Treatment of ulcerative colitis with adalimumab or infliximab: long-term follow-up of a single-centre cohort

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SUMMARY

Background
Randomized, controlled trials have demonstrated that anti-TNF agents are efficacious in inducing remission in cases of Crohn’s disease and ulcerative colitis. However, response rates for anti-TNF agents in ‘real life’ clinical practice are less well-defined.

Aims
To examine the response rates and long-term outcomes of infliximab and adalimumab treatment for out-patients with ulcerative colitis and to study the variables associated with response rates.

Methods
In a prospective study, a single-centre out-patient cohort was treated and followed up according to a structured protocol of clinical care. Response to treatment was assessed using a physician’s global assessment that focused on normalization of bowel frequency, absence of blood with defecation and tapering of corticosteroids to zero.

Results
Fifty-three ulcerative colitis patients were included in the study. Responses to induction therapy were 96.4% (27/28) for infliximab and 80% (20/25) for adalimumab (P = 0.0889). Responses to maintenance therapy were similar: infliximab 77.8% (14/18) and adalimumab 70.0% (14/20) (P = 0.7190). Multivariate analyses of the induction and maintenance responses did not reveal confounding elements. No new safety signals were identified.

Conclusions
This long-term follow-up of a single-centre cohort of ulcerative colitis patients demonstrates that ‘real-life’ out-patient treatment with infliximab and adalimumab is effective in induction and maintenance of response.

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INTRODUCTION
Ulcerative colitis (UC) is an inflammatory bowel disease that affects the mucosa of the large intestine. Presenting symptoms include rectal bleeding, diarrhoea, urgency, tenesmus and abdominal pain. Goals of therapy include induction and maintenance of remission, improved quality of life and avoidance of disease-related and treatment-related complications.

Medical therapy for ulcerative colitis includes mesalamine, corticosteroids and immunosuppressive agents. More recently, randomized, controlled trials have shown the anti-TNF biological therapy infliximab (IFX) to be efficacious in inducing and maintaining remission, and adalimumab (ADA) (currently presented in abstract form) to be efficacious in induction of remission of UC.

Anti-TNF therapies have also been shown to be effective in the treatment of Crohn’s disease. These anti-TNF medications work by inducing apoptosis of the TNF-x-expressing inflammatory cells; they neutralize soluble TNF, as well as deplete the number of immune cells through antibody-dependent cell-mediated and complement-dependent cytotoxicity. Anti-TNF therapies, IFX and ADA, are generally reserved for the treatment of moderate-to-severe IBD that has not responded to corticosteroids and/or immunosuppressive agents, or when the patient experiences an adverse event or becomes unable to tolerate corticosteroids and/or immunosuppressive agents.

Randomized, controlled trials are widely regarded as providing the highest strength of evidence. However, the efficacy results from published randomized clinical trials are not always equivalent to those seen in ‘real-life’ clinical practice. Several factors may contribute to this phenomenon, including the relative closeness of follow-up within the clinical trial, everyday non-adherence to treatment and therapeutic alliance (or lack thereof). For instance, examining the treatment of Helicobacter pylori, Graham et al. identified that eradication success rates in clinical trials were generally in the 90% range, yet ‘real-life’ clinical practice has overall eradication success rates in the range of 60–85%. Furthermore, studies of mesalamine use for UC treatment have found that only 40% of patients adhere to therapy. Such non-adherence obviously increases the risk of relapse.

The primary objective of the current study was to examine adalimumab and infliximab treatment responses for induction and maintenance of ulcerative colitis in a ‘real-life’ clinical practice environment. A secondary objective was to determine, through multivariate analysis, factors affecting UC’s response to infliximab or adalimumab.

MATERIALS AND METHODS

Patient population
Fifty-three (60% male) patients with histologically and endoscopically confirmed ulcerative colitis were included in this study and treated with anti-TNF therapy between January 2003 and July 2009. A structured protocol for a ‘step-up’ regional approach to anti-TNF therapy for patients with ulcerative colitis was followed; specifically, eligible patients had to have experienced a poor response, adverse events, or a lost response to mesalamine, corticosteroids and immunosuppressive therapy. Thus, corticosteroid therapy had failed in all patients in this cohort, and the patients had either failed or had an adverse event in response to immunosuppressive therapy. None of the patients received infliximab or adalimumab in response to acute severe UC that was nonresponsive to corticosteroids in hospital.

