Infliximab in the treatment of steroid-dependent ulcerative colitis


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Abstract. – Background and objectives: Infliximab has proven efficacious in the treatment of Crohn’s disease. Limited and contrasting data are available on effectiveness of anti-TNF alpha therapy in ulcerative colitis. We evaluated the efficacy of infliximab in the management of steroid-dependent ulcerative colitis.

Methods: We report preliminary data from a randomized, open-label, methylprednisolone-controlled trial of infliximab in the induction and maintenance of remission of patients with moderate to severe steroid-dependent ulcerative colitis. Twenty patients received either three infusion of infliximab (5 mg/kg) at 0, 2 and 6 weeks and thereafter every 8 weeks (group A) or methylprednisolone (0.7-1 mg/kg) daily for one week followed by a tapering regimen up to the minimal dose to maintain a symptom-free condition (group B). Clinical remission was defined as a DAI score less than 3.

Results: Ten patients in group A (DAI: 8.9 ± 1.4) achieved remission after the first infusion (DAI: 1.6 ± 0.7; p = 0.005) and steroids were progressively discontinued. At present (mean follow-up: 9.8 ± 1.1 months), 9 out of 10 patients maintain clinical remission, while one patient relapsed at 3 months. Ten patients in group B (DAI: 8.7 ± 1.4) reached clinical remission at one week (DAI: 1.9 ± 0.3; p = 0.005). Eight out of 10 patients were maintained at a minimal steroid dosage without any relapse at 9.7 ± 1.0 months follow-up. Two patients relapsed at 6 and 8 months, respectively.

Conclusions: Infliximab seems to be as effective as steroids in the management of moderate to severe steroid-dependent ulcerative colitis. These preliminary data suggest the potential efficacy of repeated treatment with infliximab for short-term maintenance of remission and steroid withdrawal in glucocorticoid-dependent ulcerative colitis.

Key Words:
Steroid-dependent ulcerative colitis, Infliximab, Anti-TNF alpha monoclonal antibody.

Introduction

Tumour necrosis factor alpha (TNF-α) is recognized as a key cytokine involved in the development and progression of several immune mediated inflammatory disorders, including inflammatory bowel disease. The cytokine profiles of Crohn’s disease and ulcerative colitis (UC) are usually different. The former is associated with an overexpression of Th1 related pro-inflammatory cytokines (e.g., TNF-α), the latter, conversely, is associated with an increased production of Th2 related inflammatory molecules (e.g., interleukin 4 and 5)1. However, increased serum and colonic mucosa concentrations of TNF-α have been reported also in patient with UC2-5, suggesting a possible role in the pathogenesis of the disease.

Infliximab, a IgG1 chimeric monoclonal antibody that effectively neutralizes TNF-α, has been shown to have potent anti-inflammatory and disease modifying effects in an expanding list of diseases, including rheumatoid arthritis, ankylosing spondylitis and Crohn’s disease6. There are limited and contrasting data on the role of antibodies to TNF-α in the therapy of ulcerative colitis (UC)7-14. Steroid-dependency may account for up to 20% of UC, usually applying to patients who cannot taper or rapidly flare (e.g., within 6 months) after steroid-withdrawal15. The aim of the study was to evaluate the effectiveness of infliximab in the management of glucocorticoid-dependent UC.

Methods

In a randomized, open-label, methylprednisolone controlled trial conducted in our
IBD unit, we evaluated the role of infliximab in the treatment of patients with moderate to severe glucocorticoid-dependent UC. Patients were included in the study if they had (1) an established diagnosis of UC (endoscopy plus histological confirmation), (2) moderate to severe disease according to a disease activity index (DAI) score more than 6, (3) minimum of one year of continuous steroid-dependent UC, (4) negative stool microscopy and culture, (5) negative immunohistochemistry for CMV on bowel biopsies, (6) absence of known serious infection in the previous three months, (7) no need of urgent colectomy.

Consecutive patients who met the inclusion criteria were 1:1 randomised to receive either infusion of infliximab (5 mg/kg body weight) at 0, 2 and 6 weeks and thereafter every 8 weeks (Group A) or methylprednisolone (0.71 mg/kg body weight) daily for one week followed by a tapering regimen up to the minimal dose to maintain a symptom-free condition.

Disease activity was assessed at recruitment, within two weeks after the first infliximab infusion and every 8 weeks thereafter. Clinical remission was defined as a DAI score less than 3.

Results

Twenty patients were studied (10 in each group). Population demographics and disease characteristics are summarised in Table I. All patients in group A (DAI: 8.9 ± 1.4) achieved remission after the first infusion (DAI: 1.6 ± 0.7; p = 0.005) and steroids were progressively

<table>
<thead>
<tr>
<th>Steroid group</th>
<th>Infliximab group</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>36.3 (24-53)</td>
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<tr>
<td>Extensive UC</td>
<td>4</td>
</tr>
<tr>
<td>Left sided UC</td>
<td>3</td>
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<tr>
<td>Distal UC</td>
<td>3</td>
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<tr>
<td>Duration of UC (y)</td>
<td>5.5 (2-10)</td>
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<tr>
<td>Prednisolone equivalent (gm/day)</td>
<td>15.5 (10-25)</td>
</tr>
<tr>
<td>DAI (mean ± SD)</td>
<td>8.7 ± 1.4</td>
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</tbody>
</table>

Table I. Demographic and disease characteristic of patients at week 0.
discontinued. At present (mean follow-up: 9.8 ± 1.1 months), 9 out of 10 patients maintain clinical remission (Figure 1). One patient relapsed after 3 and 7 months requiring shorter intervals between infliximab infusions in the first and steroids in the last occasion to achieve remission. Finally, the patient underwent elective colectomy after relapsing again after 11 months. Infusions with infliximab produced no significant adverse events. All patients in group B (DAI: 8.7 ± 1.4) reached clinical remission (DAI: 1.9 ± 0.3; p = 0.005). Eight out of 10 patients were maintained at a minimal steroid dosage (residual dose of steroids – prednisolone equivalent: 16.25 ± 5.2 mg/day) without any relapse at 9.7 ± 1.0 months follow-up. Two patients relapsed at 6 and 8 months, respectively. They were then offered infliximab treatment: one patient, although with marked evidence of clinical improvement, refused control colonoscopy and was lost to follow-up. The second patient achieved clinical remission, but relapsed after 10 months requiring again steroid treatment to obtain remission.

References


6) Sandos BE. Crohn’s disease: not all anti-TNFs are the same! Inflamm Bowel Dis 2002; 8: 232-235.


