PostScript

MATTERS ARISING

Long acting somatostatin analogue for the treatment of refractory RA

We read with interest the article by Paran and colleagues on a pilot study of a long acting somatostatin analogue for the treatment of refractory rheumatoid arthritis (RA).[1] The role of peptidergic sensory neurons and the "neurogenic inflammation" in RA and, particularly, in the involvement of substance P (SP) in the articular destruction in experimental arthritis has been demonstrated.[2] High levels of SP have been detected in synovial fluid[3] and plasma[4] samples of patients with RA. It has also been shown that somatostatin inhibits SP release from sensory nerves.[5] Matucci-Cerinic *et al* have demonstrated that intra-articular somatostatin induces clinical improvement in patients with RA.[6]

We would like to report our experience, based on a pilot study of treatment for RA with somatostatin analogue (sandostatin). Eleven female patients with classical or definite RA according to American Rheumatism Association criteria were selected for this study with a mean age of 57.4 years and average duration of disease period of 14.5 years. All the patients had previously received multiple disease modifying antirheumatic drugs, but complete remission could not be achieved. Patients who had received any drug except non-steroidal anti-inflammatory drugs during the eight weeks before the start of the study, who had severe cardiovascular, pulmonary, renal, or hepatic disease, and who were hypersensitive against penicillin analogue were not included in the study group. During this treatment, patients were allowed to receive piroxicam and indometacin group NSAIDs.

Sandostatin (Sandoz) is a synthetic octapeptide derivative of naturally occurring somatostatin with similar pharmacological effects, but with a considerably prolonged duration of action. Sandostatin 0.1 mg was injected subcutaneously every day for eight weeks.

Clinical evaluations, such as joint tenderness, grip strength, duration of morning stiffness, 15 m walking time, and visual analogue scale for pain, were performed by the same investigator at baseline and at two, four, six, and eight weeks. Sedimentation rate, C reactive protein (CRP), alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, fasting plasma glucose, leucocytes, thrombocytes, and erythrocyte levels were measured at two, four, six, and eight weeks. Additionally, abdominal ultrasound was carried out at the fourth and eighth week of treatment.

Table 1 shows the patients' characteristics at the beginning of the study.

Eleven patients were enrolled in the study. The data from two patients were not included in the statistical analyses. One of them had severe diarrhoea and abdominal cramps within the first week of the somatostatin treatment and treatment was stopped. A persistent increase in fasting plasma glucose level was seen in the other patient and she also left the study.

In comparison with the values recorded at the beginning of the study, pain intensity and walking time had decreased and the left hand grip strength had increased by the fourth week; these differences were not statistically significant. There was a significant reduction in the duration of morning stiffness and in joint sensitivity ($p<0.05$). Two female patients were withdrawn from the follow up at the end of the fourth week. At the end of the eighth week, the remaining seven patients had a reduced duration of morning stiffness, a decrease in walking time, and an increase in the grip strength of both hands. The laboratory variables CRP and erythrocyte sedimentation rate (ESR) were reduced. None of these differences were significant ($p>0.005$). In comparison with entry values, a significant decrease was found in pain intensity and joint sensitivity ($p<0.05$). Neither adverse clinical effects nor changes in laboratory values were serious enough to stop the treatment with somatostatin in any patient.

Our results are similar to those of Paran and colleagues[1]; a significant improvement ($p<0.05$) was noted in the mean visual analogue scales of pain, doctor's and patient's global assessment of disease activity, and in the mean number of swollen joints, but no statistically significant improvements were seen in the mean number of tender joints. Although there was a trend towards reduction of the mean ESR and CRP values of the 10 patients as a group, this did not reach statistical significance. However, these findings are insufficient to conclude that somatostatin is useful and effective in RA treatment. We hope that the results of these studies will stimulate further research on the use of somatostatin in RA, particularly in determining the appropriate effective dose.

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Table 1 Patients' characteristics at the beginning of the study

Patient	Age	Duration of RA	Disease stage*	Drugs used before somatostatin†	Drugs used while taking somatostatin	Rheumatoid factor
1	60	13	III	1, 2, 6, 7, 9	Indometacin	+
2	66	20	III	1, 2, 6, 7, 9	Indometacin	+
3	70	25	III	1, 2, 4, 6, 8, 9	Indometacin	+
4	60	7	II	1, 3, 6, 9	Piroxicam	+
5	63	30	III	1, 2, 6, 9	Indometacin	–
6	55	8	II	1, 3, 6, 7, 9	Indometacin	+
7	60	15	III	1, 4, 6, 7, 9	Indometacin	+
8	42	8	II	1, 2, 6, 9	Piroxicam	+
9	55	7	II	1, 2, 6, 8, 9	Indometacin	+
10	57	14	III	1, 2, 3, 6, 9	Indometacin	+
11	55	6	II	1, 5, 6, 9	Indometacin	+

*Classified using the criteria of Steinbrocker, *et al*.
†Drugs: 1, non-steroidal anti-inflammatory drug; 2, hydroxychoroquine; 3, gold; 4, penicillamine; 5, methotrexate; 6, corticosteroids; 7, cyclosporin; 8, interferon α; 9, sulfasalazine.

