejection fraction after one year of the treatment. The results suggest that infliximab has no direct harmful effects in the majority of patients and development of heart side effects is unrelated to the duration of the treatment. TNF-α level rises significantly in patients with heart failure and correlates well with the stage of the heart failure (3). This provided the background to interventional study with anti TNF-α blockers in heart failure, prematurely terminated due to the side effects and infectivity. A rapid decrease of TNF-α level might in some circumstances produce a serious imbalance in heart function. This may explain why, in some patients, serious side effects develop and is especially dangerous, without preceding symptoms and signs. Routine screening (echocardiography, ECG, and clinical evaluation) is inadequate to detect patients predisposed to the development of heart side effects. The introduction of the latest biochemical markers of heart failure may bring hope, e.g. brain natiuretic peptide (BNP) endothelins (ET). BNP and ET-1 are nowadays recognized as very sensitive and specific markers of heart failure with levels increased significantly before clinical symptoms are apparent (4, 5). Those markers might be also useful to detect patients on anti-TNF-α treatment who are at high risk of developing serious heart side effects.

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Reply

Sirs,

We agree with Kotyla and colleagues on the difficulty to identify rheumatoid arthritis (RA) patients susceptible to new onset or worsening heart failure with anti-tumour necrosis factor (TNF) therapy. A recent paper suggested that brain natriuretic peptide is a potentially useful screening tool for the detection of cardiovascular disease in patients with RA (1). However, the investigation of brain natriuretic peptide as a predictive factor for heart failure in RA patients after initiation of anti-TNF therapy may be difficult considering the low incidence of this particular adverse event in such patients. Markers of inflammation confer a significant additional risk for cardiovascular death among patients with RA, even after controlling for traditional cardiovascular risk factors and comorbidities such as personal history of coronary heart disease, congestive heart failure, smoking, hypertension, dyslipidemia, body mass index and diabetes mellitus (2). Then, neutralizing inflammation with anti-TNF therapy could theoretically reduce cardiovascular morbidity in RA patients. Such a protective effect was suggested by a few recent studies that reported a lower incidence of heart failure (3), first cardiovascular events (4) or hospitalization for congestive heart failure (5) in RA patients treated anti-TNF versus not treated.

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Successful treatment with methotrexate of a child with atlantoaxial subluxation from enthesitis-related arthritis

Sirs,

Enthesitis-related arthritis (ERA) belongs to the family of juvenile idiopathic arthritis (JIA) (1). ERA patients have enthesitis and its related arthritis of a few joints including vertebra, but atlantoaxial subluxation is a rare complication during their childhood (2). To our knowledge there have not been any reports about an effective medication for atlantoaxial subluxation caused by JIA.

A 12-year-old boy complained of arthralgia in both heels in November, 1997 and walked on tiptoe in September, 1998. Localized treatment of steroid (dexamethasone 2mg) was started, however, cervical pain and arthralgia of the left elbow accompanied. He did not have psoriasis and acute uveitis during the course, and all antinuclear antibodies and rheumatoid factor were negative. C-reactive protein (CRP) was 1.5 mg/dl, erythrocyte sedimentation rate (ESR) was 64 mm/h, and HLA-B27 was present. Radiographs of his neck and pelvis were normal. T1-weighted magnetic resonance imaging (MRI) with intravenous gadolinium-DTPA showed enhancements of both Achilles tendon attachment regions, both origins of the plantar fascia to the calcaneum. T2-weighted MRI of his left elbow showed stagnation of synovial fluids. The diagnosis of ERA was made based on the above findings.

Treatment with anti-inflammatory drugs (NSAIDs) and rehabilitation were started. Three months after medication, his neck was flexed forward and movement was limited by painful spasms of his paracervical muscles without neurological disturbance. A lateral radiograph of his cervical spine revealed that the distance between the anterior margin of the odontoid and the posterior margin of the anterior arch of C1 was widened (11 mm). Calcification and erosion was not observed in the disc or ligaments. In T2-weighted MRI, the regions were shown at high intensity, and the cord-like structure was observed at low intensity. One possible explanation is that synovial fluid with punnus formation in front of the atlantoaxial joint was the cause of anterior atlantoaxial subluxation (AAS). Treatment with sulfasalazine was begun, but radiographs showed that subluxation had worsened (17 mm on forward extension, Fig. 1A). MRI showed the inflammatory synovial change (Fig. 2A), and laboratory findings showed no improvement. He had been afebrile and blood culture was negative.

