Successful treatment of refractory anterior scleritis in primary Sjögren’s syndrome with rituximab

K Ahmadi-Simab, P Lamprecht, B Nölle, M Ai, W L Gross


Anterior scleritis is an inflammation of the superficial, subconjunctival sclera which may follow infection or occur in rheumatic disease. Anterior scleritis due to secondary immune complex mediated vasculitis is an extremely rare extraglandular manifestation in primary Sjögren’s syndrome. Symptoms of anterior scleritis are pain, tearing, and photophobia. If left untreated, anterior scleritis may progress to scleromalacia and, ultimately, threaten eyesight by affecting the uvea. Here we report on the successful induction of remission with the B cell directed monoclonal anti-CD20 antibody in a case of refractory anterior scleritis with episcleritis in primary Sjögren’s syndrome.

CASE REPORT

Primary Sjögren’s syndrome was diagnosed in a 60 year old white woman according to the criteria of the European study group. Ocular and oral sicca symptoms included for more than 3 months, a pathological Schirmer test (<5 mm/5 min), and pathological salivary scintigraphy. Antinuclear antibodies and Ro (SSA) were detected and, later on, anti-fodrin antibodies. Complement levels were normal, cryoglobulin bodies and Ro (SSA) were detected and, later on, anti-fodrin and pathological salivary scintigraphy. Antinuclear antibodies were noted in primary Sjögren’s syndrome. We suggested that B cell depletion might favour induction of remission. To our knowledge this is the first report to show successful induction of rituximab in primary Sjögren’s syndrome. Rituximab successfully induced remission in a number of cases of refractory systemic lupus erythematosus, dermatomyositis, and cryoglobulinaemic vasculitis associated with hepatitis C virus. An immunosuppressive combination treatment with rituximab also induces remission in refractory rheumatoid arthritis.3 B cells may play an important part in primary Sjögren’s syndrome. Ectopic lymphoid tissue formation and lymphoproliferation are a hallmark of primary Sjögren’s syndrome. The risk for malignant B cell lymphoma is increased nearly 40-fold in patients with Sjögren’s syndrome. Alterations in the B cell compartment have been noted in primary Sjögren’s syndrome. A significant reduction in circulating memory CD27 B cells and accumulation of memory B cells in the salivary glands is seen in primary Sjögren’s syndrome.

These studies provided the rationale for the use of rituximab in our patient with refractory anterior scleritis in primary Sjögren’s syndrome. We suggested that B cell depletion might favour induction of remission. To our knowledge this is the first report to show successful induction with rituximab in primary Sjögren’s syndrome. We cannot totally rule out the possibility of delayed effects as a result of previous drug treatment, but induction of remission paralleled the complete depletion of circulating B cells induced by rituximab. Remission was subsequently maintained with mycophenolate mofetil in the presence of persistent peripheral B cell depletion.

Our report suggests that specific B cell depletion may be one successful strategy in the treatment of refractory primary Sjögren’s syndrome. However, further studies are needed to determine the place of B cell depletion strategies in the treatment of severe organ manifestations in primary Sjögren’s syndrome.

DISCUSSION

Killing of CD20 positive cells mediated by rituximab is caused by several mechanisms, including complement dependent cytotoxicity, antibody dependent cell mediated cytotoxicity, and induction of apoptosis. Rituximab induces remission of malignant B cell lymphomas. Clinical findings, data from animal models, and in vitro experiments suggest that B cells have a pivotal role in a number of rheumatic conditions such as rheumatoid arthritis and primary Sjögren’s syndrome.

REFERENCES


Figure 1. (A) Anterior scleritis and flow cytometric analysis of B cell population in primary Sjögren’s syndrome before treatment with the monoclonal anti-CD20 antibody rituximab. (B) Induction of remission with rituximab. For flow cytometric analysis peripheral blood mononuclear cells were stained with fluorochrome conjugated monoclonal antibodies for cell surface antigens or appropriate negative (isotype) controls. Four colour flow cytometric analysis was performed using a FACSCalibur flow cytometer (Becton Dickinson) and CELL-Quest software (Becton Dickinson). Lymphocytes were gated for analysis based on light scattering properties. A second gate was set based on light scattering properties and CD45 perCP staining properties. Positively and negatively stained populations were calculated by quadrant dot plot analysis determined by isotype controls. Quadrant markers were positioned to include >99% of control (isotype) immunoglobulin stained cells in the lower left quadrant. The numbers given in the upper right quadrant of the FACS refer to the fraction of cells detected in each quadrant. B cells display CD19 expression. Before treatment about 10% of the circulating CD19+ B cell population belong to the CD5+ (B1) B cell fraction. After successful treatment with rituximab no circulating CD19+ B cells can be detected.
The radiographs and the magnetic resonance imaging findings (figs 1A and B) of the right shoulder showed erosions of the acromioclavicular joint and the humerus consistent with rheumatoid arthritis, as well as degenerative changes. Hands and elbows were radiologically normal.