Overall, twenty-eight patients were treated with IFX (median age 31.1 years; range 17–53 years), and 25 patients were treated with ADA (median age 33.8 years; range 18–57 years). Inflixiamb was used ‘on-label’ in accordance with the regional Alberta Health and Wellness ‘step-up’ formulary approach as described above. Adalimumab was used ‘off-label’, based on published open-label experience and observational studies. Pending completion of the randomized controlled trial with UC adalimumab was administered in accordance with the same regional ‘step-up’ formulary approach used for infliximab. None of the patients who received adalimumab had previously received infliximab.

Definitions
The IFX-induction response at 14 weeks and the maintenance response at the patient’s last follow-up were determined by a physician’s global assessment that included the combination of the following three clinical features: normalization of bowel frequency, absence of blood with defecation, and the tapering of corticosteroids to zero. All three features had to be satisfied for the response definition to be fulfilled. The physicians who completed the assessments were expert gastroenterologists at an IBD referral centre.

The ADA-induction response at 14 weeks and the maintenance response at the patient’s last follow-up were
determined according to the physician’s global assessment described above.

For both IFX and ADA treatments, there were IBD nurse assessments to ensure that the patients were improving every 2–4 weeks. However, the physician global assessments were completed at week 14 and then every 8–12 weeks during maintenance therapy.

Failure of response was defined as the need for any therapeutic intervention or surgery for the UC during the patient’s study interval. Adverse events were defined as any adverse experience attributed by the IBD healthcare team to the anti-TNF agent.

Anti-TNF administration

Infliximab-treated patients received an induction dose of 5 mg/kg at 0 week, 2 weeks and 6 weeks, followed by a maintenance dose of 5 mg/kg every 8 weeks. If necessary, physicians could increase the maintenance dose to 10 mg/kg every 8 weeks or 5 mg/kg every 4 weeks to maintain clinical benefit for a patient. Adalimumab-treated patients received induction doses at 0 week, 2 weeks and 4 weeks of 160 mg, 80 mg and 40 mg respectively followed by a maintenance dose of 40 mg every other week. If necessary, physicians could intensify the maintenance dose to 40 mg every week to maintain clinical benefit.

Statistics

The Chi-square test was used to compare the proportion of patients in each treatment group with responses (or loss of function) at the induction (or maintenance) phase. The exact method was chosen if the sizes of each cell in a 2 × 2 table were very small (<5). Demographics such as age and gender and other clinical factors were compared between ADA and IFX groups using chi-square tests, t-tests, or Wilcoxon signed-rank tests, as appropriate.

To test the association of treatment use and response to treatment, as adjusted for other concomitant factors, exact logistic analysis was employed in a model-building fashion. Factors that were significant according to univariate level tests became candidates for multivariate logistic regression. The final model, based on theoretical relevance and stepwise selection procedure, looked at the relationship of response to treatment group, as adjusted for important prognostic variables. A secondary endpoint was derived from modelling the time to loss of function (or relapse) via survival methods. Patients whose response was maintained from induction to the end of the maintenance phase were considered censored cases.

Kaplan–Meier curves were generated and treatment groups compared using log-rank tests. Each prognostic factor was likewise modelled, one factor at a time, using Cox regression analysis. The final model was derived as the treatment modality adjusted simultaneously for other factors. The statistical software packages used to run all statistical analyses were SAS 9.1 (Cary, NC, USA) and S-PLUS 8.0 (Seattle, WA, USA) for statistical graphs. Significance was determined as a P value of less than 5%.

RESULTS

Patient demographics

Patient demographics for this cohort are summarized in Table 1. The infliximab (IFX) population was 64.3% male and 96.4% Caucasian, while the adalimumab (ADA) group was 56.0% male and 88.0% Caucasian. The mean age at diagnosis was 26.2 years for IFX (range: 14–51) and 27.5 years for ADA (range: 14–56), with the mean ages for first infusion being 31.1 years for IFX (range: 17–53) and 33.8 years for ADA (range: 18–57). The average C-reactive protein level prior to induction was 27.87 mg/L for IFX and 13.57 mg/L for ADA.

