Recommendations for the treatment of ulcerative colitis with infliximab: A gastroenterology expert group consensus

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Treatment;
Consensus;
Colectomy;
TNF inhibitor;

Abstract

Background and aims: Infliximab is currently the only biologic approved for treatment of adults with moderate to severe, active ulcerative colitis (UC) unresponsive to conventional therapies. It rapidly controls symptoms, induces and sustains steroid-free remission, stimulates mucosal healing, and reduces serious complications. Although infliximab tends to be reserved for...
patients with severe disease, it may be even more beneficial for moderate disease earlier in the disease course. Therefore, it is important to identify which patients are candidates for infliximab therapy.

Methods: A collaborative Delphi survey was used to obtain consensus on use of biologic therapy in patients with UC from an expert panel of 12 gastroenterologists with substantial experience using infliximab in clinical practice and clinical trials. The panel also addressed issues that influence the use of infliximab in UC, including its potential as an alternative to surgery.

Results: The panel agreed that: (1) it is necessary to adopt additional treatment goals beyond symptom control, i.e., complete mucosal healing, steroid-free remission, improved QoL, and reduced long-term complications; (2) it may be possible to achieve these treatment goals with infliximab, especially if it is used earlier in the course of UC; and (3) infliximab should be offered as an alternative to surgery in patients being considered for colectomy. The panel also agreed on factors for identifying candidates for infliximab therapy (e.g., persistently active UC, steroid-dependent/refractory disease, and high C-reactive protein).

Conclusions: This consensus statement provides useful and practical information on how to achieve evolving treatment goals with infliximab in moderate to severe UC.

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It is now recognized that treatment goals must go beyond controlling symptoms, to influencing the underlying cause of UC via fast, sustained control of inflammation. UC treatment should aim to rapidly induce steroid-free remission, achieve complete mucosal healing (an objective indicator of inflammation control and bowel normalisation), avoid serious complications (e.g., hospitalisations and surgeries), minimize side effects, and improve patient quality of life (QoL).\textsuperscript{2} Achievement of these challenging treatment goals is possible in more patients since the introduction of biologic therapies.

Currently, infliximab is the only biologic therapy approved for treatment of UC. It was approved in 2006 by the European Commission for the treatment of moderate to severe, active UC in patients with an inadequate response to conventional therapy, including corticosteroids and 6-MP or AZA, or who are intolerant or have medical contraindications to such therapies.\textsuperscript{6} In addition, the European Crohn’s and Colitis Organisation (ECCO) UC management guidelines recommend infliximab in steroid-refractory and thiopurine-refractory UC.\textsuperscript{7} Infliximab tends to be used as a third-line therapy in patients with moderate to severe UC or as a rescue therapy. However, experts have proposed that earlier use during less severe disease states (i.e., moderate UC) could benefit many patients.\textsuperscript{5} Furthermore, infliximab can potentially attain the new treatment goals beyond symptom control in these patients.\textsuperscript{8–10} Interestingly, combination therapy with infliximab and AZA may be the new best approach, according to results from a double-blind, randomized, controlled trial (RCT) presented at the ECCO conference,\textsuperscript{11} but not yet published in full.

The objective of the present survey was to assess current expert practices and establish pragmatic principles for candidate selection and timing of infliximab therapy. It is hoped that the results of this cooperative effort will assist clinical practice.

2. Materials and methods

2.1. Survey participants

A steering committee comprising 3 gastroenterologists (WR, GvA, and JP) with extensive experience using biologic therapy to treat UC, both in clinical trials and the clinical setting, helmed the Delphi process. Committee members developed topics for the survey and helped with design and methodology (Table 1), but did not participate in the survey. When complete, the survey was reviewed by the steering committee and then independently tested to ensure that the questions were understandable, with no ambiguities.

Twelve gastroenterologists from Europe, Canada, and Australia agreed to form an expert panel and to participate in the survey under the supervision of the steering group. The members of the expert panel were selected based on their substantial level of expertise in using biologic therapy in the treatment of UC in both clinical practice and clinical studies (Table 1).

2.2. Delphi methodology

The Delphi methodology, developed by Linstone and Turoff, provides an evidence-based method for structured group communication that allows a group of individuals to effectively explore and solve complex problems.\textsuperscript{12} A major strength of this approach is that it can be used to look at a specific problem/argument from all angles, determine the pros and cons of different approaches to the problem, and help clarify the impact and acceptability of specific ideas and opinions.\textsuperscript{12,13} The Delphi methodology modifies individual viewpoints and leads to a merging of opinion within a group.

The Delphi methodology has been modified to allow establishment of a consensus. Known as the “collaborative Delphi,” this modification uses a combination of surveys and meetings. The approach involves a steering group that identifies the issues surrounding a complex problem, and a survey questionnaire to which an expert panel anonymously responds. By undergoing repeated rounds of the survey and subsequent analysis/modification of the questions, it is possible to reach a group consensus.

In this study, consensus was reached using the collaborative Delphi method, which was executed in 2 rounds of an anonymous survey (rounds 1 and 2) followed by a meeting (round 3). During the meeting, the anonymity of the expert panel members was relinquished. Individual survey responses were not disclosed, however, to maintain objectivity. Consensus was reached on many topics at the end of the meeting, and additional questions were developed which were then sent to the expert panel to be answered anonymously (round 4).

Table 1 Qualifications and responsibilities of the Delphi participants.

