Authors' affiliations

P Alonso-Bartolome, A Canga, Division of Radiology, Hospital Universitario Marqués de Valdecilla, Santander, Spain

V M Martínez-Taboada, R Blanco, Division of Rheumatology, Hospital Universitario Marqués de Valdecilla, Santander, Spain

Correspondence to: Dr V M Martínez-Taboada, Rheumatology Division, Hospital Universitario "Marqués de Valdecilla", Avda, Valdecilla s/n, 39008, Santander, Spain; vmartinez@medynet.com

Accepted 15 October 2005

REFERENCES

- 1 Ragab AH, Frech RS, Vielti TJ. Osteoporotic fractures secondary to methotrexate therapy of acute leukemia in remission. *Cancer* 1970;**25**:580-5.
- 2 Arnet FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315-24.
- 3 Maenaut K, Westhovens R, Dequeker J. Methotrexate osteopathy, does it exist? *J Rheumatol* 1996;**23**:2156-9.
- 4 Wijlans M, Burgers P. Stress fracture in long term methotrexate treatment for psoriatic arthritis. *Ann Rheum Dis* 2001;**60**:736-8.
- 5 Bologna C, Sany J, Jorgensen C. Possible role of methotrexate in the distal tibia fractures in a patient with rheumatoid arthritis. *Clin Exp Rheumatol* 1996;**14**:343-4.
- 6 Rubler M, Pouchot J, Paycha F, Gentelle S, Grasland A, Vinceneux P. Low dose methotrexate osteopathy in a patient with polyarticular juvenile idiopathic arthritis. *Ann Rheum Dis* 2003;**62**:588-9.
- 7 Quinn MA, Green MJ, Gough AKS. Low dose methotrexate osteopathy in a patient with polyarticular juvenile idiopathic arthritis. *Ann Rheum Dis* 2003;**62**:1123-4.
- 8 Rozin AP. Is methotrexate osteopathy a form of bone idiosyncrasy? *Ann Rheum Dis* 2003;**62**:1123.
- 9 Bennett JE, Reiking MF, Pluemer B, Pentel A, Seaton M, Killian C. Factors contributing to the development of medial tibial stress syndrome in high school runners. *J Orthop Sports Phys Ther* 2001;**31**:504-10.
- 10 Magnusson HI, Ahlberg HG, Karlsson C, Nyquist F, Karlsson MK. Low regional tibial bone density in athletes with medial tibial stress syndrome normalizes after recovery from symptoms. *Am J Sports Med* 2003;**31**:596-600.

Leflunomide and methotrexate combination therapy in daily clinical practice

A Dendooven, L De Rycke, X Verhelst, H Mielants, E M Veys, F De Keyser

Ann Rheum Dis 2006;**65**:833-834. doi: 10.1136/ard.2005.043620

A few years ago, the immunomodulatory molecule leflunomide was licensed as a new disease modifying anti-rheumatic drug (DMARD) for the treatment of rheumatoid arthritis (RA). Several randomised clinical trials have established its safety and efficacy, which is comparable to that of sulfasalazine and methotrexate.^{1,2} Some questions remain about the performance of this agent in current therapeutic strategies.³ One particular important query about the applicability of leflunomide is its use in combination therapy with methotrexate. Although there have been some conflicting opinions, it was shown by van Riel and Weinblatt *et al* that such combination therapy is safe and more effective than treatment with leflunomide or methotrexate alone.^{4,5} A major tool to confirm the usefulness of a drug in daily practice is a survival study. It informs clinicians about potential discrepancies with the results from randomised clinical trials, because patients included in a trial might differ from a real population in age, comorbidity, and atypical or refractory disease.

