Determination of anti-CCP antibodies in patients with suspected rheumatoid arthritis: does it help to predict the diagnosis before referral to a rheumatologist?

I K Gao, A Haas-Wöhrle, K G Mueller, H-M Lorenz, C Fiehn


Prognosis in rheumatoid arthritis (RA) depends critically on early diagnosis and timely treatment with immune modulating drugs. As a consequence, early referral and access of patients with suspected RA to rheumatologists is mandatory for the establishment of diagnosis and initiation of treatment.

Measurement of antibodies to cyclic citrullinated peptide (CCP) is a novel and highly specific test for the diagnosis of RA. Detection of anti-CCP antibodies—in particular, if the second generation of anti-CCP2 tests is used—has been shown to be of prognostic significance and to be helpful in early diagnosis of RA.1–9

The goal of this work was to investigate whether the measurement of anti-CCP antibodies alone or in combination with easily determinable parameters of a patient’s complaints and routine laboratory tests might help to identify prospectively patients with a high probability for RA.

For this study 102 patients from a routine rheumatology clinic were examined. All were referred by general practitioners, orthopaedic surgeons, or other non-rheumatological subspecialties because of suspected RA. In all patients the value of the anti-CCP antibody (second generation anti-CCP2 test; Euroimmun, Lübeck, Germany), IgM rheumatoid factor (RF, as determined by nephelometry; Beckman Coulter, Krefeld, Germany), C reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were measured, and physical, laboratory, and radiological examinations were performed. RA was diagnosed according to the American College of Rheumatology (ACR) criteria revised in 1987.10 All patients were questioned about the presence of morning stiffness of the joints and muscles and about the presence of polyarticular pain, which was interpreted as positive if at least four tender joints were reported.

Sensitivity and specificity and—to obtain better information about the diagnostic value with a low pretest probability—the positive and negative predictive values (PPV and NPV) of the tests were calculated. For the latter, the following formulæ were used:

\[
PPV = \frac{a}{a + b} \quad NPV = \frac{d}{c + d}
\]

where \(a\) = test positive, disease positive; \(b\) = test positive, disease negative; \(c\) = test negative, disease positive; \(d\) = test negative, disease negative.

Moreover, the relative risk of fulfilling the ACR criteria for RA, whether or not the test criteria were present, was determined.

Twenty eight of the 102 patients fulfilled the diagnosis of RA according to the ACR criteria (pretest probability of 27%).10 The other patients were classified as having unclassified monarthritis, polyarthritis, or oligoarthritis (n = 21), arthralgias of unknown origin (n = 20), osteoarthritis of the fingers (n = 20), psoriatic arthritis (n = 4), fibromyalgia (n = 3), polymyalgia rheumatica (n = 2), cervicobrachialgia (n = 2), periostitis (n = 1), and reactive arthritis (n = 1).

If a patient was positive for anti-CCP, the PPV, or in other words the probability of fulfilling the ACR criteria for RA, increased to 55% (table 1).

This relatively low predictive value of the anti-CCP test was increased when it was combined with easily obtainable

<table>
<thead>
<tr>
<th>Test Combination</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>RR</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CCP</td>
<td>43</td>
<td>86</td>
<td>55</td>
<td>80</td>
<td>2.7</td>
<td>1.5 to 4.9</td>
</tr>
<tr>
<td>Anti-CCP plus ESR</td>
<td>21</td>
<td>95</td>
<td>60</td>
<td>76</td>
<td>2.5</td>
<td>1.3 to 4.7</td>
</tr>
<tr>
<td>Anti-CCP plus RF</td>
<td>36</td>
<td>91</td>
<td>59</td>
<td>79</td>
<td>2.8</td>
<td>1.6 to 4.9</td>
</tr>
<tr>
<td>Anti-CCP plus CRP</td>
<td>25</td>
<td>97</td>
<td>78</td>
<td>77</td>
<td>3.4</td>
<td>2.1 to 5.8</td>
</tr>
<tr>
<td>Anti-CCP plus polyarticular pain</td>
<td>43</td>
<td>95</td>
<td>78</td>
<td>81</td>
<td>4.0</td>
<td>2.4 to 6.8</td>
</tr>
<tr>
<td>Anti-CCP plus morning stiffness</td>
<td>29</td>
<td>99</td>
<td>89</td>
<td>78</td>
<td>4.1</td>
<td>2.7 to 6.5</td>
</tr>
<tr>
<td>RF</td>
<td>46</td>
<td>78</td>
<td>45</td>
<td>79</td>
<td>2.2</td>
<td>1.2 to 4.0</td>
</tr>
<tr>
<td>RF plus ESR</td>
<td>18</td>
<td>93</td>
<td>50</td>
<td>75</td>
<td>2.0</td>
<td>0.9 to 4.1</td>
</tr>
<tr>
<td>RF plus CRP</td>
<td>18</td>
<td>96</td>
<td>63</td>
<td>76</td>
<td>2.6</td>
<td>1.3 to 4.9</td>
</tr>
<tr>
<td>RF plus polyarticular pain</td>
<td>46</td>
<td>92</td>
<td>68</td>
<td>82</td>
<td>3.8</td>
<td>2.2 to 6.6</td>
</tr>
<tr>
<td>RF plus morning stiffness</td>
<td>30</td>
<td>97</td>
<td>80</td>
<td>78</td>
<td>3.7</td>
<td>2.2 to 6.0</td>
</tr>
</tbody>
</table>

