Low dose of infliximab is inadequate in most patients with spondylarthropathies

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ABSTRACT

Objectives. The recommended starting dose for infliximab for ankylosing spondylitis 5mg/kg is higher than that for rheumatoid arthritis. Because of the high expense of the drug lower doses may be considered. We report our experience with lower initial doses.

Methods. Thirty patients with active SpA (16 psoriatic arthritis, 12 ankylosing spondylitis and 2 undifferentiated) received 6 infliximab infusions. Patients had substantial axial disease (mean BASDAI at baseline 5.5). Concomitant therapy (methotrexate or prednisolone) remained stable throughout treatment period. The mean initial dose of infliximab was 3.5 mg/kg/infusion. Clinical efficacy was assessed by BASDAI. The criterion for dose adjustment was a BASDAI improvement of less than 50%. The primary end-points were the proportion of patients requiring a dose adjustment and the percentage of patients achieving 50% improvement in BASDAI after 6 infusions.

Results. In this cohort, 2 patients discontinued therapy, 1 for pulmonary infection and 1 for allergic reaction. Twelve patients (40%) showed 50% improvement in BASDAI between baseline and prior to the 7th infusion, while 15 patients (50%) had an improvement >2 points. To achieve clinical response the frequency and/or the dose of infliximab infusions were increased in 63% of patients. The mean infliximab dose increased from 3.5 mg/kg at the first infusion to 4.3 mg/kg (p < 0.001) at the 7th infusion, resulting in a cumulative dose at the end of the study period comparable to the recommended one.

Conclusions. In the majority of our SpA patients low starting doses of infliximab required subsequent adjustment. In these patients infliximab should be administered at the recommended dose of 5mg/kg/infusion.

Introduction

The spondylarthropathies (SpA) are a heterogeneous group of inflammatory arthropathies that share common genetic, clinical and radiologic features. These include ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, arthritis associated with inflammatory bowel disease and undifferentiated spondylarthropathies (uSpA).

Materials and methods

Patients. This was an uncontrolled, open-label, study with patients from two rheumatology clinics, one in northern and the other in southern Greece. Patients with a diagnosis of AS fulfilled the modified New York classification criteria whereas patients in the other subgroups fulfilled the European Spondylarthropathy Study Group criteria for SpA.

Thirty consecutive patients were selected because of active SpA (mean BASDAI at baseline 5.5), despite current or previous treatment with NSAIDs and DMARDs.
**Treatment**
Methotrexate was continued in 18 patients at a mean dose of 12.8 mg/wk (range 7.5–20) (Table I), while concomitant prednisolone was used in 3 (mean dose 6.7 mg/d, range 5.75). Patients received infliximab at a mean initial dose of 3.5 mg/kg/infusion (range 3.5–5 mg/kg). Twenty of them were initially treated with 3mg/kg. Changes in dosage and/or infusion intervals of infliximab were made following the third infusion (6th week) and were dictated by the clinical response as assessed by BASDAI. The criterion for dose adjustment was BASDAI improvement of < 50%.

**Patient evaluation: Assessment of disease activity**
Routine laboratory tests such as complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood urea nitrogen, creatinine, liver function tests and urinalysis were performed. A chest radiograph and a skin test with purified protein derivative (PPD) were performed on study enrollment. Patients were evaluated clinically at baseline and prior to each infusion by visual analogue scales (VAS 0-100) for axial pain, level of morning stiffness and the patient’s global assessment. The BASDAI was used for assessment of axial disease activity.

**Primary and secondary end-points**
The primary end-points were 50% improvement in BASDAI after 6 infliximab infusions or the requirement of a dose adjustment. Secondary end-points were a 2 point absolute improvement (on a 0-10 scale) in the BASDAI score and a reduction of spinal pain greater or equal to 2 units.

**Statistical analysis**
Statistical evaluation within groups was done by the use of paired Student’s t-test. A p value less than 0.05 (two-tailed) was considered as statistically significant.

**Results**
**Patients’ demographics and disease characteristics**
Thirty patients, 22 males 8 females, with a mean age of 41.3 (±12) years, a mean disease duration, of 13.4 (± 8.6) years, and active axial disease (mean BASDAI at baseline 5.5) were selected (Table I). Sixteen patients had psoriatic arthritis, 12 ankylosing spondylitis and 2 undifferentiated spondylarthropathy. All patients had considerable axial disease. Thus, the mean BASDAI at baseline was 5.5 with 83% of the patients fulfilling the BASDAI cut-off value of moderate to severe disease (≥ 4). All patients had BASDAI > 3. Twenty-eight had concomitant peripheral arthritis. Among 16 patients with evaluable information on peripheral arthritis, the mean baseline DAS index was 3.2; 4/16 had high level disease activity (DAS ≥ 3.7) while 8/16 had moderate disease activity (DAS > 2.4). The majority of the patients had failed other therapies. The mean number of DMARDs that had been used was 2.1 (1-4), and were usually methotrexate and sulfasalazine (Table I). Methotrexate (MTX) was continued in 18 patients while concomitant prednisolone was used in 3 (Table I). The mean initial dose of infliximab was 3.5 mg/kg/infusion. Patients were followed up to the 7th infusion (mean treatment period 36.8 weeks).

**Side effects**
In this cohort, 2 patients discontinued therapy because of side effects. The first was due to a serious allergic reaction during the second infliximab infusion, while the second was a pulmonary infection with pleural effusion of unknown etiology.

