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EXTENDED REPORT

INFLIXIMAB IN SPONDYLOARTHROPATHY ASSOCIATED WITH CROHN’S DISEASE: AN OPEN STUDY ON THE EFFICACY IN INDUCING AND MAINTAINING REMISSION OF MUSCULOSKELETAL AND GUT MANIFESTATIONS

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**Objective:** To evaluate the efficacy and tolerability of anti-TNF-alpha mAb (Infliximab) in the treatment of spondyloarthropathies (SpA) associated with active and inactive Crohn’s Disease (CD).

**Methods:** Twenty-four patients affected by SpA associated with active or inactive CD (16 active and 8 quiescent) were treated with anti-TNF-alpha mAb (Infliximab) with repeated infusions for a period varying from 12 to 18 months. The main targets of the treatment were the amelioration of general musculoskeletal and spinal pain, disappearance of peripheral arthritis and enthesitis, decrease of BASDAI score, modification of acute phase reactants, and the reduction of CD activity (CDAI).

**Results:** Infliximab improved both gastrointestinal (p < 0.01) and overall articular symptoms (BASDAI = p < 0.01; general musculoskeletal and spinal pain = p < 0.01; peripheral arthritis = p < 0.01) in patients with active CD. Infliximab was also very effective in patients with inactive CD and low inflammatory markers, controlling not only axial involvement and peripheral arthritis but also enthesitis (p < 0.01) and preventing inflammatory bowel disease reactivation. The amelioration of gut and musculoskeletal involvement persisted up to 12 months.

**Conclusion:** Infliximab may act on inflammation of entheses and of periarticular structures, which usually do not induce alteration of hematological parameters but are the main promoters of pain and joint ankylosis in spondyloarthropathies. The contemporary efficacy in the induction and maintenance of CD remission, suggests Infliximab as a first choice drug for the treatment of active and severe spondyloarthropathies associated with active or quiescent CD.

**Key words:** Infliximab, Crohn’s Disease, Spondyloarthropathy

**Running title:** Infliximab in the spondyloarthropathy of Crohn’s disease
Musculoskeletal manifestations are the most common extra-intestinal complication of inflammatory bowel disease (IBD), in particular Crohn’s Disease (CD). These manifestations are usually included in the clinical spectrum of spondylarthropathies (SpA). The strong link between bowel and locomotor system in SpA is also supported by the evidence that inflammatory alterations of intestinal mucosa and its permeability (usually at the ileum) are present with mild or subclinical symptoms in a high percentage of patients affected by any SpA without a manifest IBD (1). Different patterns of articular involvement have been recognized in IBD: type I, peripheral pauciarticular arthritis; type II, peripheral nonsymmetric polyarthritis; and type III, a SpA resembling idiopathic ankylosing spondylitis, sometimes with peripheral joint involvement (2). In addition to axial and peripheral articular symptoms, enthesitis, tenosynovitis, and dactylitis commonly occur, sometimes representing the only manifestation (3) and often causing severe and continuous discomfort with a significant reduction of the quality of life of the patient. Type I arthritis may precede the diagnosis of IBD and, once established, often parallels the activity of the intestinal manifestation. Types II and III arthritis do not reflect the activity of the underlying IBD and rarely precede the diagnosis of IBD.

The management of these conditions, especially when associated, is difficult in terms of efficacy and safety. In fact, SpA are often poorly responsive to disease modifying drugs and the possibility of a drug-triggered intestinal activation or relapse significantly limits the use of several drugs.

Tumor Necrosis Factor alpha (TNFα) is a so called “master cytokine” carrying on a key role in the regulation of innate immunity and in the local inflammatory response of several pathogenetically distinct diseases (4). In particular, TNFα is important in the genesis and maintenance of synovitis in rheumatic disorders and of mucosal inflammation in inflammatory bowel diseases.
Infliximab is a chimeric anti-TNF-α monoclonal IgG-I antibody, neutralising soluble cytokines as well blocking membrane-bound cytokines (5). For this reason, Infliximab has been initially successfully used in patients with rheumatoid arthritis (RA) (6, 7). Infliximab is remarkably effective in patients with RA presenting persistent active disease despite adequate treatment with methotrexate (8). The clinical response after one year of treatment (ACR 20%) has reached 42-59% of efficacy (9).

Infliximab has been also used in CD. It induces remission of symptoms, closure of fistulae, healing of lesions and improvement in quality of life. A beneficial effect on extraintestinal complications, including articular complications, has been observed (10-14).