Initially, because of a suspicion of pneumoconiosis and clinical signs of rheumatoid arthritis, the preferred diagnosis was Caplan’s syndrome—a form of rheumatoid arthritis marked by the intercurrent onset of polyarthritis and pneumoconiosis (usually silicosis), but x-ray examination and computed tomography of the thorax showed post-inflammatory changes in the right upper lung field and bullae in the left upper field; (D) chronic fibrous synovialitis with multiple ill-defined epithelioid granulomas (stars); inset: Langhans’ giant cell.

**Table 1** Abnormal initial laboratory variables and autoantibodies

<table>
<thead>
<tr>
<th>Variables/autoantibodies</th>
<th>Normal value</th>
<th>Patient’s values</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR (mm/1st h)</td>
<td>&lt;10/20</td>
<td>58/78</td>
</tr>
<tr>
<td>C reactive protein (mg/l)</td>
<td>&lt;5</td>
<td>53.6</td>
</tr>
<tr>
<td>α 2 Globulin (%)</td>
<td>6.3–10.5</td>
<td>10.9</td>
</tr>
<tr>
<td>β 2 Globulin (%)</td>
<td>7.7–12.6</td>
<td>13.2</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>50–70</td>
<td>80.7</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>25–40</td>
<td>13.5</td>
</tr>
<tr>
<td>Platelets (×10^12/l)</td>
<td>120–450</td>
<td>468</td>
</tr>
<tr>
<td>Antinuclear antibodies</td>
<td>Negative</td>
<td>1/640 (fine granular cytoplasmic)</td>
</tr>
<tr>
<td>Anticardiolipin antibodies (IgG) (IU/ml)</td>
<td>&lt;48 (ELISA)</td>
<td>305.5</td>
</tr>
<tr>
<td>Rheumatoid factors (IgM) (IU)</td>
<td>&lt;20 (ELISA)</td>
<td>47</td>
</tr>
<tr>
<td>Rheumatoid factors (IgG) (IU)</td>
<td>Negative (latex test)</td>
<td>Negative</td>
</tr>
<tr>
<td>Circulating immune complexes (µg/ml)</td>
<td>&lt;5 (C1q-EUSA)</td>
<td>67</td>
</tr>
<tr>
<td>Borrelia antibody IgM</td>
<td>Negative (EUSA)</td>
<td>Negative</td>
</tr>
<tr>
<td>Borrelia antibody IgG</td>
<td>Negative (EUSA)</td>
<td>Positive (42 units)</td>
</tr>
</tbody>
</table>

The radiographs and the magnetic resonance imaging findings (figs 1A and B) of the right shoulder showed erosions of the acromioclavicular joint and the humerus consistent with rheumatoid arthritis, as well as degenerative changes. Hands and elbows were radiologically normal.

Initially, because of a suspicion of pneumoconiosis and clinical signs of rheumatoid arthritis, the preferred diagnosis was Caplan’s syndrome—a form of rheumatoid arthritis marked by the intercurrent onset of polyarthritis and pneumoconiosis (usually silicosis), but x-ray examination and computed tomography of the thorax showed post-inflammatory changes in the right upper lung field, bullae in the left lung, and pleural thickening with characteristic asbestos related plaques without signs of silicosis (fig 1C).

Histology displayed ill-defined epithelioid granulomas and chronic fibrous synovialitis (fig 1D), therefore sarcoidosis was also considered but thought unlikely in view of an unremarkable CD4/CD8 ratio in the bronchial fluid, normal angiotensin converting enzyme values, and the absence of small joint involvement.

In the presence of undifferentiated autoantibody phenomena and raised inflammatory variables (table 1) without convincing evidence for sarcoidosis or acute tuberculosis, early undifferentiated connective tissue disease was diagnosed and treatment with azathioprine and prednisolone was started under isoniazid cover (considering a positive Multimerieux tuberculin test).

Surprisingly, after three weeks Mycobacteria were cultured in the fluid from the right shoulder and characterised as \( M \) *kansasii* (16S rRNA gene sequencing). As recommended, the patient was prescribed a triple combination of isoniazid (300 mg/daily), rifampicin (600 mg/daily), and ethambutol (3×500 mg/daily) for 18 months and the firm swelling around the left elbow and autoantibody phenomena resolved completely. Azathioprine was discontinued, prednisolone reduced.

Today (2 years after completing treatment) the patient reports occasional arthralgia of the shoulder joints, interpreted as degenerative changes and responding to NSAIDs.