**Efficacy**
Just prior to the 7th infliximab infusion 40% of the patients (12/30) were responders (≥50% improvement in BASDAI), while 60% had ≥ 20% improvement in BASDAI. When applying as a criterion of improvement a > 2-point decrease in the BASDAI score, 50% of the patients were responders. Moreover, 78% of our patients showed a reduction in spinal pain of at least 2 points on a 0-10 scale. The mean BASDAI of the cohort on the 7th infusion was 3.6, being significantly improved compared to the baseline value (baseline 5.5, p<0.002). Statistically signifi-
cant improvements were noticed in the patients’ global assessment, in the assessment of axial pain on a visual analog scale (VAS) and in the level of morning stiffness (Table II). For 16 of the patients with evaluable information on peripheral arthritis, the DAS was also significantly improved between baseline and the 7th infusion (mean DAS 3.2 and 1.7 respectively, \( p < 0.002 \)). 12/16 patients (75%) with peripheral arthritis were responders (7 good and 5 moderate) according to the EULAR response criteria.

**Dose adjustments**

To achieve the clinical response described above, the frequency and/or dose of infliximab infusions were increased in 63% of patients. The dose was increased in 11 patients, both a dose increase and shortening of the infusion interval were introduced in 6 patients, and in 2 patients the infusion intervals were shortened. The mean infliximab dose increased from 3.5 mg/kg at the first infusion to 4.3 mg/kg (\( p < 0.001 \)) after 6 infusions. Only 5 of the 20 patients who were started on 3 mg/kg continued on a stable infliximab dose. The cumulative dose of infliximab per patient was increased and was comparable to that had the recommended dose of 5 mg/kg been initiated from the beginning of the study (25.7 mg/kg/patient was administered in a period of 36.8 weeks, compared to 30 mg/kg/patient administered in 38 weeks if the recommended dosing was followed).

**Discussion**

Treatment of AS and other inflammatory diseases with axial involvement requires a multidisciplinary approach consisting of physical therapy, NSAIDs, sulfasalazine and often methotrexate, to control pain and prevent ankylosis. None of the aforementioned modalities have a significant impact on disease progression. Based on data showing evidence of TNFα involvement in the pathogenesis of AS, biologic agents that block this proinflammatory cytokine were tested in clinical trials of patients with AS and in other subgroups of SpA patients (7, 8, 11).

Data from randomized clinical trials are of paramount importance to determine clinical efficacy of new therapies, but they have limitations related to their applicability in a general, unselected population. Observational studies and clinical protocols provide useful additional information about long-term outcomes and side effects. Although the size of this cohort was modest, we believe it represents a “real-life” SpA population of clinical practice. Thus, most patients had long-standing disease (mean disease duration 13.4 years) with multiple DMARD failure (mean 2.1), considerable axial (mean baseline BASDAI 5.5) and substantial peripheral disease activity (mean baseline DAS 3.2).

Patients with AS show comparable disability and reduced health-related quality of life to patients with rheumatoid arthritis (12). Although there is evidence from short-term clinical trials for an improvement in the quality of life of AS patients treated with infliximab, there are no data for the cost-effectiveness of this treatment. Considering the high cost of biologic treatment, we wondered whether we could initiate therapy with lower than the recommended dose. Following patients up to the 7th infusion, it was shown that in the majority of them (63%) the frequency and/or the dose of infliximab had to be increased in order to achieve or maintain clinical efficacy. Seventy-five percent (15/20) of the patients who were started on 3 mg/kg were switched to a higher dose. The cumulative dose after dose adjustments was 25.7 mg/kg/patient over 36.8 weeks (or 26.5 mg/kg/patient in 38 weeks), culminating in a final dose that was close to the recommended level (30 mg/kg/patient in 38 weeks). Individualization of infliximab dosing, an approach that is applied in patients with rheumatoid arthritis, may also be helpful for patients with AS.

The trend for higher than 3 mg/kg doses in our study is comparable to published data from other studies where the dose usually applied is 5 mg/kg (6, 7). On the contrary, in a small cohort of 21 AS patients studied by Maksymowych et al., it was found that after 14 weeks of treatment the majority of the patients could be effectively treated with a low (3 mg/kg) infliximab regimen, but long-term data on this group are not available (13). Additional evidence supporting the efficacy of the lower dose scheme comes from a small group of Mexican patients, but again long-term efficacy data are lacking (14).

In this study, dose adjustments were dictated by clinical efficacy as assessed by the BASDAI, which represents the patient’s perception of disease activity. Although BASDAI has been evaluated only in patients with AS it was applied in our study because all patients had substantial axial disease and this was the main indication for infliximab treatment. The mean BASDAI was significantly improved just prior to 7th infusion compared to the baseline evaluation (3.6 compared to 5.5, \( p < 0.002 \)). Forty percent of the patients responded prior to the 7th infusion. This efficacy is comparable to that reported by other groups (15). However, the data on efficacy in this study have to be interpreted with caution. Because this was an open label study, we cannot completely rule out the possibility that a placebo effect or regression to the mean may have influenced the response rates.

Anti-TNFα agents are potent immune modulators that may prove to be the first disease controlling agents for SpA. Issues like their considerable cost and safety profile call for patient selection criteria as well as guidelines for monitoring clinical efficacy such as those recently published (16), so as to optimize cost effectiveness and the everyday clinical application of biologic therapy in patients with SpA. The concomitant use of immunosuppressive agents like methotrexate or azathioprine in order to reduce immunogenicity and increase the long-term efficacy of infliximab has to be further investigated (17).

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References