References

1 **Paran D**, Elkayam O, Mayo A, Paran H, Amit M, Yaron M, *et al*. A pilot study of a long acting somatostatin analogue for the treatment of refractory rheumatoid arthritis. Ann Rheum Dis 2001;60:888–91.
2 **Levine JD**, Collier DH, Basbaum AJ, Moskowitz MA, Helms CA.The nervous system may contribute to the pathophysiology of rheumatoid arthritis. J Rheumatol 1985;12:406–11.
3 **Marabini S**, Matucci-Cerinic M, Geppetti P, Del Bianco E, Marchesoni A, Tosi S, *et al*. Substance P and somatostatin levels in rheumatoid arthritis, osteoarthritis and psoriatic arthritis synovial fluid. Ann N Y Acad Sci 1991;632:435–6.
4 **Marshall WK**, Chiu B, Inman RD. Substance P and arthritis: analysis of plasma and synovial fluid levels. Arthritis Rheum 1990;33:87–90.
5 **Gazelius B**, Brodin E, Olgart L, Panopoulos P. Evidence that substance P is a mediator of antidromic vasodilatation using somatostatin as a release inhibitor. Acta Physiol Scand 1981;113:155–9.
6 **Matucci Cerinic M**, Marabini S. Somatostatin treatment for pain in rheumatoid arthritis: a double blind versus placebo study in knee involvement. Med Sci Res 1988;16:223–4.

Authors' response

We read with interest the letter by Drs Koseoglu and Koseoglu, in which they report a pilot study on the effect of somatostatin analogue treatment in refractory rheumatoid arthritis (RA). Their study is similar to our

study in size and patient characteristics but differs in three major points: the dose of somatostatin analogue and the preparation used; the length of the study; and the criteria employed to assess a therapeutic response.

The dose of octreotide (sandostatin) used in their study was low (100 μg once a day). When using subcutaneous octreotide 100 μg/day injections to treat other conditions, such as acromegaly, the accepted dose is 100 μg three times a day owing to the peptide's short half life. A dose of subcutaneous octreotide 100 μg/day may not be sufficient to achieve a significant effect. This may explain the more marked effect seen in our study, where octreotide was given as a long acting preparation that produces therapeutic doses of octreotide (equivalent to 100 μg subcutaneously three times a day) for a period of four weeks after injection.

Koseoglu and Koseoglu conducted a shorter study of only eight weeks as compared with our 14 week study, where we saw continued improvement after eight weeks.

Moreover, accepted American College of Rheumatology criteria for the evaluation of response to treatment in patients with RA were not used, making it difficult to compare the results. Despite the different methodology Koseoglu and Koseoglu showed a similar, significant beneficial effect of somatostatin analogue treatment on the assessment of pain: "pain intensity", and "joint sensitivity", with only mild adverse effects.

This pilot study supports our conclusion that treatment with a somatostatin analogue may be beneficial in the treatment of RA, and that further large, placebo controlled studies are required to evaluate this drug as a potential disease modifying antirheumatic drug for patients with RA.

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NOTICE

MSc Programme in Clinical Rheumatology

Applications are invited for places on this MSc programme, starting September 2002, which provides an excellent basis for those aiming at a career in rheumatology or a related subject. Applicants should be medically qualified and should have had at least two years of clinical experience after qualification. Previous experience in rheumatology is desirable, but not essential. The programme is undertaken part time over two years and is now well established, entering its eighth year.

Topics covered will include: basic science, clinical skills, peripheral joint problems, spinal problems, connective tissue disease and vasculitis, and the epidemiology of rheumatic diseases. A supervised project, which may be either clinical or laboratory based, is an integral part of the programme.