**DISCUSSION**

*M kansasii* was first described by Buhler and Pollack in 1953. Infections with *M kansasii* are environmentally acquired. Interestingly, *M kansasii* is primarily restricted to tap water and can survive for up to 12 months.1,2 Usually *M kansasii* affects the lungs similarly to tuberculosis and rarely affects joints, tendons or bone.1,4

Among the non-tuberculous Mycobacteria, *M kansasii* is the commonest cause of monarthritis, usually exhibiting erosive
Etanercept in treatment of Felty’s syndrome

A Ghavami, S Genevay, T Fulpius, C Gabay

Felty’s syndrome (FS) is an uncommon extra-articular manifestation of rheumatoid arthritis (RA). It is more prevalent among women around 60 with a long history of severe articular disease, positive rheumatoid factor, and who carry the HLA-DR4 allele. Felty’s syndrome has a poor prognosis, with an increased mortality due to a higher incidence of severe infection. We describe a patient with seropositive, erosive RA and history of extra-articular manifestations, including vasculitis and FS. Treatment with etanercept gradually decreased the neutrophil count over 20 months. Discontinuation of etanercept and initiation of methotrexate was followed by a dramatic and sustained improvement of neutrophil count.

CASE REPORT
A 75 year old white woman with a 19 year history of seropositive RA with extra-articular manifestations including mononeuropathy multiplex (1998) and at least a 4 year history of FS (idiopathic neutropenia reported since 1994 and splenomegaly described on abdominal ultrasonography since 1999) was followed up at the Division of Rheumatology at the Geneva University Hospital.

She was treated with azathioprine and prednisone and had a mean white blood cell (WBC) count of 2.0×10^9/l (ranging from 1.6 to 2.7×10^9/l) and absolute neutrophil count (ANC) of 1.4×10^9/l (ranging from 1.1 to 2.2×10^9/l) since May 1999.

In October 2000 treatment with azathioprine was decreased and replaced by etanercept 25 mg (twice a week, subcutaneously) due to synovitis, morning stiffness, and biological signs of inflammation. Improvement in morning stiffness and synovitis was noted, with a decrease of the mean erythrocyte sedimentation rate and C reactive protein.

Prednisone was tapered to 5–7.5 mg daily. During the treatment with etanercept the patient had one infectious complication (right knee septic arthritis in February 2001). Treatment with azathioprine was then discontinued.

Despite the improvement of inflammatory articular manifestations, the WBC count and ANC decreased during a 14 month follow up, resulting in a total WBC count of 1.6×10^9/l and an ANC of 0.3×10^9/l (fig 1). Haematological disorders were excluded by flow cytometry. Treatment with etanercept was discontinued and replaced by oral methotrexate 10 mg and folic acid 5 mg weekly. The WBC count and ANC increased immediately to achieve a normal range (ANC >2.0×10^9/l) within 3 months. The initial dose of methotrexate was increased from 10 mg to 12.5 mg weekly owing to wrist synovitis, with subsequent improvement of articular inflammation. A 2 year follow up shows that the WBC count stabilised.

DISCUSSION
In this patient with seropositive, erosive RA and extra-articular manifestations, administration of etanercept resulted in progressive neutropenia. Discontinuation of etanercept and initiation of methotrexate was associated with a dramatic increase in the WBC count and ANC.

Systemic immunosuppressive treatment is considered to be the most appropriate form of treatment for FS. Experience with cyclophosphamide, ciclosporin, azathioprine, or leflu- nomide in FS is limited. Methotrexate is usually effective in FS. Low dose oral pulse therapy results in improvement in most patients.

Although articular inflammation in our patient responded well to etanercept, a threatening decrease in the WBC count and ANC occurred. The exact mechanism of this observation remains unclear. On the basis of a few reports on pancytopenia and aplastic anaemia after etanercept treatment, a direct effect of etanercept on the WBC count cannot be ruled out completely. Natural evolution of FS might also be postulated. However, the rapid increase of the WBC count and ANC after the introduction of methotrexate and the sustained effect during the following years does not support
this hypothesis. Finally, a lack of efficacy of etanercept in controlling FS must also be considered. This possibility is supported by a recent report on the lack of efficacy of etanercept on FS in a patient with RA and secondary amyloidosis.8 At present, we call for caution when etanercept is used for patients with FS.