The results of the positive predictive value (PPV) are highlighted. The patient group tested comprised 102 patients with suspected RA who were referred to a rheumatologist. Twenty eight of them fulfilled the ACR criteria for RA (pretest probability of 27%).

PPV, positive predictive value; NPV, negative predictive value; RR, relative risk; 95% CI, 95% confidence interval for relative risk; anti-CCP, anti-CCP values above normal (10 U/l); RF, rheumatoid factor above normal (20 U/l); CRP, C reactive protein value above normal (15 mg/l); ESR, erythrocyte sedimentation rate >20 mm/1st h; morning stiffness, morning stiffness of at least 60 minutes; polyarticular pain, pain in at least four joints or muscular regions.

Table 1 Values of the anti-CCP and the rheumatoid factor (RF) test alone or in combination with different laboratory parameters and patient’s complaints for the diagnosis of RA.
information about the patient’s complaints: if a patient had a positive anti-CCP test and at the same time morning stiffness of at least 60 min the PPV was 89%. In fact, the only patient who was positive for both measures without fulfilling the ACR criteria for RA was thought by the examining rheumatologist to have early RA. Polyarticular pain is a symptom which was present in all patients with RA and, additionally, in the patients with arthralgias, undifferentiated polyarthritis, fibromyalgia and polymyalgia rheumatica. If anti-CCP positive patients had polyarticular pain, a PPV of 78% and a NPV of 81% was obtained. In contrast, the combination of anti-CCP and RF, as was suggested by other reports, did not result in a similar increase of the PPV or NPV (59% and 79%, respectively). The rather low sensitivity and specificity of the anti-CCP test (table 1) was in accordance with other reports with similar results obtained in unselected rheumatological patients who were not subjected to a prolonged follow up.11

In conclusion, if information about morning stiffness of the joints or polyarticular pain is added, anti-CCP gives us a tool which more accurately predicts the presence of RA. This tool might be important to identify patients with early RA and facilitate a more precise selection of patients for rapid access to rheumatologists.

Safety of 15-deoxyspergualin in the treatment of glomerulonephritis associated with active systemic lupus erythematosus

H-M Lorenz, M Grunke, J Wendler, P A Heinzl, J R Kalden

Optimal treatment for patients with relapsing lupus nephritis remains unclear. The ability of 15-deoxyspergualin (gusperimus: 15-DSG) to suppress systemic lupus erythematosus (SLE)-like diseases has been demonstrated in animals and humans.14 15-DSG exerted no nephrotoxicity or hepatotoxicity but reversibly induced leucocytopenia.4 6

In this study we aimed at evaluating the safety of 15-DSG in the treatment of glomerulonephritis associated with SLE.

CASE REPORTS

Table 1 shows the patient characteristics. 15-DSG was provided by Nippon Kayaku Co Ltd, Tokyo, Japan. Patients gave their informed consent, and 15-DSG 0.5 mg/kg normal body weight (height in cm minus 100)/day was self administered subcutaneously for 14 days, followed by a break of 7 days (=1 cycle). The dose was adjusted (dependent on efficacy or safety, or both) after cycles 4 and 6 to 0.35 mg/kg and 0.25 mg/kg, or 0.7 mg/kg and 1.0 mg/kg.

Patient 1

After a bolus, daily corticosteroids could be decreased to 5 mg after 9 weeks. The patient received six cycles of 15-DSG without major problems. Leucocyte counts were always >4 x 10^9 cells/l, no infection was seen, no (serious) adverse events and occurred with the exception of paraguesia. GN resolved and her SLE associated activity measures improved (table 1, fig 1). After the sixth cycle the patient was switched from 15-DSG to a combination of ciclosporin A (CSA) and azathioprine, and later azathioprine alone. Renal function was normal at the end of the trial, SELENA-SLEDAI (Safety of Oestrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index) decreased from 12 to 0, and the corticosteroid dosage was reduced to 5 mg/day.

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Treatment was switched to 150 mg oral cyclophosphamide. During her last visit to our clinic the anaemia had improved (115 g/l), proteinuria was stable (1100 mg/day), and erythrocyturia was present without signs of active GN.

