A major subset of patients with ankylosing spondylitis followed up in tertiary clinical care require anti-tumour necrosis factor α biological treatments according to the current guidelines

M Temel, P Atاغunduz, H Direskeneli

Therapeutic options for severe ankylosing spondylitis (AS) have been limited to non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and to some traditional disease modifying drugs (DMARDs) such as sulfasalazine and methotrexate. In view of open label and controlled trials of treatment with a monoclonal chimeric tumour necrosis factor (TNF) antibody (infliximab), and with recombinant human TNF receptor (etanercept), the need for more effective second line treatments in AS seems to be met.1–4

In this study we aimed at determining the proportion of patients with active AS, despite treatment with NSAIDs and second line treatments (sulfasalazine, methotrexate), using current guidelines for anti-TNF treatment in a tertiary clinical care.

METHODS AND RESULTS

Study patients were selected according to the Modified New York criteria. ASAS and SPARTAN guidelines for biological treatments of AS were used.5 6 Ninety three patients with AS (M/F = 46/47, mean (SD) age 39.5 (11.5) years, mean (SD) disease duration 13.7 (10.5) years) were screened. The University of Marmara Institutional review board approved the study and informed consent was given by the study patients.

Eighty patients (86%) were receiving NSAIDs: 67/93 (72%) sulfasalazine and 32/93 (34%) methotrexate. Disease duration, age, disease activity defined by the Bath AS Disease Activity Index (BASDAI), and drugs used did not differ significantly between male and female patients. Of the 93 patients, 32 (34%; M/F = 17/15) and 37 patients (40%; M/F = 18/15) were defined as having active AS according to SPARTAN and ASAS guidelines, respectively.

Although high mean C reactive protein (CRP) values are considered critical in defining active AS, the higher mean CRP values detected in the male patients (male v female mean CRP, 259 v 69 mg/l, p = 0.054) did not correlate with the ratio of men and women considered to have active AS (ASAS = 8M/17F, SPARTAN = 17M/15F). Higher CRP values in this group correlated negatively with the use of sulfasalazine (r = −0.764, p = 0.05).

DISCUSSION

Our study showed that a significant number of patients had active AS (34–40%) in our patient tertiary care clinic. A recent study reflects the same need for effective treatment in AS, though that study had a higher proportion of patients with active AS (65%).3 In that study, NSAIDs were used as the first line treatment option and use of sulfasalazine and methotrexate was limited. We used combined methotrexate with sulfasalazine for persistent peripheral arthritis, which might have had modifying effects on disease activity in our study group, despite a lack of evidence that conventional DMARDs alter the course of established axial disease, and might explain the differences between the two studies.

According to current diagnostic criteria, patients with AS must have x ray changes for the diagnosis, which take months to years to establish. Two separate studies from Europe emphasise that a substantial period of active disease was already present before the diagnosis.4 5 As we now know, treatment with biological agents improves the signs and symptoms of axial disease in AS where traditional DMARDs fail.4 5 Starting DMARDs at an earlier stage of AS after the diagnosis might provide a chance to assess the effect of conventional treatment in patients with shorter disease duration and enable use of anti-TNF treatment for patients with refractory disease before the radiographic signs of established disease occur.

In a similar study of rheumatoid arthritis6 the eligibility of patients receiving routine care to receive treatment with TNFα agents, according to the inclusion criteria of the studies for biological agents, was also low (prevalence of 8%). However, current criteria for defining patients with active AS eligible for anti-TNF treatment, and patient selection criteria of major clinical trials with biological agents, do parallel each other, suggesting that current guidelines for selecting patients with active AS are suitable for routine clinical care.

In conclusion, a significant subset of the patients with AS followed up in our tertiary care clinic require more effective treatment according to current guidelines despite intensive conventional second line treatment.