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### REFERENCES

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### Positron emission tomography use in the diagnosis and follow up of Takayasu’s arteritis

D Moreno, J R Yuste, M Rodriguez, M J Garcia-Velloso, J Prieto

**Abstract**

Takayasu’s arteritis (TA) is an uncommon chronic vasculitis of unknown origin that affects large and medium sized arteries, especially the aorta, its branches and pulmonary arteries.1,2 TA may present as fever of unknown origin (FUO),3 and inflammatory cells have been shown to take up [18F]fluorodeoxyglucose ([18F]FDG) avidly.4,5

### CASE REPORTS

**Patient 1**

A 27 year old woman was admitted for FUO, headache, and interscapular pain, radiating to the neck and shoulders in the past 2 months. Physical and vascular examinations were normal. Laboratory tests showed anaemia (haemoglobin 84 g/l) and a raised erythrocyte sedimentation rate (ESR 79 mm/1st h). Blood cultures, a Venereal Disease Research Laboratory (VDRL) test, and autoimmune serological findings were negative. Vascular magnetic resonance (VMR) was normal. [18F]FDG positron emission tomography ([18F]FDG-PET) showed hypermetabolism in the brachiocephalic trunk, left carotid artery, and thoracic aorta (fig 1A).

Treatment was started with methylprednisolone (1 mg/kg/day; 60 mg) and methotrexate (15 mg/week). The pain disappeared quickly after starting treatment. At 7 months of follow up the patient remained asymptomatic. Laboratory tests improved (haemoglobin 110 g/l; ESR 8 mm/1st h).
FDG metabolism was normal (fig 1B). When the methylprednisolone dose was reduced below 16 mg/day, the pain reappeared in the left cervical zone, upper chest, and back. The ESR was higher (16 mm/1st h) and [18F]FDG-PET showed hypermetabolism again, matching the painful zones (fig 1C).

**Patient 2**
A 21 year old woman presented with FUO within the past year and neck pain radiating to the left shoulder within the past month. Physical examination showed a thrill in the right supraclavicular fossa, but no bruits were detected. Upper limbs pulses were normal. Laboratory tests showed anaemia (haemoglobin 80 g/l) and a raised ESR (72 mm/1st h). Blood cultures, VDRL test, and autoimmune serological findings were negative. VMR was normal. [18F]FDG-PET showed hypermetabolism in the thoracic aorta, carotids, brachiocephalic trunk, and pulmonary trunk (fig 2A).

Treatment was started with methylprednisolone (1 mg/kg/day; 60 mg) and methotrexate (15 mg/week), with fast clinical and biochemical response. At 4 months of follow up she remained asymptomatic, but radial pulse and blood pressure were undetectable in the left arm. Doppler ultrasonography showed brachial artery thrombosis with collateral neovascularure. Laboratory tests showed haemoglobin 110 g/l and ESR 11 mm/1st h. The dose of methylprednisolone was maintained at 30 mg/day. No other symptoms appeared until 3 months later, when methylprednisolone was reduced to 20 mg/day. She presented with upper thoracic pain and weakness in both arms. Haemoglobin was 111 g/l but ESR was 77 mm/1st h. [18F]FDG-PET showed significant inflammatory activity (fig 2B).

**DISCUSSION**
[18F]FDG-PET has been shown to be a useful diagnostic tool in FUO and in some types of vasculitis, including TA. It allows an early diagnosis of TA during the inflammatory or “pre-pulseless” phase, when other techniques such as VMR or arteriography may be normal. This point is crucial because the “pre-pulseless” phase will not fulfil the American College of Rheumatology criteria for TA, which are mostly based on advanced disease. An early diagnosis allows early treatment and, theoretically, it might reduce the risk of complications.

Moreover, [18F]FDG-PET can identify more vascular regions affected by the inflammatory process than VMR.
and quantify the inflammatory activity of the disease. This is important, because 44% of patients in clinical remission have histologically proven inflammatory activity and blood inflammatory markers are still limited. In addition, $[^{18}F]$FDG-PET is useful in assessing the effectiveness of different treatments during follow up and could be used in randomised controlled trials. However, $[^{18}F]$FDG-PET should be compared with more standardised techniques, such as angiography, VMR, computed tomography, or Doppler ultrasound to obtain firm support for its value in clinical practice.

The accuracy of $[^{18}F]$FDG-PET for diagnosing TA has been estimated as 94% and false positives are not found in normal patients aged under 40. In our patients PET was the only technique with a positive result for diagnosing TA and showed good correlation with disease activity. Our experience also confirms previous reports of relapsing TA after tapering the corticoid dose, even though methotrexate was started after diagnosis.

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**REFERENCES**


Production of anti-CCP antibodies and matrix metalloproteinase-3 by human rheumatoid arthritis synovial tissues using SCID mice

S Iwaki-Egawa, H Matsuno, Y Ogawa, Y Watanabe


The diagnosis of rheumatoid arthritis (RA) remains imprecise, particularly early in the course of the disease. Up to now, rheumatoid factor (RF) has been used as a typical marker for RA; however, RF has a low specificity because it also occurs in many inflammatory diseases as well as in healthy people. It has recently been shown that autoantibodies directed toward cyclic citrullinated peptides (anti-CCP) are potentially important serological markers for diagnosis and prognosis in RA.