**Patient 3**

After a bolus, corticosteroids could be tapered to 5 mg/day (end of cycle 3). Maximum proteinuria was 10 300 mg/day at entry into 15-DSG treatment (fig 1; table 1). By the end of cycle 3, proteinuria had decreased to <1000 mg/day (fig 1). Within cycles 3 and 4 she had a prolonged urogenital infection, possibly related to leucocytopenia (3.9×10^3 cells/l at the end of cycle 3, 1.7×10^4 cells/l at the end of cycle 4). She now experienced a flare of her GN (increased proteinuria up to 7100 mg/day at the end of cycle 5; fig 1). We increased the corticosteroids to 60 mg/day, continued 15-DSG as previous success was excellent, but decreased the dosage to 0.35 mg/kg/day because of (possibly 15-DSG-related?) leucocytopenia and the infectious episodes. In addition, we prescribed low dose CSA (2.5 mg/kg/day) as 15-DSG had been successfully used together with CSA.7 Subsequently, corticosteroids could be tapered to 5 mg/day within 7 weeks. Proteinuria decreased to 780 mg/day (cycle 9; fig 1); creatinine was always normal. No infections were reported during the 15-DSG + CSA treatment. She is now receiving CSA alone. SELENA-SLEDAI decreased from 14 to 6; the corticosteroid dosage was reduced to 5 mg/day at the end of the study.

**CONCLUSION**

As far as we know, this is the first report on safety of 15-DSG in the treatment of active SLE-GN. Two of the three patients had non-severe infectious episodes, but otherwise 15-DSG was well tolerated. We are currently conducting a phase I/II trial with 15-DSG in patients with SLE and active GN which will also focus on efficacy measurement.

**ACKNOWLEDGEMENTS**

We thank our patients for their collaboration and help in performing this trial.

**Authors’ affiliations**

H-M Lorenz, Division of Rheumatology, Department of Medicine V, University of Heidelberg, Heidelberg, Germany

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**Table 1** Details of the patients’ history, especially previous immunosuppressive treatment, signs of SLE-GN activity or general SLE activity at entry, and indicators for response during/after 15-DSG treatment

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age (years)</th>
<th>First diagnosed</th>
<th>Previous treatment</th>
<th>Signs of SLE-GN activity/general SLE activity</th>
<th>Indicators for response</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>23</td>
<td>1993</td>
<td>Meaningsial proliferative GN, later diffuse proliferative meaningsial GN (biopsy 3 months before 15-DSG), arthralgias, serology</td>
<td>CYC IV 1993–94, MTX 1994–95, AZA 1995–2002, CYC IV 2002</td>
<td>Increasing proteinuria despite CYC (max 6 g/day), active urin sediment, arterial hypertension, anaemia, dDNA Abs titre rising, C3/C4 decreased/arthralgias</td>
<td>Loss of oedema, fatigue, arthralgias, active urin sediment, arterial hypertension improvement in: proteinuria (1.1 g/day) anaemia, required steroid dosage unchanged: dDNA Abs titre, C3, C4</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>1998</td>
<td>Arthritis, leucocytopenia, molar rash, serology, meaningsial GN (biopsy 2 months before 15-DSG), Antimalarial drugs 1998–99, MTX 1999–2000, AZA 2000, CYC IV 2000–01, AZA 2001–02, MMF 2002–03</td>
<td>Increasing proteinuria despite MMF (max 10.3 g/day), active urin sediment, arterial hypertension, anaemia, dDNA Abs titre rising, C3/C4 decreased, oedema/rash, leucocytopenia, molar rash, serology, night sweat</td>
<td>Loss of oedema, anaemia, arthralgias, haematuria, molar rash, start of detection of auto-Ab, arthralgias, required steroid dosage, arterial hypertension unchanged: rash, leucocytopenia (15-DSG + SIE induced), Sm, RNP Ab</td>
<td>15-DSG 0.5 mg/kg/day cycles 1–4, flare cycles 4–5 after infection (leucocytopenia), steroids increased, 15-DSG 0.35 mg/kg/day + CSA cycles 5–9</td>
</tr>
</tbody>
</table>

CYC, cyclophosphamide; CSA, ciclosporin A; MTX, methotrexate; AZA, azathioprine; MMF, mycophenolate mofetil.
Autoimmune hepatitis associated with infliximab in a patient with psoriatic arthritis

V Germano, A Picchianti Diamanti, G Baccano, E Natale, A Onetti Muda, R Priori, G Valesini

We read with interest the debate about liver toxicity of infliximab in psoriatic arthritis (PsA).1 2 We describe the case of a 53 year old woman with a 4 year history of refractory PsA who developed transaminasitis during infliximab treatment.

