Cross cultural adaptation and validation of the Arabic version of the CHAQ for measuring functional status in children with JIA

Sirs,

I have read with great interest the article by El Miedany *et al*. (1), wherein the authors evaluated the validity and reliability of the modified translated version of CHAQ in Arab children with JIA. The cohort included 30 Saudi Arabian children with JIA. With all due respect, as a Pediatric Rheumatologist working at the single tertiary care center for pediatric rheumatic diseases in Saudi Arabia, I found the number of Saudi children is too large to be followed outside the country without our prior awareness and as the authors did not specify the collaborative centers, I would like to know in greater detail the methodology of recruitment of a such large Saudi cohort.

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Reply

Sirs,

The Saudi Arabian children suffering from juvenile arthritis were consecutively recruited for the study from those attending or that had been referred to the rheumatology clinic in the Saudi German Hospital, Jeddah, over the period from 5th of March 1995 till the end of April 1997, as well as the Rheumatology Clinic in the insurance hospital and Dar El Shefaa Hospital, Riyadh, Saudi Arabia over the year 2000 where the first and second authors were working. The patients were diagnosed, assessed and followed up in Saudi Arabia.

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Pulmonary aspergillosis in a patient with rheumatoid arthritis treated by etanercept

Sirs

Etanercept is a fusion protein that binds free TNF-α and has been shown in previous trials to be effective against RA, juvenile arthritis and psoriatic arthritis. Concerns have been raised about the increased risk of infections with immunomodulating agents such as etanercept. However, fungal infections in patients treated with TNF-α antagonists are rare and have only been reported with infliximab therapy. We report a case of pulmonary aspergillosis in a patient with RAtreated with etanercept.

In December 2001 a 55-year-old woman with a 10-year history of severe rheumatoid arthritis (RA) was admitted to hospital because of pulmonary infection. She has been treated with oral methotrexate for 6 years, and then with leflunomide for 6 months. In February 2001 leflunomide was stopped because of refractory disease and etanercept was started at 25 mg twice a week in association with prednisolone 5 mg/day; this led to rapid clinical improvement. Five days before admission, however, she presented high fever, dyspnea and a productive cough. A chest roentgenogram showed basal infiltrates in the left lung with middle bilateral pleuritis. Laboratory tests revealed an increased C-reactive protein concentration (150 mg/l) and leukocytosis. Bronchoalveolar-lavage fluid and pleural fluid puncture yielded *Staphylococus aureus* and treatment with amoxicillin-clavulanic acid was started.

Five days after her admission the patient developed respiratory failure associated with pneumopyothorax. A computed tomography scan was highly suggestive of a fungal ball aspergilloma in the pulmonary cavity of the right lung. Etanercept was stopped and treatment with voriconazole was started (6 mg/kg/day) in association with drainage of the pneumothorax. Culture of pleural fluid yielded *Aspergillus fumigatus* on day 15 and was negative for tuberculosis. A few days after beginning fungal therapy, her clinical condition significantly improved. At month three, the pulmonary aspergilloma has completely disappeared.

The role of TNFα in the immune response is very complex. It may limit the extent and duration of inflammation. Etanercept, a recombinant human tumor necrosis factor alpha (TNFα) inhibitor that binds both soluble and cell-bound TNFα, has been shown to reduce disease activity and inhibit joint destruction when administered to patients with RA. Infliximab, another TNF antagonist, is a chimeric mouse-human monoclonal IgG1 antibody that has been approved for the treatment of RA in combination with methotrexate. The number of patients who have been treated with etanercept or infliximab are quite similar.

Because of the potential immunosuppressive properties of TNFα antagonists, adverse events related to infections are a major concern connected with the use of both agents (1, 2). A role for TNFα in susceptibility to infection is clearly suggested by data from animals models of TNFα inhibition and blockade (3). However, in patients treated with infliximab the incidence of tuberculosis and various opportunistic infections (histoplasmosis, listeriosis etc.) seems to be higher with infliximab than with etanercept (1-4). Possible explanations for the disproportionate number of cases associated with infliximab therapy in comparaison to etanercept may related to the different ways in which the two agents neutralize TNFα (4).

Pulmonary aspergillosis has been reported in patients treated with infliximab; however, as far as we know, there have been no cases reported in etanercept-treated patients. Importantly, our patient had no known risk factors for aspergillosis except for immunosuppressive treatment with etanercept and low dose corticosteroids. She had no underlying respiratory disorder which would have predisposed to pulmonary aspergillosis. This complication occurred more than 9 months after leflunomide was withdrawn, at a time when its residual concentration would have been negligible given the half life of this molecule (5). Although there is no available data regarding the long-term effects of leflunomide on the immune response, it should be mentioned that opportunistic infections have rarely been reported in patients treated with leflunomide (6). Our data strongly suggest an association between treatment with etanercept and the development of aspergillosis in this patient.