Disease distribution was mostly pancolitic: 25/28 (89.3%) of IFX patients and 24/25 (96%) of ADA patients. For the IFX cohort, 15/28 (53.4%) patients were on concomitant immunosuppressive therapy (azathioprine or methotrexate) while significantly fewer, only 5/25 (20%) (P = 0.0118) of the ADA group received these drugs. Ten patients from each cohort (35.7% IFX; 40% ADA) were taking mesalazine during their respective treatment phases. At induction, 17/28 (60.7%) from the IFX group and 13/28 (52%) of the ADA patients were on oral corticosteroids.

Induction response (Table 2)

All of the 28 IFX patients completed the induction phase, which was a three-dose induction regime (at 0 week, 2 weeks and 6 weeks). As assessed at week 14 using the physician’s global assessment (see above), 27/28 (96.4%) patients experienced a clinical response.

Twenty-five patients received the three-dose adalimumab regimen. At week 14, 20/25 (80.0%) of the patients had a clinical response, as measured by physician’s global assessment.

Overall, 47/53 (88.7%) patients had a clinical response to anti-TNF therapy; the response rates were not statistically different between adalimumab and infliximab groups (P = 0.0889). Multivariate analysis for demographic and concomitant treatment variables did not find
any specific factors that might have influenced the induction response.

Maintenance response (Table 3)
Thirty-eight patients (20 ADA and 18 IFX) completed the induction phase with a clinical response and were entered into the maintenance phase of treatment. The number of patients evaluable in the IFX maintenance arm (n = 18) was, in the end, smaller than the actual number of those who responded to induction (n = 27) because of loss of insurance (n = 4), patient self-withdrawal from treatment (n = 1), physician recommendation (n = 2) and loss to follow-up (n = 2).

Of the patients who entered the maintenance treatment phase, 14/20 ADA (70.0%) experienced a response up to the end of follow-up, and 14/18 (77.8%) of the IFX cohort had a response up to the end of follow-up. The median duration for the maintenance phase was 54.5 weeks (range 3–108 weeks) for the ADA group and 64.5 weeks (range 8–180 weeks) for the IFX group. More patients in the IFX-treated group were on concomitant immunosuppression and mesalazine therapies.

During maintenance, escalation of therapy (dose or frequency) was at the discretion of the treating physician and occurred in 40% (8/20) of ADA patients and 39% (7/18) of IFX patients.

Of the six ADA patients who lost response, two chose colectomy as therapy, one chose switch to IFX and three were treated with another course of corticosteroids. Of the four IFX patients who lost response, one chose colectomy as therapy and three were treated with another course of corticosteroids.

Figure 1 shows the proportion of patients who experienced a sustained treatment response over time using Kaplan–Meier analysis. The last date of follow-up for both groups of patients was 17 December 2009. No significant difference in the time to treatment failure (TTF) was found between the two treatment groups.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient demographics prior to anti-TNF therapy</th>
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<tbody>
<tr>
<td>Characteristic</td>
<td>Adalimumab (n = 25)</td>
</tr>
<tr>
<td>Male/Female (%)</td>
<td>14/11 (56.0/44.0)</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>22 (88.0)</td>
</tr>
<tr>
<td>Median age at diagnosis (range)</td>
<td>27.5 years (14–56)</td>
</tr>
<tr>
<td>Extent of disease</td>
<td></td>
</tr>
<tr>
<td>Proctitis (%)</td>
<td>0</td>
</tr>
<tr>
<td>Proctosigmoiditis (%)</td>
<td>0</td>
</tr>
<tr>
<td>Left-sided colitis (%)</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Pancolitis (%)</td>
<td>24 (96.0)</td>
</tr>
<tr>
<td>C-reactive protein at 1st infusion</td>
<td>13.6 ± 9.2 mg/L</td>
</tr>
<tr>
<td>Concomitant therapy at 1st infusion</td>
<td></td>
</tr>
<tr>
<td>Mesalazine (%)</td>
<td>10 (40.0)</td>
</tr>
<tr>
<td>Corticosteroids (%)</td>
<td>13 (52.0)</td>
</tr>
<tr>
<td>Immunosuppression* (%)</td>
<td>5 (20.0)</td>
</tr>
</tbody>
</table>