These observations and the close relation between gut inflammation and joint involvement in patients with SpA, have suggested the use of Infliximab in ankylosing spondylitis. Although the bulk of experience in this disease is not comparable to that of RA and CD, there are now substantial evidences that Infliximab is highly effective and well tolerated for both axial and peripheral joint disease in patients with active ankylosing spondylitis (15-17). There are also some reports about the use of Infliximab in other SpA (18-21). By contrast with ankylosing spondylitis, few studies have addressed the specific treatment of spondyloarthropathy associated with CD. One open, short term study on 4 patients with SpA associated with active CD (3 patients with peripheral arthritis and 1 with preminent axial involvement) has shown that Infliximab induces a fast improvement of articular manifestations and remission of active intestinal disease (22). Another prospective open-label study from Herfarth et al (23) has evaluated the incidence of arthritis and arthralgia in a population with chronic active CD (153 patients) and the effect of Infliximab on articular symptomatology after 12 weeks of treatment. All the patients presenting any musculoskeletal symptom, and not only those with a clear spondyloarthropathy, were included in the study. Musculoskeletal symptoms were evaluated on clinical examination and graded on a four point scale (severe, moderate, mild and none) with no distinction between the different patterns of articular involvement (peripheral arthritis, axial
involvement, enthesitis). Infliximab induced a significant reduction of arthritis/arthralgia score in this cohort of patients.

TNF-α blockade with the other biologic agent Etanercept is effective in the treatment of SpA but not in the treatment of colitis. The persistence or flaring of Crohn’s disease despite the complete resolution of spinal pathology in two patients treated with etanercept has been reported (24). The aim of our work was to investigate the efficacy and safety of a short and long term regimen of Infliximab in the treatment of SpA who also presented or had experienced in the past intestinal inflammation due to CD.

PATIENTS AND METHODS

Twentyfour patients (14 M, 10 F; mean age 44 ± 10 yrs) referred to the Departments of Medicine of the University of Florence and L’Aquila (Italy) and affected by active spondyloarthropathy associated with CD were selected for the study. At baseline, 16 patients presented active CD (mean disease duration 9.9 ± 5.3 yrs), while 8 patients had quiescent CD (mean disease duration 10.3 ± 4.6 yrs). Other 12 additional patients presenting active CD (mean disease duration 9.16 ± 3.3 yrs) and similar articular disease were used as controls and treated with conventional therapies (see below).

All patients suffered from active and severe SpA (mean disease duration 9.9 ± 6.3 yrs) fulfilling ESSG criteria (25) and characterized by axial involvement (25 out of 36 subjects) and/or peripheral arthritis (23 out of 36) and/or enthesopathy (25 out of 36), poorly or not responsive to conventional treatments (NSAIDs, sulfasalazine, systemic and local steroids, physiotherapy) or in which there was evidence that previous treatments had induced a worsening or a relapse of the gastrointestinal symptoms.

Disease activity was assessed by mean of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); visual analogic scale (VAS) for general musculoskeletal pain; separate VAS
for spinal pain; presence of peripheral arthritis/synovitis; presence of active enthesitis or periarticular inflammation. The diagnosis of peripheral arthritis and active enthesitis was confirmed by ultrasonographic (US) evaluation. Peripheral arthritis was considered present when at least one peripheral joint showed swelling and tenderness with documented joint effusion. The count of involved joints was not taken into account because most of the patients with peripheral arthritis had mono or pauciarticular involvement. Enthesitis and periarticular inflammation were defined both clinically (pain at pressure or mobilisation) and by US in the most frequently involved sites of insertion (great trocanter, ischial tuberosity, pubis, patellar poles and tibial tuberosity, posterior and inferior calcaneus, medial and lateral epicondyles, chondrosternal and manubriosternalis junctions). US examination (ESAOTE AU5 epi, linear probe 7.5-12 Mhz, pwD dynamic range 50sB, PRF 750 Hz) was performed by experienced echographist blinded to clinical and biological findings. Oedema, thickening, erosions at the enthesal junction and increased flow by pwD were considered as pathological. Enthesitis was considered active in the presence of both pain and US abnormalities due to present inflammation (oedema, thickening and increased flow). Enthesitis was considered present when at least one site showed signs of active inflammation.

SpA was considered active in patients presenting BASDAI > 40 and VAS for general musculoskeletal pain > 40, persisting for at least 4 months.

All the parameters were assessed at baseline and then at each Infliximab infusion.