The proteolytic pathways associated with cellular interactions also seem to have an important role in joint cartilage destruction of RA. Matrix metalloproteinase-3 (MMP-3) is secreted by fibroblasts and synovial cells, and it has been shown to be increased in RA serum, not only in the late stage but also in the early stage of the disease. Therefore, MMP-3 is a useful marker for predicting bone damage in early RA.

In many early cases of RA, patients will not always fulfill the American College of Rheumatology criteria. Therefore, it is important to detect the point at which disease-specific autoantibodies and proteinases appear in RA serum. In this study we directly investigated the production of anti-CCP and MMP-3 using a severe combined immunodeficiency (SCID) mutant mouse, into which human RA synovial tissue was transferred.

SCID mice are a well known model for analysing the developmental mechanism of T and B cells. We previously developed SCID mice (CB.17/Scid-Charles River Japan, Tokyo, Japan) in which human RA synovial tissue was grafted (SCID-HuRAG), and we evaluated them as models for RA. The histological features of RA were observed in all SCID-HuRAG mice and these mice induced the production of human antibodies. Proliferative synovial fibroblasts and infiltration of inflammatory cells were also seen in the pannus.

The serum levels of anti-CCP and human MMP-3 of SCID-HuRAG mice were examined weekly after implantation. Non-implanted SCID mice sera were used as controls. Figure 1 shows representative results of independent experiments from two patients. The mean (SD) anti-CCP and MMP-3 levels in the serum of the patients were 702 (26.9) U/ml and 321 (12.0) ng/ml, respectively. Human, not mouse, MMP-3 appeared in mouse serum shortly after implantation and decreased immediately. On the other hand, anti-CCP increased gradually and reached a plateau from the fifth week. It is reported that anti-CCP are produced locally in the inflamed synovial tissue from RA. Therefore we think it is reasonable that the surviving, activated human B cells can produce autoantibodies, and the proliferative synovial fibroblasts around the engrafted tissue can produce MMP-3, and that producing autoantibodies spontaneously takes much longer than inducing enzyme. In our previous report, both human RF and interleukin 6 were also detected in these mice sera and not in mice with tissue implants from osteoarthritis synovia (data not shown).

MRL-lpr/lpr mice develop an autoimmune syndrome resembling human systemic lupus erythematosus. Anti-CCP were present in these mice and (NZW × B6)F1-hbcl-2 transgenic mice, which have defects in the regulation of B cell apoptosis. However, these animals showed not only antibody reactivity against the citrullinated peptide clc1-cyc peptide, but also against the non-citrullinated control peptide; therefore, Vossenaar et al reported that the antibodies in these mice are not citrulline specific, and citrulline-specific auto-antibodies are present only in human patients with RA and not in animal models of autoimmune disease. We think that the main problem is that citrulline-specific autoantibodies detected by both groups were of mouse origin. On the contrary, all the target cells within SCID-HuRAG mice which we used were of human origin, having migrated from the implanted tissue, and anti-CCP and MMP-3 were of human origin, too.

In conclusion, we showed the point at which disease-specific autoantibodies and proteinases appear in RA. SCID-HuRAG mice will be worth using in the study and development of new drugs for RA.
Absence of anti-cyclic citrullinated peptide antibodies in erosive osteoarthritis: further serological evidence of the disease as a subset of osteoarthritis

G Morozzi, F Bellisai, A Fioravanti, M Galeazzi

Erosive osteoarthritis (EOA) is considered to be a rare subset of osteoarthritis (OA) characterised by destructive changes involving the proximal interphalangeal and distal interphalangeal joints.1-3 Laboratory findings are usually negative even though a slight increase of erythrocyte sedimentation rate may occur.2,3 Radiologically, central erosions and the “gull wing” deformity characterise the disorder.1 Synovial pathology shows changes consistent with both rheumatoid arthritis (RA) and OA.1,2 Histological examination of synovium from patients with EOA shows lining cell hyperplasia, lymphocytic infiltration, and pannus formation, features indistinguishable from those of RA.1

The relationship between EOA and classical OA is controversial, as some authors consider it to be a separate disease entity, some regard it as one end of the spectrum of OA, and some regard it as an interface between OA and RA.4 A relationship between EOA and RA was first suggested by Ehrlich,1 who noted the superimposition of clinical, laboratory, and imaging findings of RA in 62 of 170 patients initially diagnosed with EOA. Moreover, in the early stages of the disease, the differential diagnosis between EOA and other arthritides, as RA or psoriatic arthritis, may pose a challenge, requiring a number of laboratory tests and investigations.5-8 It is well known that anti-cyclic citrullinated peptides are a specific serological marker for RA, but their role in EOA is still under debate.9-11

REFERENCES

Leflunomide is a pyrimidine synthesis inhibitor with proven teratogenic and fetotoxic effects in animal studies, and its active metabolite is detectable in plasma up to 2 years after discontinuation of the drug. Hence, for this reason the fetus could have in utero exposure to leflunomide up to 2 years after the end of treatment unless an oral cholestyramine regimen, 8 g three times daily for 11 days, is administered to obtain undetectable plasmatic levels.