In conclusion, physicians prescribing etanercepts such as infliximab should be aware of the risk of opportunistic infection including pulmonary aspergillosis. More rigorous monitoring may be needed for patients prior to and during etanercept therapy.

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Infliximab-induced lupus or rheumatoid arthritis (RA) overlapping with systemic lupus erythematosus (SLE) unmasked by infliximab

Sirs,

Various studies have reported no clinical significance of autoantibodies such as antinuclear (ANA) and anti-doubled-stranded DNA (anti-ds-DNA) antibodies in RA patients during anti-TNF-α treatment with infliximab and etanercept (1,2) although several cases of drug-induced lupus (DIL) have been described (1, 3-7). We report the case of an RApatient who developed clinical and laboratory signs of SLE during infliximab treatment, which persisted after drug discontinuation.

A 53-year-old woman with 19-year history of RAwas admitted in May 2001 with morning stiffness 420 min, tender joint count 16, and swollen joint count 26 despite therapy with methotrexate (MTX) 12.5 mg weekly and methylprednisolone 12 mg daily. ESR was 65 mm/h, CRP 63 mg/ml (normal < 5 mg/ml), and RF 1070 IU/ml. ANA, ENA and anti-ds-DNA were negative, C3 and were C4 normal. She was started on infliximab following the usual regimen (3 mg/kg, weeks 0, 2 and 6, and then every 8 weeks), while continuing with the same MTX and methylprednisolone dosage.

Articular manifestations rapidly improved (no morning stiffness, tender joint count 5, swollen joint count 8). ESR was 50 mm/h, CRP 5.1 mg/ml, and ANAand anti-dsDNA were negative. However, 4 weeks after the 4th infusion the patient was re-admitted with acute polyarthritis and photosensitive rash on the face, neck, arms and legs. She had a fever of 37.8ºC and a dry cough. A chest radiograph showed right pleural effusion. ESR was 92 mm/h, CRP 111 mg/ml. Blood and pleural effusion for bacteria were negative. The patient was unsuccessfully treated with gentamycin and amoxycillin with clavulonic acid.

Laboratory tests revealed ANA1:320, anti-dsDNA 64.6 by ELISA (normal < 60), C3 0.66, C4 0.09. ENA and anti-phospholipid antibodies (aPL) were negative, anti-histone antibodies not performed. Hemoglobin was 112g/l. Total white cell, platelet count, renal and liver function tests were normal; there was no proteinuria. A diagnosis of SLE (worsening of polyarthritis, pleural effusion, photosensitive macular rash, positive ANA and anti-dsDNA, low complement levels) was established. Infliximab was discontinued and oral methylprednisolone increased to 32 mg daily. She promptly became afebrile, pleural effusion resolved after 15 days, and arthritis improved slowly. The dosage of MTX was increased to 17.5 mg weekly and methylprednisolone tapered to 12 mg. A year later she had morning stiffness 90 min., tender joint count 14, swollen joint count 15, ESR 45 mm/h, CRP 21 mg/ml, C3 and C4 slightly decreased. ANA was 1:320, anti-ds-DNA139, and there was no anti–ENA and aPL. Photosensitive rash on the face and neck improved slightly after hydroxychloroquine 400 mg daily.

Our patient had RA, with joint erosions documented by X-ray and no previous signs of SLE. After the 4th infusion of infliximab she developed clinical and laboratory signs of acute lupus, raising the question of a possible DIL. The formal diagnostic criteria for DIL, especially in patients with an underlying inflammatory arthritis such as RA, is a matter of concern (7). There are several reports discussing the development of DIL associated with infliximab and etanercept with characteristic resolution of the symptoms after discontinuation of treatment (3-7). However, the cases of some patients with a possible pre-existing overlap with SLE which became overt after exposure to etanercept, but clinically resolved on drug withdrawal, suggest a possible further association of DIL with etanercept (4, 5, 7, 9). We report a patient who had a definitive diagnosis of RA and developed both clinical and laboratory signs of SLE associated with infliximab. Since these criteria did not disappear a year and half after the discontinuation of treatment we cannot speak about DIL. We believe she has RAoverlapping with SLE unmasked by infliximab. Her HLA-haplotype (B8, DR 3) speaks in favour of this hypothesis. Clinicians should be aware that anti-TNF-α therapies may be associated with acute lupus-like symptoms but further monitoring of the patient is needed to evaluate whether it is a real DIL or a pre-existing RA-SLE overlap unmasked by anti-TNF-α therapy.

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