Further details can be obtained from: Miss Lisa McClair, ARC Epidemiology Unit, Stopford Building, University of Manchester, Oxford Road, Manchester, M13 9PT, UK. Tel: (0) 161 275 5993. Fax: (0) 161 275 5043. Email: Lisa@fs1.ser.man.ac.uk

FORTHCOMING EVENTS

Annual European Congress of Rheumatology

12–15 June 2002; Stockholm, Sweden

Contact: Fred Wyss, Executive Secretary EULAR, Witikonerstrasse 15, CH-8032, Zurich, Switzerland
Tel: +41 1 383 9690
Fax: +41 1 383 9810
Email: eular@bluewin.ch
Website: www.eular.org

10th International Congress on Behçet's Disease

27–29 June 2002; Berlin, Germany
Under the auspices of the International Society for Behçet's Disease
Up to eight young investigator awards, each of $500, will be awarded on the basis of abstracts submitted
Contact: Professor Ch C Zouboulis, Department of Dermatology, University Medical Centre Benjamin Franklin, The Free University of Berlin, Fabeckstrasse 60–62, 14195 Berlin, Germany
Fax: 49 30 84456908
Email: zoubbere@zedat.fu-berlin.de
Website: www.userpages.fu-berlin.de/~zoubbere
ISBD website: www.behcet.ws

29th Scandinavian Congress of Rheumatology

15–18 Aug 2002; Tromso, Norway
Contact: Hans Nossent, Department of Rheumatology, University Hospital Tromso, Norway
Tel: 47 776 27294
Fax: 47 776 27258
Email: 29scr2002@rito.no or revhan@rito.no

24th Annual Meeting of the American Society for Bone and Mineral Research

20–24 Sep 2002; San Antonio, TX, USA
Contact: ASBMR, 2025 M Street, NW, Suite 800, Washington DC 20036-3309, USA
Tel: +1 202 367 1161
Fax: +1 202 857 1880
Email: asbmr@dc.sba.com

Translational Research in Autoimmunity

21–22 Sep 2002; Pavia, Italy
Contact: Organising secretariat: eventi S.R.L., Corso Cavour, 18/20 - 27100 Pavia, Italy
Email: tra@e20pr.com
Website: www.e20pr.com
Congress website: www.medicine.ucsd.edu/albani/2001 meeting

OsteoArthritis Research Society International (OARSI) World Congress

22–25 Sep 2002; Sydney, Australia
Contact: OsteoArthritis Research Society International (OARSI), 2025 M Street, NW, Suite 800, Washington DC 20036, USA
Tel: +1 202 367 1177
Fax: +1 202 367 2177
Email: oarsi@oarsi.org
Website: www.oarsi.org

Third International Conference on Familial Mediterranean Fever and Hereditary Inflammatory Disorders

23–27 September 2002; La Grande Motte, France
Contact: Dr Isabelle Touitou, Laboratoire de Génétique Moleculaire et Chromosomique, Hôpital A de Villeneuve, Montpellier, France
Tel: 33 4 67 33 58 59
Fax: 33 4 67 33 58 62
Email: isabelle.touitou@igh.cnrs.fr
Website: www.congres.igh.cnrs.fr.FMF/2002

10th International Congress on Antiphospholipid Antibodies

29 Sep–3 Oct 2002; Sicily, Italy
Contact: Secretariat, 10th International Congress on Antiphospholipid Antibodies, c/o Kenes International, PO Box 50006, Tel Aviv 61500, Israel
Tel: 972 3 5140018/9
Fax: 972 3 5140077 or 972 3 5172484
Email: aps@kenes.com
Website: www.kenes.com/aps

Third International Congress on Spondyloarthropathies

2–5 Oct 2002, Gent, Belgium
Topics covered will be:
- Innate immunity
- Genetics and HLA-B27
- Animal models and pathogenesis
- Clinical research and therapy

Contact: Organisation and secretariat, Medicongress, Waalpoel 28–34, B-9960 Assenede, Belgium
Tel: +32 9 344 39 59
Fax: +32 9 344 40 10
Email: congresses@medicongress.com
Website: www.medicongress.com

7th International Conference on Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation and Related Diseases

14–17 Oct 2002; Nashville, Tennessee, USA
Contact: Lawrence J Marnett, Biochemistry Department, Vanderbilt University, School of Medicine, Nashville TN 37232-0146, USA
Tel: (615) 343 7329
Fax: (615) 343 7534
Website: www.eicosanoids.science.eayne.edu

66th American College of Rheumatology AGM

25–29 Oct 2002; New Orleans, USA
Contact: ACR, Ronald F Olejko, Director of Conferences and Meetings, 1800 Century Place, Suite 250, Atlanta, Georgia 30045–4300, USA
Tel: +1 404 633 3777
Fax: +1 404 633 1870
Email: acr@rheumatology.org
Website: www.rheumatology.org