

# Beneficial effects of leflunomide in glucocorticoid- and methotrexate-resistant Takayasu's arteritis

Sir,

Takayasu's arteritis (TA) is a chronic inflammatory large-vessel vasculitis of unknown origin involving the aorta and its major branches. Morbidity results from arterial stenosis which may lead to stroke, myocardial infarction, peripheral claudication, mesenteric vascular insufficiency, renovascular hypertension, malaise, cephalgia, arthralgias, musculoskeletal pain, weight loss and fever. Females are more frequently affected than males. TA is heterogeneous in presentation, progression and response to therapy (1-4).

Elective vascular bypass surgery has an important role to play in the treatment of TA and should be considered during periods when the disease is apparently inactive. An elevated erythrocyte sedimentation rate (ESR) is understood by most physicians to be an indicator of active disease and its reduction is taken to signify a positive response to treatment (2,3).

Glucocorticosteroids (GC) are primarily used to reduce the activity of the vascular inflammation in TA. Between 20% and 100% of patients are reported to respond positively to GC therapy. In patients with GC-resistant disease the use of cytotoxic drugs, mainly methotrexate (MTX) but also azathioprine, cyclophosphamide and cyclosporin A, is warranted (5-7). However, a subgroup of TA patients (<15%) suffering from chronic, unremitting disease does not

respond to GC + MTX therapy.

Leflunomide (LEFLU), a new immunosuppressive and immunomodulating agent which is registered for the treatment of rheumatoid arthritis, has been tried in patients with ANCA-associated vasculitis in pilot studies and shown to be an effective remission-maintaining drug without any serious side effects in patients with generalized Wegener's granulomatosis (7,8). Here we report our experience with LEFLU therapy in a female patient with GC- and MTX-resistant TA.

A 28-year old female of Turkish origin was referred to our rheumatology department for evaluation of malaise, cephalgia, bilateral shoulder pain and myalgias of 4 years' duration. The family history was negative for rheumatic diseases. Blood pressure was 90/60 mm Hg only in the right arm and not measurable in the left arm. Radial and brachial pulses were palpable in the right arm only. An echocardiogram and routine chest X-ray were normal.

Laboratory results were: red blood cell count 3.61 M/mm<sup>3</sup>, hemoglobin 8.4 g/dl, white blood cell count 5,800/mm<sup>3</sup>, platelets 429,000/mm<sup>3</sup>, ESR of 96 mm/h, C-reactive protein (CRP) 73 mg/dl (normal < 12 mg/dl). Serum chemistry including BUN, creatinine, electrolytes, calcium, liver enzymes, thyroid function, and urinalysis were normal. Complement components C3 and C4 were normal; antinuclear antibody and subsets, ANCA, rheumatoid factor and anticardiolipin antibody tests were negative. The IgM serum level was slightly elevated, while IgA and IgG were within the normal range.

Further evaluation with CATs and invasive

angiography revealed significant stenotic changes in the left common carotid, the left subclavian artery and only moderate changes in the right common carotid, the right subclavian artery, the right vertebral artery, according to TA. Involvement of the heart, the thoracic aorta, the abdominal aorta and the pulmonary arteries were excluded.

The ischemia of the left arm limiting daily routine activities and the perhaps critical stenosis of the left common carotid suggested surgical intervention. The patient was placed for 3 months on oral prednisone (1 mg-0.4 mg/kg/day) and oral MTX (20 mg/week) to reduce vascular inflammation; however, only a moderate decrease of the ESR (<15%) was observed.

Because of recurrent syncope and headache, a left common carotid and left subclavian bypass procedure was done at an early stage. Histological examination of a specimen of the left subclavian artery showed an active granulomatous inflammation and giant cells within the media and adventitia. During the following 6 months, the patient was once more given oral prednisone (0.3 - 0.8 mg/kg/day) and oral MTX (7.5-20 mg/week). Again no satisfactory response to GC+MTX treatment could be observed. ESR (90 mm/h-106 mm/h), CRP (51-108 mg/dl), serum amyloid A (SAA) (117-155 mg/dl) and interleucine-6 (IL-6) (46 - 63 pg/ml) remained elevated; soluble CD44-isoform variant 5 (sCD44v5), a slow-acting parameter of rheumatic disease activity (9, 10) also remained between narrow limits (22 - 29 ng/ml).

There was only a slight elevation of the blood pressure and the patient still reported headache and episodes of malaise.

Subsequently MTX was replaced by LEFLU (30 mg/day). Over the next 2 months GC was slowly tapered to 2 mg/day and then withdrawn. Six month after initiating LEFLU therapy, ESR (22 mm/h), CRP (12 mg/dl), SAA (8 mg/dl) and IL-6 (16 pg/ml) had significantly decreased to nearly normal values. Even sCD44v5 decreased to 9 ng/ml (Fig.1). Finally, the patient's blood pressure rose to 110/70 mmHg in the right arm and to 90/55 mmHg in the left arm, and radial pulses were palpable in both arms. The patient no longer complained of syncope, headache or any limitations of routine daily activities. LEFLU treatment was tolerated very well and no side effects were observed.