CASE REPORT

Despite combination treatment (ciclosporin 300 mg/day, fluocortolone 10 mg/day, and methotrexate (MTX) 15 mg/week intramuscularly), disease activity was still high, and intravenous infliximab at 3 mg/kg was administered initially at weeks 0, 2, 6, 14 and then every 6 weeks. Ciclosporin was withdrawn.

Within 3 weeks she improved, fluocortolone was gradually stopped while methotrexate (MTX) 20 mg/week intramuscularly, was continued. After the sixth infusion, she developed a mild transaminasitis and MTX, initially tapered, was stopped. After the eighth infusion transaminases continued to rise and in the absence of any other plausible cause, infliximab was withdrawn.

She was admitted to our department with persistently high values of aspartate aminotransferase and alanine aminotransferase and a flare of PsA.

The erythrocyte sedimentation rate was 30 mm/1st h, C reactive protein 170 mg/l, aspartate aminotransferase 143 IU (normal 5–40), alanine aminotransferase 234 IU (normal 5–55), anti-patelial cell antibodies and liver and kidney microsomal antigen were absent, and serology for hepatitis viruses, cytomegalovirus and Epstein-Barr virus, was negative. The new appearance of anti-dsDNA (IgG) 1/20 (indirect immunofluorescence on Citrhidium luciliae), anti-smooth muscle antibodies (ASMA) 1/640 was observed, while the titre of antinuclear antibodies (ANA), previously present at a serum dilution of 1/80, increased to 1/160. Liver ultrasonography showed steatosis. A liver biopsy revealed intense and diffuse portal lymphoplasmacytic, granulocytic inflammatory infiltration and severe interface hepatitis. Mild perportal fibrosis was also evident (figs 1A and B). Fluocortolone 20 mg daily was started and the joints improved. Within a few months, transaminases declined and finally normalised; ANA remained positive, while anti-dsDNA and ASMA disappeared.

DISCUSSION

Feletar et al found a high incidence of liver toxicity in patients with PsA treated with infliximab,1 even if, as Provenzano pointed out,2 in some cases this association was debatable because of the concomitant use of MTX and the lack of exclusion of viral infections. In one of the largest studies on the use of infliximab in rheumatoid arthritis (RA),3 no liver disease was recorded, but recently two possible cases of liver disease associated with infliximab use have been observed in Crohn’s disease and PsA.4 5 In our patient the chronological relationship between transaminasitis and treatment (fig 2), linked to the peculiar histology, is suggestive of autoimmune hepatitis induced by infliximab. The high titre of ASMA, notoriously associated with autoimmune hepatitis, supports this hypothesis. Our patient was concomitantly treated with MTX for almost 30 weeks. MTX can produce steatosis, fibrosis and, ultimately, cirrhosis; its hepatotoxicity in psoriasis is well known. A 2.5–5.0-fold increase in liver damage for psoriasis compared with RA has been reported.6

Moreover, patients with PsA seem more prone to liver toxicity during infliximab treatment than those with RA.1 A dissimilar toxicity profile for disease modifying antirheumatic drugs in various diseases has been linked to differences in pathophysiology, genetic background, drinking behaviour, and age.
However, our patient had received less than a third (900 mg in the past 4 years) of the cumulative dose known to be a risk for hepatic toxicity. In this case, infliximab might have led to the acute damage—that is, severe portal inflammation and initial neoductulogenesis, whereas MTX might have been responsible for the chronic hepatic injury—that is, mild fibrosis and steatosis. The introduction of corticosteroids probably hastened liver recovery with subsequent normalisation of transaminases.

The appearance of autoantibodies, occasionally associated with mild and transitory autoimmune diseases, during antitumour necrosis factor α treatment has been documented and reflects the complex relationship between tumour necrosis factor α blockade and autoimmunity. This report confirms the need to monitor liver enzymes carefully and perform liver biopsy, if necessary, not only in patients with PsA using combination treatment with MTX and infliximab but also for those using infliximab alone, especially in the presence of pre-existent serological signs of autoimmunity such as ANA. Such signs might be a risk factor for further development of clinical autoimmunity during infliximab treatment.

**Authors’ affiliations**

V Germano, A Picchianti Diamanti, G Baccano, R Priori, G Valesini, Division of Rheumatology, University of Rome “La Sapienza”, Italy

E Natale, A Onetti Muda, Department of Experimental Medicine and Pathology, University of Rome “La Sapienza”, Rome

Correspondence to: Professor G Valesini, Divisione di Reumatologia, Dipartimento di Terapia e Clinica Medica Applicata, Policlinico Umberto I, Viale del Policlinico, 00161 Roma, Italy; g.valesini@uniroma1.it

Accepted 14 March 2005

**REFERENCES**


Letters

Alleviation of polyarticular syndrome in multicentric reticulohistiocytosis with intravenous zoledronate

C P Mavragani, K Batziou, K Aroni, D Pikazis, M N Manoussakis


A 67 year old previously healthy women presented with a 12 month history of generalised symmetric arthralgias and bilateral hand contractures. Her past medical history was unremarkable, except for heavy smoking.