In this context, we examined the survival of leflunomide with or without concomitant methotrexate treatment in a Belgian clinical setting for a follow up period of 30 months. Our cohort consisted of 60 patients with RA with established disease and fulfilling the American College of Rheumatology classification criteria for RA.⁶ According to their rheumatologist, treatment with classical DMARDs was insufficient in all patients. They were treated with leflunomide as part of a compassionate sampling programme, for which enrolment took place between August 2000 and April 2002 in the rheumatology departments of three Belgian Centres (St Augustinus Hospital Antwerp, University Hospital Ghent, Elisabeth Hospital Sijsele-Damme).

All patients received a loading dose of 100 mg leflunomide for three consecutive days. Afterwards, leflunomide was given at a dose of 20 mg/day, with or without methotrexate, and this according to the rheumatologist's decision. Forty of 60 patients received concomitant methotrexate from the start, at different doses. Twenty patients received leflunomide monotherapy. After 30 months, 37 (62%) of the 60 patients

with RA were still receiving leflunomide treatment. In the groups with concomitant methotrexate and with leflunomide monotherapy 26/40 (65%), and 11/20 (55%), respectively, continued treatment (fig 1). Two major reasons for discontinuation were inefficacy and adverse events (respectively 18.3% and 15.0% at 30 months). The number and nature of adverse events were comparable in both groups and were mainly gastrointestinal (nausea, diarrhoea, raised liver enzymes), alopecia, anaemia, skin rashes, and hypertension. These side effects are consistent with those reported in previous studies.^{1,2,5}

Another interesting observation is that whereas the leflunomide dosage remained stable during 30 months in the majority of the patients, the methotrexate dose was decreased in a substantial number of patients: it was reduced in 14 (35%) and even stopped in an additional 11 (27.5%) patients with RA. In contrast, it was increased in only four (10%) and remained stable in 11 (27.5%) patients with RA. This further supports the beneficial effect of combining both drugs.

Figure 1 Treatment duration and the percentage of patients still receiving leflunomide after 30 months in the total leflunomide cohort and in the leflunomide cohorts with and without concomitant methotrexate.

Our observations indicate that combination therapy of leflunomide and methotrexate is useful in the treatment of RA in daily practice.

Leen De Rycke was supported by a grant from the "Vlaams instituut voor de bevordering van het wetenschappelijk-technologisch onderzoek in de industrie" (IWT/SB/11127).

Authors' affiliations

A Dendooven, L De Rycke, X Verhelst, H Mielants, E M Veys, F De Keyser, Department of Rheumatology, Ghent University Hospital, Ghent, Belgium

Correspondence to: Dr F De Keyser, Department of Rheumatology, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium; Filip.DeKeyser@Ugent.be

Accepted 3 October 2005

REFERENCES

- 1 Dougados M, Emery P, Lemmel EM, de la Serna R, Zerbini CA, Brin S, *et al*. Efficacy and safety of leflunomide and predisposing factors for treatment response in patients with rheumatoid arthritis: RELIEF 6-month data. *J Rheumatol* 2003;**30**:2572-9.
- 2 Osiri M, Shea B, Robinson V, Suarez-Almazor M, Strand V, Tugwell P, *et al*. Leflunomide for the treatment of rheumatoid arthritis: a systematic review and meta-analysis. *J Rheumatol* 2003;**30**:1182-90.
- 3 Kremer JM. What I would like to know about leflunomide. *J Rheumatol* 2004;**31**:1029-31.
- 4 van Riel P. Leflunomide improves the clinical response in patients with active rheumatoid arthritis treated with methotrexate. *Clin Exp Rheumatol* 2003;**21**:695-6.
- 5 Weinblatt ME, Kremer JM, Coblyn JS, Maier AL, Helfgott SM, Morrell M, *et al*. Pharmacokinetics, safety and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. *Arthritis Rheum* 1999;**42**:1322-8.
- 6 Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315-4.