* Includes azathioprine, mercaptopurine or methotrexate.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Patients receiving induction anti-TNF therapy: demographics and response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 53)</td>
<td>Adalimumab (n = 25)</td>
</tr>
<tr>
<td>Induction response (%)*</td>
<td>47 (88.7)</td>
</tr>
<tr>
<td>Males (%)</td>
<td>32 (60.4)</td>
</tr>
<tr>
<td>Age, mean ± s.d.</td>
<td>32 ± 11</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>30 (24–37)</td>
</tr>
</tbody>
</table>

* Response defined by physician’s global assessment that included the combination of the following three clinical features: normalization of bowel frequency, absence of blood with defecation and the tapering of corticosteroids to zero. All three features had to be satisfied for the definition of response.
However, the seventy-fifth percentile for the TTF was 84 days (12 weeks) for ADA and 280 days (40 weeks) for the IFX group (hazard ratio 0.6; 95% CI range 0.2–2.3).

Multivariate analysis for the maintenance phase found no confounding factors.

Concomitant IBD therapy

**Induction treatment.** During the induction therapy phase, 24.0% \((n = 6)\) ADA-treated patients received concomitant immunosuppression, as compared with 53.4% \((n = 15)\) of IFX-treated patients \((P = 0.0118)\). However, multivariate analysis did not identify concomitant immunosuppressive therapy as a significant co-variant \((P = 0.6990)\). Similar numbers of patients in each group received mesalazine \([40.0\% \text{ ADA} (10/25) \text{ and } 35.7\% \text{ IFX} (10/28); \ P = 0.7480]\) and corticosteroids \([52\% \text{ ADA} (13/25) \text{ and } 60.7\% \text{ IFX} (17/28); P = 0.5228]\).

**Maintenance treatment.** During maintenance therapy, 16.7% \((3/20)\) of ADA-treated patients received concomitant immunosuppression, as compared to 61.1% \((11/18)\) of IFX-treated patients \((P = 0.0153)\). Similarly, the number of patients on mesalazine was lower in the ADA–treated patients, at 30.0% \((n = 6)\), than in the IFX-treated patients, at 66.7% \((n = 12)\) \((P = 0.0455)\). Tapering of corticosteroids to zero was accomplished for almost all patients who entered the maintenance phase.
This withdrawal of corticosteroids was similar for adalimumab and infliximab.

**Adverse events**

During the induction phase, two of the IFX-treated patients experienced mild infusion reactions and one experienced an IFX-attributed headache. During the maintenance phase, three IFX-treated patients experienced mild infusion reactions and one patient experienced IFX-attributed nausea. In the ADA cohort, one patient had a mild injection reaction during the induction phase. No withdrawal of therapy for adverse events took place in either group. No cases of tuberculosis, malignancy, or death were seen in either the IFX or the ADA group.

**Colectomy**

Three patients in the cohort eventually underwent colectomy; two were ADA-treated patients and one patient had been treated with both ADA and IFX. The first ADA-treated patient experienced an initial response, but had worsening symptoms by the end of the induction phase. The second ADA-treated patient had an induction response, but experienced worsening symptoms shortly into the maintenance period. Both patients underwent colectomy at the point of disease worsening. The third patient developed worsening of symptoms in the ADA maintenance phase and was switched over to IFX. The patient’s disease showed no response to the drug at the end of the IFX induction period, and the patient subsequently underwent colectomy.

**Patients who switched**

Four patients who started on ADA were switched to IFX. No patients were switched from IFX to ADA due to local regulatory issues. Two ADA-treated patients switched to IFX during the induction phase due to failed responses. Upon switching, one experienced a response to IFX, while the other did not, but required colectomy (as discussed above). Two other ADA-treated patients switched to IFX during their maintenance treatment period; their IFX induction results were not evaluable.