On physical examination, she had tight incapacitating flexion contractures of both hands, and small cutaneous non-tender well circumscribed nodules (3–6 mm diameter) on the dorsum of the fingers and over the proximal and distal interphalangeal joints (fig 1). A symmetric polyarthralgia affecting the shoulders, elbows, proximal and distal interphalangeal joints, and the knees was prominent. Blood counts, biochemical profile and inflammatory markers, antinuclear antibodies, and rheumatoid factor were within normal limits. A hand x-ray examination showed erosive deforming arthropathy of the styloid processes. Biopsy samples of a skin nodule and of synovial membrane disclosed infiltrates of multinucleated giant cells and histiocytes, indicative of multicentric reticulohistiocytosis (MRH). The infiltrating histiocytes were macrophages, as illustrated by positive staining for CD68 marker and negative staining for S-100 (Langerhans’ dendritic cell marker) and HHF-35 actin (fibroblast marker).

The well described association of MRH with malignancies1–3 had prompted the screening for underlying malignancies, which disclosed a 10-fold increase of CA-125. A pelvic computed tomographic scan was normal; however, magnetic resonance imaging showed the presence of a small well circumscribed mass at the left parametrial space, which was subsequently removed by laparotomy and diagnosed as poorly differentiated ovarian adenocarcinoma without metastatic spread. The patient was given intravenous combination treatment of carbaplatin and cyclophosphamide.

Three months later, the cutaneous nodules resolved, but the polyarthritis persisted and the patient gradually developed a generalised painful stiffness of the trunk and extremities, which required the use of narcotic analgesics and confined her to bed. Intravenous methylprednisolone pulses were also administered, without response. Based on the recently reported effectiveness of intravenous alendronate for MRH,4 zoledronate (4 mg) was given intravenously, because alendronate was unavailable locally. Two weeks later, the stiffness and arthralgias were dramatically reduced. The patient is now completely free of pain and ambulatory.

DISCUSSION

MRH is a rare disorder of unknown cause, characterised by destructive symmetric arthritis associated with cutaneous papulonodular lesions. In about one third of patients, musculoskeletal symptoms may precede or follow an underlying malignancy (such as breast and ovarian cancer, melanoma or mesothelioma).5 MRH should be differentiated from fibroblastic rheumatism, which is also rare.6 Although strict differentiating histological criteria are lacking, multinucleated foreign body-type giant cells appear to denote MRH, whereas the predominance of myofibroblasts and excessive collagen production characterises fibroblastic rheumatism.5 The inclusion of fibroblastic rheumatism in the broader spectrum of non-Langerhans’ cell histiocytosis has been recently proposed.7

To date, the decision for systemic therapeutic intervention in MRH remains largely empirical. Treatment with steroids and various cytotoxic agents is of questionable efficacy,7 and in our patient it resulted only in resolution of the cutaneous nodules. Recently, the beneficial role of tumour necrosis factor blockers has been suggested7; however, these are contraindicated in patients with concomitant neoplasia. Intravenous alendronate has been also advocated in the management of MRH.4 In our patient, the administration of the parenteral bisphosphonate zoledronate, so far used for the treatment of osteoporosis4 and of hypercalcaemia of malignancy,7 dramatically alleviated the incapacitating joint symptoms.

The precise mechanism of bisphosphonate action on MRH is unclear. However, after intravenous injection, bisphosphonates have been previously shown to deposit in the reticuloendothelial system,9 to inhibit the metalloprotease activity and matrix metalloproteinase-9 expression of infiltrating macrophages,10 and to induce apoptosis of macrophage-like cells.11 Therefore, one may speculate that their favourable effect in MRH is due to the inhibition of tissue infiltration by histiocytes, possibly through induction of apoptosis.

ACKNOWLEDGEMENTS

We are indebted to Professor HM Moutsopoulos for inspiration and fruitful suggestions.

Authors’ affiliations
C P Mavragani, K Batziou, D Pikazis, M N Manoussakis, Department of Pathophysiology, Medical School, National University School of Athens, Athens, Greece
K Aroni, Department of Pathology, Medical School, National University School of Athens, Athens, Greece

Figure 1 Contraction flexures and cutaneous nodules in the dorsum of the fingers (arrows).
Acetaminophen may act through β endorphin
H Sprott, H Shen, S Gay, A Aeschlimann

Acetaminophen, also known as paracetamol, is a non-steroidal anti-inflammatory drug (NSAID) with potent antipyretic and analgesic actions but with very weak anti-inflammatory activity. The mechanism of action of acetaminophen is still not clearly understood. It has no known endogenous high affinity binding sites. In addition, acetaminophen does not appear to share with NSAIDs the ability to inhibit peripheral cyclo-oxygenase (COX) activity. Although various biochemical studies point to inhibition of central COX-2 activity, the existence of a COX activity that is selectively susceptible to acetaminophen (COX-3?) is an alternative hypothesis. However, this may hold true only for the dog. Database analysis of human COX-1 showed a frame shift induced by intron 1, possibly showing COX-3 to be a virtual protein in humans.