Treatment was switched to MTX administered orally at 7.5 mg per week. Glucocorticoid therapy was not expected to prevent pannus formation and the bone deformity. Taking into account its growth disturbance together, we had chosen a monotherapy of MTX. Laboratory findings improved rapidly, and two months later, MRI of cervical spine showed a dramatic improvement (Fig. 2B). One year later, there was improvement in movement of both his neck and arthritis of left elbow. The abnormal radiograph finding disappeared as presented in Fig 1B and 2C. At present, 4 years after starting this therapy, the patient is still in remission.

AAS in rheumatoid arthritis patients may cause severe complications, for example, tetraparesis and sudden death. It has been suggested that these complications can be avoided by early operative treatment (3). Surgical stabilization has been recommended for AAS such as size greater than 5mm, or causing spinal cord damage demonstrable by MRI (4). We initially planned the surgery, however, it was judged as harmful for the patient to undergo the operation because of the progressive inflammation in his spine by orthopedists in our hospital. MTX is an effective agent in the treatment of JIA (5-8) and presumably effective for synovitis and prevents the bone deformity. AAS was considered to be caused by synovitis and pannus formation between the arches of C1 and odontoid in our patient, and the addition of MTX dramatically improved his condition. In JIA, patients who have AAS caused by synovitis may be successfully treated with MTX before surgical management.

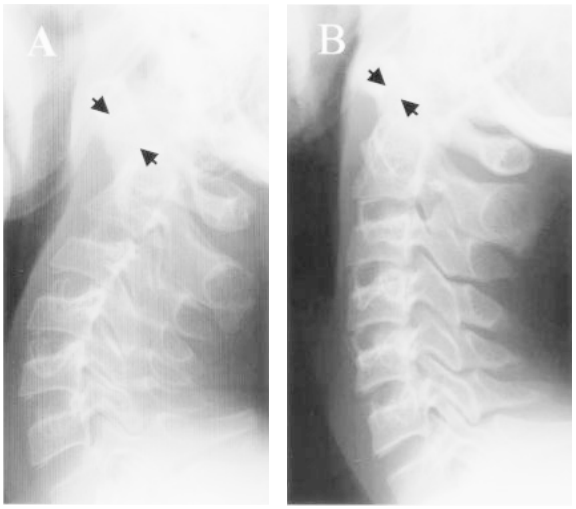

Fig. 1. Extension cervical spine radiographs before (A) and 12 months after (B) treatment with MTX. Cervical spine radiographs show a decrease in the anterior atlantodental interval (arrows) with flexion.

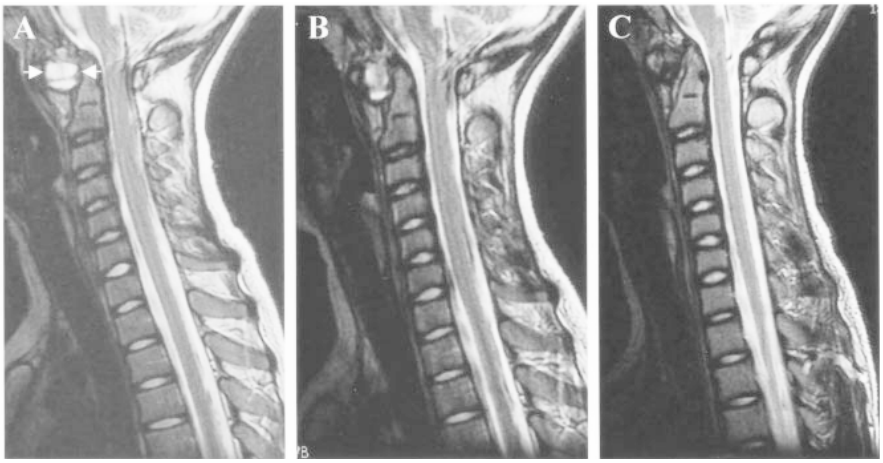

Fig. 2. Sagittal T2-weighted MRI of the cervical spine before (A) 1 month after (B) and 12 months after (C) treatment of MTX. The thickened synovium lies between the anterior arch of C1 and the odontoid (white arrows), which gradually improved after MTX treatment.

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