**DISCUSSION**

Currently, only limited data are available on the ‘real-life’ clinical practice outcomes of anti-TNF treatment for UC. A few studies have documented open-label experiences with both ADA and IFX.9–11 Two large randomized controlled trials with IFX in the induction and maintenance of UC remission have been previously published,2 and one large randomized controlled trial with ADA in the induction of UC remission has been presented in abstract form.2

Two clinical practice papers describing ADA treatment for UC have been published. The first, which had a 13-patient cohort, showed the probability of an ADA-induced response being maintained as 84.6% at 3 months and 60.6% at 6 months.11 The second study reported that 67% of a nine-patient cohort had an improvement of their symptoms.12

Similarly, the clinical practice use of IFX for UC treatment has been reported in three studies. In the first, 81/121 (67%) patients had an initial clinical response, and 68% of these initial responders experienced a sustained clinical response.13 The second study showed that, at week 8, the response rates were only 57%14 and the third study reported clinical response rates of 56%.15

The present study, in contrast, assessed the long-term efficacy of both ADA and IFX treatment for a cohort of patients with UC; the study’s median follow-up time was 1.3 years. All patients treated with ADA or IFX or both (following a switch) between January 2003 and December 2009 were included in our prospective study, which included a preset follow-up schedule for physician global assessment.

The induction response rate in this ‘real-life’ clinical practice study (within the first 14 weeks) is higher for IFX (96.4%) and ADA (80.0%) than those reported in the initial randomized placebo-controlled trials for IFX ACT I (69.4%) and II (64.5%) trials1 and ADA (54.6%).2 This is likely because our study used a physician’s global response assessment rather than a defined full Mayo score to assess induction response and because our study assessed response at week 14 of induction therapy rather than at week 8, as used in the clinical trials.

The present analysis also demonstrates the efficacy of adalimumab and infliximab treatment for the maintenance of improvement during a 1-year follow-up. Indeed, nearly three-quarters of the initial responders in our cohort experienced a maintained benefit until the end of their follow-up. The efficacy of treatment was similar across baseline characteristics and concomitant immunosuppression and for duration and location of disease. Again, these ‘real-life’ clinical practice results of UC maintenance efficacy are superior to those seen at 1-year in the randomized controlled clinical trial for IFX.1 As yet, there are no UC maintenance randomized controlled clinical trials published for ADA.

In our cohort, significantly fewer ADA-treated patients were on concomitant immunosuppressive therapy. Whether this difference in immunosuppressive use played
a role in the numerically lower induction and maintenance response rates of ADA, vs. IFX, remains to be determined. Future studies are needed to determine the exact ways concomitant immunosuppressive therapy might affect anti-TNF antibodies, serum levels and sustained responses. Nevertheless, the ACT and ACCENT trials have shown immunomodulator use to be related to less immunogenicity and fewer infusion reactions, but not to improved efficacy as compared with anti-TNF therapy alone.\(^6\)

Given the significant side-effects, over a long-term, of corticosteroids, corticosteroid-sparing is an important aim of long-term UC treatment. In the ACT I study, only 61% of the patients were on corticosteroids at baseline; of these, 21% (30/143) of those treated with IFX were in steroid-free clinical remission at 54 weeks.\(^1\) In the present cohort, steroid withdrawal over the course of maintenance was possible for 91.7% of those patients who were initially taking steroids.

In the ACT I and ACT II studies, IFX treatment reduced the colectomy rate to 10% after 1-year (compared with 17% in the placebo-treated group).\(^17\) Our study had a colectomy rate at the end of follow-up of 6% (3/53). There were no hospitalizations for the anti-TNF-treated groups in our study.

We could not identify predictors of a long-lasting response in our cohort. Overall, treatment with anti-TNF agents was very safe for our patients. Infusion and injection reactions were mild and treatable. In our cohort, no medication withdrawals were due to side-effects.

This study reflects ‘real life’ clinical practice experience with ADA and IFX treatment in patients with UC: patients were those in daily clinical practice who had failed corticosteroid and immunosuppressive therapy prior to starting anti-TNF therapy. Both IFX and ADA were effective in generating induction and maintenance responses in these UC patients, and no new safety signals were seen.

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**REFERENCES**