Our studies in osteoarthritis provide evidence of a clear effect of acetaminophen on β endorphin levels in plasma (fig 1) compared with rofecoxib 25 mg/day. Plasma β endorphin levels decreased in 10 patients with osteoarthritis after 1 month of treatment with up to 4 g/day acetaminophen orally (p = 0.017) as well as after 3 months of treatment (p = 0.028). Whereas, there were no changes in the rofecoxib group after 1 month (p = 0.73) and 3 months (p = 1.00), respectively.

Acetaminophen may play a part in the delivery of peripheral β endorphin to their receptors and thereby relieve pain.

Authors’ affiliations
H Sprott, H Shen, S Gay, Centre of Experimental Rheumatology, Department of Rheumatology and Institute of Physical Medicine, University Hospital Zurich, Switzerland
A Aeschlimann, RehaClinic Zuzach, CH-5330 Zuzach, Switzerland

Correspondence to: Dr H Sprott, Centre of Experimental Rheumatology, Department of Rheumatology and Institute of Physical Medicine, University Hospital, Gloriatrasse 25, CH-8091 Zurich, Switzerland; haiko.sprott@usz.ch

Accepted 7 February 2005

REFERENCES
RefRACTory adult onset Still’s disease and hypersensitivity to non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors: are biological agents the solution?

E H J G Aarntzen, P L C M van Riel, P Barrera


A dult onset Still’s disease (AOSD) is an autoimmune disorder characterised by periodic high fever, arthritis, and typical evanescent rashes. Non-steroidal anti-inflammatory drugs (NSAIDs) are the preferred treatment. In severe cases several disease modifying antirheumatic drugs, thalidomide, and intravenous immunoglobulin have been used. More recently, successful treatment with tumour necrosis factor α (TNFα) blocking agents1 2 and interleukin (IL) 1 neutralisation3 has also been reported.

Hypersensitivity to NSAIDs, often characterised by urticaria, angio-oedema, and asthma, has been well documented, and several studies indicate that anaphylactic reactions are related to the inhibition of cyclo-oxygenase-1 (COX-1) enzyme4–6 and that selective COX-2 inhibitors can be safe in these patients. Here we report a case of AOSD complicated by coexisting hypersensitivity to acetaminophen (paracetamol), aspirin, NSAIDs, and also to selective COX-2 inhibitors. TNFα neutralisation controlled the fever, but not the AOSD related rashes and polyarthritis or the anaphylactic reactions to NSAIDs and COX-2 inhibitors. Treatment with IL1 receptor antagonist led to full remission of the AOSD.

CASE REPORT

A patient, with known AOSD for 22 years, was admitted to our centre with a 3 week history of spiking high fever, chills, skin rash, cough, and a sore throat. Physical examination disclosed a typical AOSD related rash, polyarthritis, and enlarged inguinal lymph nodes without hepatosplenomegaly. Laboratory examination showed an increased acute phase reaction and a normochromic normocytic anaemia; white blood cell count, platelet count, and liver function tests were normal. Serological tests for viral infections, toxoplasma, Bartonella, blood and urine culture rheumatoid factor, and antinuclear antibodies were all negative.

In the past the AOSD had followed a polycyclic course, which had been successfully treated with several NSAIDs alone or in combination with acetaminophen for 10 years. In 1993, she developed an allergic reaction with angio-oedema to naproxen (fig 1), and later also to acetaminophen and sodium salicylate. Methotrexate was used for the next 10 years, but frequently corticosteroids were needed to treat the AOSD exacerbations. To avoid chronic use of corticosteroids, etanercept was started in May 2003 and the corticosteroids were tapered. This led to exacerbations of a mild polyarthritis and worsening of the rash but no fever. Because selective COX-2 inhibitors may be safe in patients with intolerance to NSAIDs,4 5 rofecoxib was successfully added to etanercept without intolerance. However, a second challenge with rofecoxib resulted in severe angio-oedema and urticarial rash and the same occurred after challenges with celecoxib and etoricoxib. IL1 receptor antagonist was started in December 2004, leading to a full remission of all AOSD related symptoms despite the withdrawal of long term steroid treatment.