The activity of CD was evaluated by mean of the “Crohn’s Disease Activity index” (CDAI) (26), recorded by the patients during the 7 days preceding each infusion and during the 4th week following the last infusion. The disease was considered active when the score was higher than 150.

Laboratory evaluation, including erythrosedimentation rate (ESR), C-reactive protein (CRP), routinary hepatic and renal parameters and complete blood count, was also performed at baseline and before each infusion of Infliximab or at the correspondig time for the control group.
Treatment. The patients with active CD received 3 infusions of 5 mg/kg Infliximab (at weeks 0, 2 and 6) and later on infusions of 3 mg/kg Infliximab, if the bowel disease had remitted, or 5 mg/kg in case of persistence, every 5-8 weeks according to the duration of therapeutic effect (medium interval between the infusions: 44.2 ± 9.3 days). The patients who presented inactive CD at baseline were treated with 3 mg/kg infliximab since the first dose with the same schedule (figure 1). All the patients were treated with Infliximab for at least 12 months. After 12 months, the patients continued the treatment (apart from those who stopped for side effects or inefficacy); however, data at 18 months are available only for 12 of them.

All the patients were allowed to continue the pharmacologic and physiotherapic treatment they were assuming before the study if no modifications had occurred during the previous months (3 months for 5-aminosalicylic acid compounds, 1 month for NSAIDs and steroids).

The control patients, all with active CD at baseline, received a variety of other drugs commonly employed in CD (oral azathioprine 2.5 mg/Kg/day, topical and systemic salycilates, topical and systemic steroids, antibiotics, metronidazole).

The continued use of oral 5-aminosalicylic acid compounds and steroid or 5-aminosalycilic enemas was allowed within the definition of remission.

Statistical analysis. Primary end points analysed were the BASDAI score, the VAS for musculoskeletal pain, ESR, CRP, and CDAI at 45 days, 6 months and 12 months after the beginning of the treatment. Variables are presented as the mean ± standard deviation, unless stated otherwise. SPSS-PC was used for data analysis. Comparison between baseline and subsequent assessments were performed using the Wilcoxon matched pairs signed rank test. The efficacy of the treatment in respect with control therapy was assessed by a variance analysis (ANOVA). The results were considered statistically significant at p<0.05. Correlations between variables were assessed using the Pearson rank correlation coefficient. A partial correlation test was used to study the relation between the same variables after the addition of the treatment.
RESULTS

Muskuloskeletal involvement. All patients treated with Infliximab had a significant improvement of the articular and peri-articular manifestations of spondyloarthropathy, both axial and peripheral (table I, figure 2c, figure 3). In these patients, the BASDAI score showed a dramatic and prompt decrease ($p < 0.01$) which persisted throughout the duration of the treatment (figure 2a). BASDAI score was also significantly reduced in the control group ($p < 0.05$) but almost never below 40 (the appointed limit for active disease). The reduction of BASDAI due to Infliximab was more significant than that due to other therapies ($p < 0.05$). Infliximab induced a significant and rapid reduction of peripheral arthritis (from 58% to 12.5% after 6 months, from 55.5 % to 11.1 % after 1 year and from 50 % to 16.6 % in the patients that prolonged the treatment up to 18 months) (figure 3a). Patients of the control group had a slower but progressive amelioration of peripheral arthritis which was comparable to the Infliximab group after 6 and 12 months (from 75% to 17% and 12.5 % respectively) (figure 3a). Since the first infusions, Infliximab obtained a clear decrease of active enthesitis (figure 4) which persisted at 6 months (from 67% to 24%), at 12 months (from 60% to 10%) and at 18 months (from 58.3 % to 16.6 %) (figure 3b). Many of the patients who did not achieve a complete remission of enthesitis had a reduction of the sites of inflammation or an improvement in the clinical manifestations of enthesitis (data not shown). The control treatments showed little effect on enthesitis (figure 3b). Finally, Infliximab was able to decrease both the general musculoskeletal and the spinal pain in a very significant extent ($p < 0.01$) (figure 2c). This effect was significantly higher than in control group ($p < 0.05$) (figure 2c).

None assumed analgesic or anti-inflammatory drugs during the period of treatment with Infliximab. At 12 months, 3 patients of the control group were turned to Infliximab treatment because of the persistence of severe spondyloarthritic symptoms (table I).
**Gastrointestinal involvement.** In patients with active CD, Infliximab induced a remarkable improvement of gastrointestinal signs and symptoms with significant reduction of CDAI after the first two infusions (p < 0.01), that was maintained over 45 days (p < 0.01), 3, 6 and 12 months (p < 0.01) (table I). After 6 months, 4 patients still presented active CD and for this reason 3 of them had to assume oral steroids. After 12 months, 2 patients stopped the treatment with Infliximab because of CD relapse and underwent other immunosuppressant drugs (table I). None of the 8 patients with inactive CD at baseline encountered exacerbation during the course of the study.