**Table 1** Characteristics of our patients and controls

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Age (years) Mean (SD)</th>
<th>Sex</th>
<th>Disease duration (years) Mean (SD)</th>
<th>IgM RF positive No (%)</th>
<th>IgG anti-CCP positive No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOA</td>
<td>32</td>
<td>59.3 (11.4)</td>
<td>26F; 6M</td>
<td>8.3 (3.6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NOA</td>
<td>35</td>
<td>61.5 (9.2)</td>
<td>21F; 14M</td>
<td>9.1 (3.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RA</td>
<td>45</td>
<td>52 (16)</td>
<td>32F; 13M</td>
<td>10.6 (6.5)</td>
<td>28 (62)</td>
<td>31 (69)</td>
</tr>
<tr>
<td>Healthy subjects</td>
<td>50</td>
<td>54.4 (18 2)</td>
<td>39F; 11M</td>
<td>–</td>
<td>2 (4)</td>
<td>0</td>
</tr>
</tbody>
</table>

**REFERENCES**


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**Paternal and maternal exposure to leflunomide: pregnancy and neonatal outcome**

M De Santis, G Straface, A Cavaliere, B Carducci, A Caruso

Paternal and maternal exposure to leflunomide: pregnancy and neonatal outcome

M De Santis, G Straface, A Cavaliere, B Carducci, A Caruso

Leflunomide is a pyrimidine synthesis inhibitor with proven teratogenic and fetotoxic effects in animal studies, and its active metabolite is detectable in plasma up to 2 years after discontinuation of the drug. Hence, for this reason the fetus could have in utero exposure to leflunomide up to 2 years after the end of treatment unless an oral cholestyramine regimen, 8 g three times daily for 11 days, is administered to obtain undetectable plasmatic levels.
Leflunomide has been classified as pregnancy category X by the Federal Drug Administration and the manufacturer recommends that for women of childbearing age “treatment with leflunomide must not be started until pregnancy is excluded and it has been confirmed that reliable contraception is being used”.1, 4 Label instructions about paternal exposure recommend a washout procedure to minimise any possible risk.1 To date, there have been no epidemiological human studies of pregnancies after or during paternal or maternal leflunomide exposure, and current knowledge is restricted to a few cases.2, 4

CASE REPORTS
We report on five cases of women who conceived within 2 years after the discontinuation of, or during, leflunomide treatment, and one case of pregnancy during paternal exposure (table 1). They were referred to our teratogen information service between July 2002 and January 2004.

Four women were exposed in the first trimester and one conceived 6½ months after stopping the treatment. Despite our recommendation, none of the women performed the washout procedure, resulting, therefore, in fetal exposure to therapeutic drug levels during organogenesis. In the case of paternal exposure, leflunomide was taken from 6 months before conception and during the whole pregnancy with intercourse without a condom during the gestation.

Three women had voluntary abortions owing to the fear of malformation and three women had live births with healthy babies (two maternal and one paternal exposure). In one of the two cases of maternal exposure the leflunomide treatment was given until 6½ months before the conception, in the other until the 9th week of gestation. They delivered their babies at 39 and 36 weeks, both by caesarean section, weighing 2600 and 2200 g respectively, with normal neonatal outcome. These cases increase the number of previously reported cases, bringing to four the number of live birth normal babies with complete follow up. To date there has been no report of human congenital malformation after prenatal leflunomide exposure. In the case of paternal treatment, a normal baby of 3350 g was delivered by caesarean section at 38 weeks—the first reported case.