Authors’ affiliations

M Temel, P Atاغunduz, H Direskeneli, Department of Rheumatology, Marmara University Medical Faculty, Istanbul, Turkey

Correspondence to: Dr H Direskeneli, Division of Rheumatology, Marmara Medical School Hospital, Tophanelioglu Cad. 13/15, 81190, Altunizade, Istanbul, Turkey; direskeneli@superonline.com

Accepted 30 January 2005

REFERENCES


Colchicine responsive periodic fever syndrome associated with pyrin I591T


Familial Mediterranean fever (FMF) is a recessively inherited disorder characterised by recurrent attacks of fever and serositis that usually begin in childhood, last for fewer than 3 days, and which can largely be prevented by colchicine prophylaxis. Identification of the gene associated with FMF, MEFV, has facilitated genotype:phenotype studies, and we report here on a patient with a little described exon 9 mutation associated with an atypical inflammatory syndrome.

CASE REPORT
A 56 year old white French woman presented with normochromic anaemia, haemoglobin 61 g/l, and recent onset fatigue and headaches. Extensive investigations including upper and lower gastrointestinal endoscopy, autoantibody screens, bone marrow examination, and whole body computed tomography proved normal. There was no family history of note or consanguinity.

Over the following 9 years her symptoms—comprising pyrexia, headache, and drenching night sweats—intensified, occurring about every fourth day and lasting for 24 hours. She required intermittent blood transfusions and her erythrocyte sedimentation rate remained markedly raised. Repeat bone marrow, echocardiogram, radiolabelled white cell scan, and computed tomographic imaging were normal. An investigation for infectious disease was non-diagnostic.

The possibility of atypical FMF was considered and was supported by complete resolution of symptoms after the introduction of colchicine 1 mg daily. Before treatment, her median serum amyloid A protein was 338 mg/l and C reactive protein 56 mg/l. Both markers were in the healthy range of <10 mg/l with colchicine (fig 1).

Sequencing of MEFV showed a single exon 9 mutation, encoding pyrin I591T; no mutations were found in exons 2, 3, 5, or 10. The TNFRSF1A gene, associated with TRAPS (tumour necrosis factor receptor associated periodic fever syndrome) was wild type. A reduction in colchicine to 0.5 mg/day led to recurrence of symptoms and acute phase response, which resolved when the dose was increased. She remains well and has a normal haemoglobin at 12 months’ follow up.

DISCUSSION
FMF is an inherited inflammatory disorder predominantly affecting people of the Mediterranean littoral, but which has been described in many populations. The gene associated with FMF, MEFV, was cloned in 1997 and comprises 10 exons. Forty eight mutations associated with FMF have been reported, just five of which are associated with 70–80% of cases. Although finding a mutation in each MEFV allele corroborates a diagnosis of FMF, the sensitivity and specificity of DNA analysis are hampered by reduced penetrance, and by the fact that only a single mutation can be identified in up to 20% of patients with classical FMF. This suggests that certain people may be especially susceptible to a single MEFV mutation, or that other as yet unidentified genes can contribute to the pathogenesis of the disease. The diagnosis of FMF therefore remains clinical, and the TEL-Hashomer criteria are well validated for this purpose.

Pyrin 1591T was first reported in 2001 with no accompanying clinical data. A Spanish kindred was subsequently described, in which three siblings were compound heterozygotes for pyrin 1591T and M694I, the latter a recognised variant causing FMF. Only one subject was symptomatic, and the contribution from 1591T was therefore unclear. However, a pathogenic role for pyrin 1591T in our patient is supported because she fulfilled diagnostic criteria for probable FMF, had attacks of characteristically short duration which responded to colchicine, and we only identified this mutation in one other case among our large referral practice, in a patient with classical FMF who had a second MEFV mutation, M694I. Furthermore, the absence of serositis and a late onset of symptoms have all been described in FMF.

Figure 1 Our patient’s acute phase response, plotted on a logarithmic scale, and the effect of colchicine treatment. Her chronic inflammatory activity responded to colchicine 1 mg/day, partially relapsed with 0.5 mg/day, and subsided again when the dose was increased again to 1 mg/day.