The patients of the control group also showed amelioration of CDAI which persisted over the 12 months of study (p < 0.01). At 12 months, one patient interrupted the treatment with conventional drugs and was turned to Infliximab because of reactivation of bowel inflammation. Notably, no significant difference in the capacity to induce and maintain remission of CD was observed between Infliximab and the control treatments. In most patients, the treatments induced a significant and rapid reduction of laboratory inflammatory parameters (ESR and CRP) (table I). Indeed, a significant reduction of these parameters was also observed in patients with inactive CD (p < 0.05) (data not shown).

**Correlations between variables.** At baseline, the following correlations were found: ESR correlated with CRP (r = 0.79; p = 0.002) and, scarcely, with CDAI (r = 0.67; p = 0.06) and peripheral arthritis (r = 0.69; p = 0.054); CRP also showed a very mild correlation with peripheral arthritis (r = 0.66; p = 0.83); BASDAI correlated only with general musculoskeletal pain (r = 0.69; p = 0.054). Notably, BASDAI, as well as axial pain and enthesitic involvement, did not correlate with acute phase reactants. The pharmacologic treatment, whatever it was, did not modify significantly these correlations.

**Tolerability.** Infliximab was well tolerated throughout the study. One patient stopped the treatment after 6 months for allergic reaction following the infusion (cough, dyspnea, flush)
(table I). Other minor side effects were headache, dizziness, transient leukopenia that regressed spontaneously and did not entail interruption. No infection was experienced.

In the control group, 2 patients treated with azathioprine had nausea and vomiting, one patient treated with mesalazine and metronidazole had a transient elevation of gamma-glutamyl transferase that required reduction of the drugs.

**DISCUSSION**

In enteropathic arthropathies, the management of bowel inflammation is the main task since this may indirectly induce remission of musculoskeletal manifestations. However, in a large number of patients, despite the amelioration or disappearance of gut inflammation, joint involvement persists (2). In these cases, non steroidal anti-inflammatory drugs must be carefully used because of the potential occurrence of gastrointestinal side effects and the possibility of inflammatory bowel disease activation. Indeed, steroids and disease modifying anti-rheumatic drugs are often uneffective in controlling axial pain and enthesis (27) and, with the exception of sulfasalazine, they cannot completely avoid relapse of bowel inflammation.

When both intestinal disease and arthropathy are in active phase, the drugs of choice are those potentially effective on the inflammation of both districts. Sometimes, whether CD is in remission and laboratory inflammatory markers are normal or scarcely altered, the musculoskeletal symptoms associated with SpA may persist and determine severe discomfort to the patient. In these cases, the control of the musculoskeletal symptoms, especially enthesitis and spinal pain that potentially mirror progression of the disease towards ankylosis (28), becomes a primary task together with the restoration of the quality of life.

Our preliminary data are generated in an open study but confirm that Infliximab controls the inflammation and the symptoms of spondyloarthropathies associated with active CD. Moreover, Infliximab significantly controls musculoskeletal pain derived not only from axial and peripheral
articular involvement but also enthesitis, even in patients with quiescent CD and with no or moderate increase of acute phase reactants.

The fact that almost all our patients reported the disappearance of enthesitis strongly suggests that Infliximab specifically acts also on inflammation of periarticular structures. It is well known that entheseal involvement does not induce alteration of hematological parameters but witnesses the persistence of disease activity and may contribute to joint ankylosis (28).

The positive results promptly achieved after the first infusions, persisted over the whole period of treatment with a reasonably good profile of tolerability. In the control group (especially in patients treated with azathioprine, data not shown) the therapy was very effective in the control of gut inflammation, peripheral arthritis and acute phase reactants but it poorly interfered with axial and enthesitic pain. These treatments achieved better results in cases with pauciarticular peripheral involvement that often parallels the activity of the intestinal manifestation, the so called “type I” (2).