DISCUSSION
Seven cases of babies born with congenital malformations were reported by Ostensen referring to a manufacturer’s safety update to 2003 about 164 pregnancies followed up completely in 310 women exposed. Of these 164 cases, 85 were full term pregnancies, 43 were voluntary abortions, and 36 miscarried.5

<table>
<thead>
<tr>
<th>Case No</th>
<th>Maternal age</th>
<th>Exposure period</th>
<th>Washout procedure</th>
<th>Neonatal outcome</th>
<th>Washout procedure</th>
<th>Neonatal follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Maternal</td>
<td>35</td>
<td>Until 6½ months before conception</td>
<td>No</td>
<td>Caesarean section at 39 weeks</td>
<td>Normal male, 2600 g</td>
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</tr>
<tr>
<td>2 Maternal</td>
<td>34</td>
<td>Until 1½ months before conception</td>
<td>No</td>
<td>Voluntary abortion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Maternal</td>
<td>30</td>
<td>Until 9 weeks of gestation</td>
<td>No</td>
<td>Voluntary abortion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Maternal</td>
<td>37</td>
<td>Until 5 weeks</td>
<td>No</td>
<td>Voluntary abortion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Maternal</td>
<td>35</td>
<td>Until 9 weeks</td>
<td>No</td>
<td>Caesarean section at 36 weeks</td>
<td>Normal male, 2200 g</td>
<td></td>
</tr>
<tr>
<td>6 Paternal</td>
<td>31</td>
<td>Throughout pregnancy</td>
<td>No</td>
<td>Caesarean section at 38 weeks</td>
<td>Normal male, 3350 g</td>
<td></td>
</tr>
</tbody>
</table>

Chakravarty et al reported 10 pregnancies in patients taking leflunomide: two cases lost at follow up, two continuing pregnancies, two legal abortions, one spontaneous abortion, two full term healthy babies, and one preterm infant without detailed follow up.4 The scarcity of published data about human pregnancy and neonatal outcome justifies the collection of as many cases as possible because in teratological counselling it is mandatory to consider all known human cases once a drug has been indicated as a potential teratogen in experimental studies. A post-marketing surveillance study has been established by the manufacturer to monitor the outcome of pregnancies, including first trimester exposures.2

At present the possible fetal and neonatal side effects of leflunomide exposure are being investigated by a Canadian OTIS (Organisation of Teratology Information Service) in a prospective study.1 We consider it advisable to warn couples that no controlled or adequate study is available and for inadvertent exposure during pregnancy it is necessary to inform them about the theoretical reproductive risk reported in animal studies and to recommend the washout procedure and accurate fetal ultrasound examinations.

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Spontaneous remission of marginal zone B cell lymphoma in a patient with seropositive rheumatoid arthritis after discontinuation of infliximab-methotrexate treatment

R Thonhofer, M Gaugg, M Kriessmayr, H J Neumann, L Erlacher

A 64 year old female patient with seropositive rheumatoid arthritis (RA) diagnosed in 1997 was referred to our hospital in March 2002, because of high disease activity despite methotrexate (MTX)-sulfasalazine treatment. After exclusion of contraindications infliximab treatment in combination with MTX was started, with good response. At clinical control before the 16th infliximab infusion the patient reported problems with her sinuses. In a computed tomography (CT) scan of that region reactive lymphatic tissue was suspected. Because of the small size (3.5 to 2.8 cm) of the lesion, lymphoma or hypopharynx carcinoma was ruled out. Despite the benign features of the lesion a biopsy was performed, because of the increased risk of malignancy in RA1–3 during disease modifying antirheumatic drug (DMARD) treatment.1–5 Histopathological evaluation and immunohistochemistry led to the diagnosis of an extranodal marginal zone B cell lymphoma of the MALT type. The DMARD treatment was immediately discontinued. Magnetic resonance imaging (MRI) of the head and neck, CT scans of the thorax and abdomen, ultrasound examination of the abdomen and groin, ileocolonoscopy, and gastroduodenoscopy were unremarkable. Biopsies of the stomach showed Helicobacter pylori infection, which was treated according to the recommendations of Mantzaris et al.4 In bone marrow examinations no evidence of lymphoma infiltration was detected. Signs of Sjögren’s syndrome were not present. After consultation of oncologists we decided not to start antineoplastic treatment. We agreed on monthly clinical and laboratory controls. The MRI scan of the head and neck carried out 3 and 6 months after primary diagnosis of the lymphoma showed no evidence of a tumour. Biopsy specimens taken again from the region of interest showed no evidence of lymphoma infiltration. We interpreted the available findings as remission of the lymphoma.

DISCUSSION

Patients with RA are at increased risk of lymphoproliferative disease.1–3 The risk is even higher in patients with increased inflammatory activity.1–3 A proportion of RA associated lymphomas have been attributed to the immunosuppressive effects of DMARDs.4 5 In the case of our patient both risk factors for lymphoma development, high inflammatory activity and DMARD treatment, were present. The patient was treated with MTX for 350 weeks and during that time 4975 mg MTX was ingested. The total dose of infliximab given was 5100 mg. It is unlikely that the marginal zone lymphoma had coexisted for a long time with treatment because of its small size. In addition, reports of the fulminant course of lymphomas after initiating a tumour necrosis factor α antagonist treatment have been published.6–9

Our strategy of waiting and watching after discontinuation of infliximab MTX treatment was based on the low malignant potential of this type of lymphoma and reported findings.3 9 We conclude that in our patient DMARD treatment most probably was responsible for induction of the lymphoma, because complete remission occurred 3 months after stopping the antirheumatic drugs.