DISCUSSION

Our case illustrates that TNFα blocking agents are only partially effective in the treatment of refractory AOSD. Partial or limited efficacy of these agents has also been also observed in patients with systemic onset juvenile idiopathic arthritis.7 8 Our case and several other reports suggest that it is not TNFα
but IL1 which has a pivotal role in the pathogenesis of AOSD
and systemic onset juvenile idiopathic arthritis.5 In these
diseases and in other rare disorders with a single amino acid
mutation in the NALP-3 gene which results in increased IL1
secretion, IL1 blockade seems to be the preferred treatment.6

Furthermore, our case suggests that hypersensitivity to
NSAIDs is not exclusively mediated by COX-1 blockade, but
can also be provoked by selective COX-2 inhibitors that can
function as haptens, resulting in anaphylaxis upon next
exposure.5 Our case shows that these reactions are not
mediated by TNFα and not altered by TNFα neutralisation.

Authors’ affiliations
E H J G Aarnntzen, P L C M van Riel, P Barrera, Department of
Rheumatology, Radboud University Nijmegen Medical Centre, PO Box
9101, 6500 HB Nijmegen, The Netherlands

Competing interests: none

Correspondence to: Dr P Barrera, p.barrera@reuma.umcn.nl

Accepted 24 June 2005
Published Online First 13 July 2005

Distal degeneration of sensory and autonomic cutaneous
nerve fibres in systemic sclerosis
V Provitera, M Nolano, N Pappone, C di Girolamo, A Stancaenelli, F Lullo, C Crisci, L Santoro

METHODS AND RESULTS
We obtained 3 mm punch skin biopsy samples from the
distal thigh and distal leg in 11 consecutive 34–70 year old
female patients with systemic sclerosis (SSc), identified by
the American College of Rheumatology classification criteria.3
We excluded patients who had been exposed to potentially
neurotoxic exogenous or endogenous conditions. The skin
appeared sclerotic in 4/11 patients in the leg and in 3/11 in
the thigh (table 1). In four patients a further skin sample
from fingertip was taken to evaluate myelinated fibres. None
of the patients complained of sensory disturbances, and
neurological and neurophysiological evaluations were normal
except in two patients, in whom a conduction velocity study
showed the presence of an entrapment syndrome. Patient
morphological findings were compared with data from a

range 34–65 years).

We studied innervation and dermal vasculature in
affected and apparently normal skin of sclerodermic
patients to evaluate the involvement of different
nerve fibre groups and to determine a possible correlation
with vascular damage in this disease. Immunohistochemical
analysis and confocal microscopic examination of skin biopsy
samples were used.

We obtained 3 mm punch skin biopsy samples from the
distal thigh and distal leg in 11 consecutive 34–70 year old
female patients with systemic sclerosis (SSc), identified by
the American College of Rheumatology classification criteria.3
We excluded patients who had been exposed to potentially
neurotoxic exogenous or endogenous conditions. The skin
appeared sclerotic in 4/11 patients in the leg and in 3/11 in
the thigh (table 1). In four patients a further skin sample
from fingertip was taken to evaluate myelinated fibres. None
of the patients complained of sensory disturbances, and
neurological and neurophysiological evaluations were normal
except in two patients, in whom a conduction velocity study
showed the presence of an entrapment syndrome. Patient
morphological findings were compared with data from a
group of 16 healthy volunteers (nine male, seven female, age
range 34–65 years).

Skin biopsy specimens were processed according to
previously published procedures.2 Floating sections were
immunostained using a panel of primary antibodies, includ-
ing the pan-neuronal marker anti-protein gene product
(PGP) 9.5, anti-myelin basic protein for myelinated fibres,
anti-vasoactive intestinal peptide (VIP) to mark autonomic
nerve fibres, and anti-collagen IV to visualise basement
membrane and blood vessels.

We quantified, as previously described, epidermal nerve
fibres (ENFs) per linear millimetre,3 Meissner corpuscles
(MCs), and myelinated papillary endings per square milli-
metre4 on confocal images using image analysis software
(Neurolucida, Microbrightfield Inc, Colchester VT, USA;
ScionImage, Scion Corporation, Frederick, MD, USA). On
the same images used to quantify ENF density, we measured
blood vessel density in µm2/100 µm of dermal tissue within
250 µm below the basement membrane.

We found a significant loss of ENFs in sclerodermic
patients in all the examined sites (table 1) without a distal-
proximal gradient, a poor subepidermal neural plexus, and a
reduced innervation of sweat glands, blood vessels, and
arrector pilorum muscles compared with controls. These
findings, evident in apparently unaffected areas (figs 1E and
F compared with 1A and B), were more severe in clinically
involved skin (figs 1C and D compared with 1A and B) and
affected both sensory and autonomic unmyelinated nerve
fibres as demonstrated by PGF and VIP immunostainings.