Fatal exacerbation of fibrosing alveolitis associated with systemic sclerosis in a patient treated with adalimumab

Y Allanore, G Devos-François, C Caramella, P Boumier, V Jounieaux, A Kahan

Ann Rheum Dis 2006;**65**:834-835. doi: 10.1136/ard.2005.044453

Several cases of fatal exacerbations of fibrosing alveolitis associated with rheumatoid arthritis after infliximab treatment have recently been reported.¹ We report here a case of fatal exacerbation of pulmonary fibrosis after adalimumab treatment in a patient with polyarthritis related to systemic sclerosis (SSc).

The patient, a 74 year old woman, had been diagnosed 5 years previously with severe Raynaud's syndrome, sclerodactyly, pulmonary fibrosis, abnormal oesophageal peristalsis, and non-specific antinuclear antibodies (1/100; indirect immunofluorescence on Hep 2 cells). She also had severe distal polyarthritis affecting the wrists, metacarpophalangeal and proximal interphalangeal joints, with demineralisation but no erosion on x ray examination. She tested negative for rheumatoid factor and anti-cyclic citrullinated peptide antibodies. Successive treatments with low dose prednisone associated with methotrexate, leflunomide or azathioprine were ineffective.

In February 2004 she had a 28 joint count Disease Activity Score (DAS28) score of 7.8, a Health Assessment Questionnaire score of 2.6/3, C reactive protein (CRP) levels of 194 mg/l without any positive infectious test. Skin involvement was consistent with a limited cutaneous SSc subtype,² and Rodnan's modified skin score was 6/51. Pulmonary evaluation showed mild peripheral honeycombing with traction bronchiectasis on computed tomographic (CT) scan (fig 1A). She had a forced vital capacity (FVC) of 72% of the predicted capacity and a carbon monoxide transfer factor divided by alveolar volume of 52% of the predicted value, with normoxia at rest and no other abnormality on systemic evaluation. In view of this refractory disabling polyarthritis we proposed adalimumab treatment (40 mg, subcutaneously every other week), which was started while continuing with azathioprine (150 mg/day) treatment.

In July 2004, the articular symptoms improved slightly, with a DAS28 score of 5.1, and a CRP concentration of 10 mg/l. Systemic disease was unaffected, with FVC at 68% of

the predicted capacity and no change on pulmonary CT scan. The dose of adalimumab was increased to 40 mg/week, in association with azathioprine.

In September 2004, the patient was admitted owing to respiratory failure; dyspnoea had increased over 1 month (grade IV NYHA) with rapid exacerbation and fever for 2 days. At the time of admission, her body temperature was 39°C without haemodynamic abnormality. The skin score was unchanged. Biological tests disclosed a normal white cell count (leucocytes $7.1 \times 10^9/l$), and a CRP value of 88 mg/l. Haemocultures and bronchoalveolar lavage remained sterile, but *Chlamydia pneumoniae* antibodies (IgM and IgG) were detected and a CT scan angiography showed aggravated lesions with extensive ground glass opacities (fig 1B). Echocardiography disclosed mild impairment in the left ventricular ejection fraction (LVEF 45%) together with an increase in systolic pulmonary arterial pressure estimation (sPAP 56 mm Hg).

The patient was treated with oxygen, diuretics, azithromycin, and methylprednisolone (1 g) for 3 days followed by prednisone (1 mg/kg/day) with azathioprine. Adalimumab treatment was stopped. The fever decreased and echocardiography improved (LVEF 55% and sPAP 40 mm Hg), but the dyspnoea continued, requiring long term oxygen treatment (6 l/min, >15 h/24 h).

Pulmonary function worsened at the start of 2005, and the patient died from respiratory distress without infection in March 2005.

Anti-tumour necrosis factor α (TNF α) treatment was given because the patient had a mild systemic disease but associated severe, active, crippling, and refractory polyarthritis. *Chlamydia* infection which may have been facilitated by anti-TNF α treatment might have contributed to the initial deterioration of pulmonary function; however, it is not recognised as a contributor to the induction of the fibrotic process and, although a natural course of the disease cannot be ruled out, we strongly suspect the involvement of