There was no difference in steroidal and non-steroidal anti-inflammatory drug use before and after diagnosis of the marginal zone B cell lymphoma, so these drugs are unlikely to have been responsible for the lymphoma remission.

Active RA is a risk factor for lymphoma development. In the follow up of our patient we recorded raised inflammatory activity after discontinuation of DMARD treatment. If disease activity is mainly responsible for the development of the lymphoma, it seems to be unlikely that remission would be achieved during phases of high inflammatory activity.

Discussion continues as to whether a monoclonal expansion of B memory lymphocytes is an inflammatory response to an infectious agent, or a real tumour formation.7 According to published reports the eradication of H pylori infection may induce lymphoma regression.8 However, when all the risk factors in the case of our patient are taken into account, it seems unlikely that antibiotic treatment contributed significantly to remission of the lymphoma.

For clinical routine in cases like ours we recommend that drugs should be withdrawn and the patient monitored closely for evidence of lymphoma regression before initiating specific treatment.

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Anti-CD20 monoclonal antibody (rituximab) as an adjunct in the treatment of giant cell arteritis

A Bhatia, P J Ell, J C W Edwards

We describe a patient with polymyalgia rheumatica/giant cell arteritis (PMR/GCA) whose disease was refractory to a reduction in the dose of her glucocorticoid to an acceptable level. Our patient improved after B lymphocyte depletion but developed respiratory problems. To our knowledge this is the first description of such a case.

CASE REPORT

An 82 year old woman presented with a 4 week history of symptoms consistent with GCA of the temporal arteries and PMR. Of significance in her past medical history she had significant chronic airflow limitation with a FEV₁/FVC (forced expiratory volume in 1 second/forced vital capacity) of 0.71/1.2. Computed tomography of her chest identified a small area of bronchiectasis in the left lower lobe of her chest. Her erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) were, 109 mm/1st h (normal 1–20) and 230 mg/l (normal 0–5.0), respectively. Treatment was started with 50 mg of prednisolone. Three weeks later the patient developed a nasal left upper visual field defect. The dose of prednisolone was gradually reduced over the next 5 months. She was, however, experiencing side effects of her prednisolone treatment, including weight gain, proximal muscle weakness, and the development of a cushingoid face. However, at a dose of 15 mg of prednisolone a day, her symptoms of GCA returned with an increase of the ESR to 53 mm/1st h. Azathioprine 100 mg/day was not tolerated. Four months later while receiving 15 mg of prednisolone her GCA again became symptomatic with transient visual field defect. The dose of prednisolone was gradually reduced over the next 5 months.

At this stage her GCA was not adequately treated and a significant number of lower respiratory tract infections have occurred in our cohort of patients with rheumatoid arthritis treated with B cell depletion (125 cycles) at University College London.5

This case illustrates the possible risk that B cell depletion may pose in patients with marginal respiratory reserve.

DISCUSSION

Our patient’s GCA was inadequately controlled with a dose of prednisolone of 20–30 mg and treatment was associated with significant side effects. An alternative treatment is needed in such cases.

The aetiology of PMR/GCA is unclear, but muscle biopsy specimens from patients with PMR show immunoglobulin deposits around fascicles,1 and serum samples from patients with PMR have been found to contain immune complexes.2 These features suggest that PMR/GCA may be mediated by a particular type of small immune complex. We have previously suggested that binding of such complexes to matrix bound FcRIIIa on fibrillin based microfibrils in muscles and in the internal elastic lamina of arteries may initiate local disease which will lead to symptoms associated with PMR and GCA.3 Taken together with overlapping clinical and immunogenetic features (HLA-DR4) this suggests that PMR/GCA might respond to new treatments being developed for RA.

B lymphocyte depletion treatment has recently proved successful in rheumatoid arthritis.6 On the basis of inadequate control of the GCA and the above theoretical considerations, a decision was made to treat this patient. Our patient’s favourable response suggests that this approach to the management of patients with GCA may be worthy of further investigation.

A significant number of lower respiratory tract infections have occurred in our cohort of patients with rheumatoid arthritis treated with B cell depletion (125 cycles) at University College London.7

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Anti-CD20 monoclonal antibody (rituximab) as an adjunct in the treatment of giant cell arteritis

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Successful treatment of refractory anterior scleritis in primary Sjögren's syndrome with rituximab

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