The mean (SD) density of blood vessels measured in µm2/100 µm of dermal tissue, was 6.4 (2.9) and 8.7 (4.7),
respectively, in the thigh and leg of patients with SSc. These
values significantly correlated with the density of epidermal
nerve fibres in both sites (r² = 0.51; p<0.05 at the thigh and
r² = 0.58; p<0.05 at the leg). In glabrous skin we found a
significant reduction of MC density compared with controls,
with a number of intrapapillary myelinated fibres still within
the normal range. Moreover, evident structural abnormalities
of the surviving mechanoreceptors and predegenerative

References
aspects of myelinated fibres, such as swellings or vacuolisation, were present.

**DISCUSSION**

Our data indicate that the cutaneous nerves in SSc are impaired. This mainly involves the unmyelinated sensory and autonomic nerve fibres, but does not completely spare the large fibres. The observation that the loss of ENFs was more significant in subjects with an evident reduction of vascular bed suggests that ischaemia may have a role in determining the neuropathic process. However, we cannot rule out the possibility that early biohumoral changes, demonstrated in apparently unaffected skin, may induce both neural and vascular damage. We speculate that the abnormalities of terminal innervation seen in the skin may be present in multiple organs in SSc. This neuropathic process, affecting

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**Figure 1** Confocal micrographs of cutaneous innervation in thigh skin samples. (A) Normal skin, (C) affected, and (E) apparently unaffected skin from a patient with SSc: samples are triple stained to visualise nerve fibres (rPGP in yellow-green), basement membrane and vessels (mColIV in red), and endothelium and epidermis (ULEX Europaeus in blue). Sweat gland images in a healthy subject (B) and in scleroderma patients from affected (D) and apparently normal (F) skin, are double stained to visualise nerve fibres (rPGP in yellow-green) and vessels (mColIV in red). A derangement of dermal architecture, of subepidermal neural plexus, and a marked reduction of ENF density are evident in affected and, although to a lesser extent, in apparently normal skin of patients with SSc (C and E compared with A). A loss of nerve fibres innervating dermal annexes such as arrector pili muscles (E compared with A) and sweat glands (D and F compared with B) in skin from sclerodermatic patients is also evident. Bar = 50 μm. E, epidermis; ENFs, epidermal nerve fibres; BM, basement membrane; V, blood vessels; SNP, subepidermal neural plexus; APM, arrector pili muscle.
primarily unmyelinated nerve fibres, may contribute to the production of abnormalities that are common in SSc, like visceral dysmotility and cardiac arrhythmias.

Table 1  Clinical and morphological data in sclerodermic patients compared with mean values in the control group

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Disease duration (years)</th>
<th>Subset</th>
<th>ENF thigh*</th>
<th>Dermal vessels density thigh†</th>
<th>ENF leg*</th>
<th>Dermal vessels density leg†</th>
<th>ENF fingertip*</th>
<th>Meissner corpuscles‡</th>
<th>Myelinated intrapapillary endings‡</th>
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<tr>
<td>1</td>
<td>62</td>
<td>1</td>
<td>lSSc</td>
<td>13.8</td>
<td>8.1</td>
<td>10.3</td>
<td>8.7</td>
<td>7.4</td>
<td>20.5</td>
<td>42.7</td>
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<td>dSSc</td>
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<td>–</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
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<td>lSSc</td>
<td>6.0</td>
<td>2.2</td>
<td>3.5</td>
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<td>–</td>
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<td>lSSc</td>
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<td>9.6</td>
<td>9.3</td>
<td>9.2</td>
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<td>–</td>
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<td>5</td>
<td>34</td>
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<td>dSSc</td>
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<td>4.7</td>
<td>(0.0)</td>
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<td>–</td>
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<td>dSSc</td>
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<td>11.8</td>
<td>(0.0)</td>
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<td>–</td>
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<td>60</td>
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<td>7.1</td>
<td>(0.0)</td>
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<tr>
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<td>2.2</td>
<td>15.0</td>
<td>37.2</td>
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</table>

Mean (SD)

Patients 56.0 (12.6) 4.3 (3.7) 9.1 (8.1) 6.4 (2.9) 7.4 (7.1) 8.7 (4.7) 3.8 (2.5) 14.8 (4.9) 40.5 (18.8)
Controls 52.6 (10.0) – 27.2 (7.7) – 19.1 (8.1) – 7.5 (3.6) 29.7 (11.2) 51.9 (20.7)

Significance p<0.00011 p<0.0011 p<0.0051 p<0.051 p<0.0051 p<0.051 p=0.341

ENF density values from affected skin are shown in parentheses.

lSSc, limited cutaneous systemic sclerosis; dSSc, diffuse cutaneous systemic sclerosis.

1 Expressed as the number of epidermal nerve fibres/mm; 2 expressed in µm2/100 µm2 of dermal tissue; 3 expressed as the number of structures/mm2;

1 Comparison of density values in the control group and in all skin samples from patients with SSc; 2 comparison of density values in the control group and in samples of apparently unaffected skin in patients with SSc.

Accepted 30 March 2005

REFERENCES