In conclusion, a female patient with GC + MTX-resistant TA responded (slowly) to LEFLU treatment with improvement of clinical symptoms, normalisation of the ESR, CRP, SAA and a remarkable reduction of IL-6 and sCD44v5 levels. In this case of TA, LEFLU appeared to be an effective (slow-acting) agent to reduce the activity of

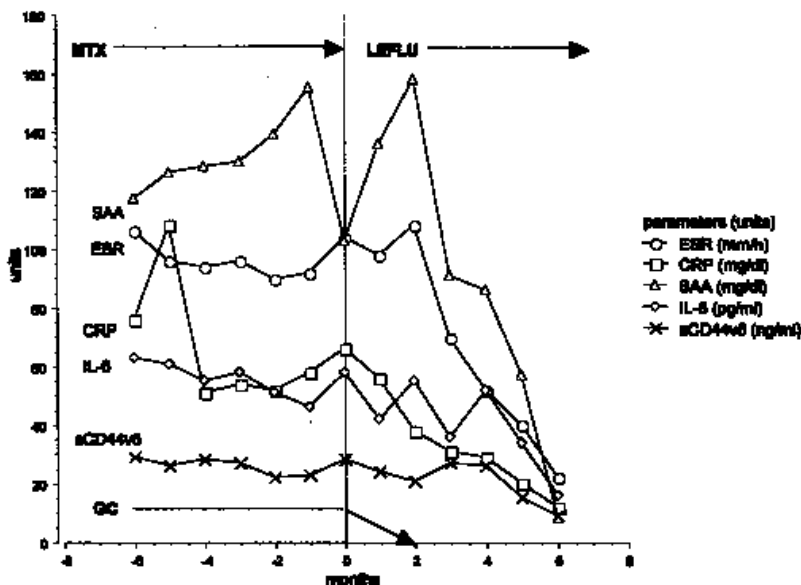


Fig. 1. The course of ESR, CRP, SAA, IL-6 and sCD44v5 in a patient with TA treated for 6 months (-6 to 0) with MTX + GC and for 6 months with LEFLU (0-6). GC was slowly tapered and withdrawn after 2 months of treatment with LEFLU.

# Letters to the Editor

inflammation. Extensive and long-term studies will be required to assess our single observation.

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## Blue coloured skin in psoriatic arthritis

Sirs,

Psoriatic arthritis (PsA) is disease that originates from many reasons (1,2). The appearance of the skin over the joint leads to the diagnosis with great probability. We have confirmed this fact by findings on a large number of patients with PsA.

We examined 650 patients with the diagnosis of PsA and 1,265 patients with rheumatoid arthritis (RA) during the period 1975 to 1998. Besides the clinical examination, we performed laboratory testing, radiographs of involved joints and axial skeleton as well as histocompatibility antigen assays accord-

ing to Terasaki and McClelland (3).

Diagnostic criteria for PsA were existence of arthritis and psoriasis at typical areas (extensor sides of elbows and knees) or at so-called hidden areas (axilla, breast, scalp, umbilicus, nails, intergluteal cleft, obstacle or hurdle) (3-6). All patients with RA fulfilled the Rome criteria and after 1988 the revised ARA criteria (7). In 484 patients with PsA (74.4%) the psoriasis appeared before arthritis; in 150 patients (23.1%) arthritis appeared first; and in 16 patients (2.5%) arthritis and psoriasis appeared simultaneously. Sixty patients (9.2%) had the monoarticular form of arthritis, 320 of them (49.2%) the oligoarticular form and 270 (41.6%) had the polyarticular form of the disease ( $P > 0.05$ ). 120 patients (18.5%) had arthritis of the distal interphalangeal joints, 62 (9.5%) had arthritis mutilans, 12 (1.9%) had symmetrical polyarthritis indistinguishable from rheumatoid arthritis, 328 patients (50.5%) had asymmetrical oligoarthritis, and 128 (19.7%) had spondyloarthritis. Thus, spondyloarthritis developed in 128 patients (19.7%), quite often in the asymmetrical form of PsA.

Blue-colored skin over and around the involved joints was found in 598 patients with PsA (92%) and in 63 patients with RA (5%). The difference was statistically significant ( $P < 0.05$ ). Regardless of psoriatic skin lesions, we observed that the skin over the involved joints in PsA has a unique bluish color of different intensity (Fig. 1), which is different from typical psoriatic skin changes. A blue to violet bluish color of the skin is seen over the inflamed joints and digits in the cases of sausage digits. This color is strongly limited to the joint, spreads over the insertion of the joint capsule and disappears. Skin folds are reduced or disappear depending on the amount of synovial effusion into the joint.

In less involved joints the blue colour develops in over a smaller area, usually on the central dorsal part of the skin over the joint. This colour never develops on the volar, plantar or flexor side of the joints. According to our observations, most patients with PsA have such a change of colour over the involved joints at the onset of the disease and during worsening of the disease. The phenomenon is confined to a period of time. It also rarely occurs with such intensity during hot days, for instance in the summer, or when the hand is immersed in warm water as well as at room temperature and in the inactive phase of the disease.

In psoriasis, the skin is desquamating and erythema appears. If some joint is close to that area, blue coloured skin develops. Therefore, we could find tinged (red-blue coloured) skin in a small region. Otherwise,

the whole skin in psoriasis is rather darker, especially in the regions exposed to the sun (hands, head, face). If psoriasis was present as well, a white blanching ring could be found around the erythema that is developing toward a blue colour (8,9). However, in Caucasians the colour of the skin on psoriasis is salmon-pink whereas rupoid (Ps rupiosa seu ostracea) are waxy-yellow to orange-brown (10), i.e. quite different from the colour of the skin in PsA.

In conclusion, we may say that we have found a sure sign of PsA - blue coloured skin over the involved joints - that is a condition almost *sine qua non* to reach the diagnosis.

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