In conclusion, Infliximab, because of its remarkable antinflammatory effect on both articular and intestinal systems, may be a pivotal treatment in severe SpA associated with active CD, often presenting with peripheral arthritis and increase of acute phase reactants. Moreover, since Infliximab has the peculiar property to act on all musculoskeletal inflammatory components of SpA and, at the same time, maintains the remission of gut inflammation, it may be a useful therapeutic tool also for patients with inactive CD and modest laboratory signs of inflammation but characterized by persistent and severe axial and enthesitic pain. The extension of the treatment beyond the canonical three infusions, usually reserved to active CD, may be advisable in both the patterns of patients if a reasonable inflammation may persist. In inflammatory bowel diseases and spondyloarthropathies, double blind studies with Infliximab are warranted to verify these data and evaluate the efficacy and tolerability of the drug in the long-term use.
REFERENCES


LEGEND TO FIGURES

Figure 1. Therapeutic flow-chart for the treatment of active spondyloarthropathies associated with active or inactive Crohn’s disease.

Figure 2 a,b,c. Clinical and laboratory data (mean) of the patients with spondyloarthropathy and Crohn’s disease at baseline and during the treatment with Infliximab, or various other conventional therapies (baseline, 45 days, 3, 6, 12, 18 months). The values of Crohn’s disease activity index (CDAI) are splitted in two additional groups: patients with active or inactive Crohn’s disease at baseline.

Figure 3. Percentage of patients presenting peripheral arthritis (A) or active enthesitis (B) at baseline and during the period of treatment (45 days, 3-6-12 months) with Infliximab or various other drugs (azathioprine, mesalazine, steroids, metronidazole, antibiotics). *The data reported in T12 are relative to patients (10 out of 21) which prolonged the treatment with Infliximab up to 12 months, no controls are available for this group.

Figure 4. (a) Thickening and omogeneous hypoechogenicity of the Achille’s tendon enthesis with distension of the retrocalcaneal bursa (arrows) which disappeared after 45 days of treatment with Infliximab (b).
<table>
<thead>
<tr>
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<th>Infliximab</th>
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<tr>
<td></td>
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<td>T45</td>
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<tr>
<td>Number of patients</td>
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<td>Discontinuances (side effects/inefficacy)</td>
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<tr>
<td>CDAI (total group)</td>
<td>252 ± 119.5</td>
<td>144 ± 47.0*</td>
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<tr>
<td>CDAI (active CD at baseline)</td>
<td>308 ± 90.3</td>
<td>154 ± 42.5*</td>
</tr>
<tr>
<td>CDAI (inactive CD at baseline)</td>
<td>118 ± 23.2</td>
<td>96 ± 17.5</td>
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<tr>
<td>ESR</td>
<td>38.5 ± 23.7</td>
<td>20.0 ± 13.2*</td>
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<tr>
<td>CRP</td>
<td>3.6 ± 2.5</td>
<td>1.1 ± 0.8**</td>
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<td>General Musculo-skeletal pain (VAS)</td>
<td>63.8 ± 15.6</td>
<td>16.8 ± 9.6**</td>
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<td>BASDAI</td>
<td>64.2 ± 12.2</td>
<td>25.7 ± 12.2**</td>
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<tr>
<td>Axial pain (VAS)</td>
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<td>17.3 ± 11.9**</td>
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<td>4/20</td>
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<tr>
<td>Active enthesitis (YES/NO)</td>
<td>15/9</td>
<td>6/18</td>
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Table I: Clinical and laboratory data of the patients with Crohn’s disease and spondyloarthropathy at baseline and during the treatment with Infliximab or various other conventional therapies (oral azathioprine 100 mg daily, topical and systemic salicylates, topical and systemic steroids, antibiotics, metronidazole). All the patients of the control group had active Crohn’s disease at baseline. Variables are presented as the mean ± standard deviation, unless stated otherwise. Comparison between baseline and subsequent assessments were performed using the Wilcoxon matched pairs signed rank test (* = p < 0.05; ** = p < 0.01).
21 active SpA

Initial cycle (3 infusions: T0, T15, T45)

- Active CD (15 pts)
  - Infliximab 5 mg/kg

- Inactive CD (6 pts)
  - Infliximab 3 mg/kg

Maintenance infusions (every 5-8 weeks)

- Active CD persisting
  - Infliximab 5 mg/kg

- Inactive CD (remission)

- Active CD (exacerbation)
  - Infliximab 3 mg/kg

- Inactive CD lasting
Figure 2c
Erythro-Sedimentation Rate

C Reactive Protein

Figure 2b
Figure 3
Infliximab in spondyloarthropathy associated with Crohn’s disease: an open study on the efficacy in inducing and maintaining remission of musculoskeletal and gut manifestations

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