<table>
<thead>
<tr>
<th>Steering committee</th>
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</thead>
<tbody>
<tr>
<td><strong>Qualifications</strong></td>
</tr>
<tr>
<td>• Possess extensive experience using biologic therapies to treat patients with moderate to severe UC</td>
</tr>
<tr>
<td>• Involved in numerous clinical trials evaluating biologic therapies in UC</td>
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<tr>
<td><strong>Responsibilities</strong></td>
</tr>
<tr>
<td>• Develop survey outline topics</td>
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<tr>
<td>• Contribute to the survey design/methodology</td>
</tr>
<tr>
<td>• Review survey data before sending to the expert panel</td>
</tr>
<tr>
<td>• Present data to the expert panel at an on-site meeting</td>
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</table>

<table>
<thead>
<tr>
<th>Expert panel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Qualifications</strong></td>
</tr>
<tr>
<td>• Possess substantial experience using biologic therapies to treat patients with UC</td>
</tr>
<tr>
<td>• Involved in some clinical trials evaluating biologic therapies in UC</td>
</tr>
<tr>
<td><strong>Responsibilities</strong></td>
</tr>
<tr>
<td>• Participate in 2 rounds (rounds 1 and 2) of an anonymous questionnaire</td>
</tr>
<tr>
<td>• Attend a group discussion meeting (round 3) of survey results to establish consensus, where possible</td>
</tr>
<tr>
<td>• Develop additional/revised questions at the meeting and respond to the revised questions (round 4)</td>
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</tbody>
</table>
2.3. Survey questionnaire

This Delphi survey focused on 5 topics relating to the use of biologic therapy in the treatment of UC. Specifically, the questionnaire addressed issues that:

1. influence the decision to use a biologic as treatment for UC.
2. influence the decision to use infliximab as treatment for UC.
3. relate to the importance of proper timing of infliximab treatment.
4. relate to surgery for UC.
5. influence the decision to use infliximab as an alternative to surgery.

Questions were formulated to measure areas of agreement, relevance, importance, and likelihood of action. A Likert scale of 1 to 9 was used, where a score of 1, 2, 3 or 4 indicated degrees of disagreement with the statement or question, and a score of 6, 7, 8 or 9 indicated increasing degrees of agreement. A score of 5 was considered neutral. The expert panel completed the internet-based questionnaire during rounds 1 and 2 of the Delphi process. A numerical identification system ensured that the participants remained anonymous.

2.4. Data analysis

After completion of round 1, the responses were collected and analyzed as a group. Median scores were calculated to obtain an accurate measure of main tendencies and discount any extreme views. During round 2, these median scores were made known to the expert panel. After this round of the Delphi process and before the round 3 meeting occurred, the variability of the responses was calculated using the interquartile range (IQR; a measure of the distance between the 75th and 25th percentiles that reflects the middle 50% of responses). IQR gives a stable measure of the response range that is not swayed by outliers or extreme responses.

The results of the survey were presented to the expert panel by the steering committee during a meeting (round 3). Key issues surrounding the use of biologic therapy in UC were discussed to establish importance, relevance to patient treatment, and likelihood of specific actions (e.g., use of cyclosporine over infliximab). To further clarify the degree of agreement with a question or statement, the median Likert scoring scale was adjusted. Statements or questions were re-categorised as "highly irrelevant, strongly disagree, or highly unlikely" (median score 1–3); "somewhat relevant or irrelevant, somewhat agree or disagree, or somewhat likely or unlikely" (median score 4–6); or "highly relevant, strongly agree, or highly likely" (median score 7–9). Positive consensus was defined as the median ≥ 7 plus the lower quartile ≥ 7 (negative consensus, median ≤ 3 and upper quartile ≤ 3). Scores can be illustrated with "boxplots" (Fig. 1). Each consensus was based on expert opinion and clinical experience.

3. Results

Delphi participants based their responses on their familiarity with and knowledge about infliximab, because at the time of this survey it was the only biologic approved for the treatment of UC.

3.1. Factors influencing the decision to use biologic therapy

The expert panel agreed that the efficacy of biologic therapy demonstrated in similar clinical conditions (median 7 [IQR 7–8]) and its ability of to change the disease course (median 8 [IQR 7–8]) play a large role in their decision to recommend biologic therapy to patients with UC. Panelists also considered these efficacy factors highly relevant: speed of clinical improvement (median 7 [IQR 7–8]); ability to achieve mucosal healing (median 7.5 [IQR 7–8]) and better QoL (median 8 [IQR 7–8]); and avoidance of colectomy (median 8 [IQR 8.0–8.25]). When focusing on patient characteristics and...

![Figure 1](https://academic.oup.com/ecco-jcc/article-abstract/6/2/248/456249/1?重要举措=md5-010c1e003127e69e9e94b3e457852d4f)
safety, the panel reached consensus that the following are important when considering biologic therapy in patients with UC:

<table>
<thead>
<tr>
<th>Previous treatment failures</th>
<th>Previous history of TB exposure (median 9 [IQR 7.5–9.0])</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Steroids (median 8 [IQR 7–8])</td>
<td>Risk of latent TB reactivation (median 8 [IQR 7–9])</td>
</tr>
<tr>
<td>• 6-MP (median 8 [IQR 7.5–8.0])</td>
<td>Patient willingness to try a biologic (median 8 [IQR 7–8])</td>
</tr>
<tr>
<td>Severity of current symptoms (median 8 [IQR 7–8])</td>
<td>and comply with treatment (median 8 [IQR 8–8])</td>
</tr>
<tr>
<td>Extraintestinal manifestations (median 7 [IQR 7.0–7.5])</td>
<td>Patient desire to avoid surgery (median 8 [IQR 8–8]).</td>
</tr>
<tr>
<td>Active infection (median 9 [IQR 8–9])</td>
<td>Poor QoL (median 8 [IQR 8–8])</td>
</tr>
<tr>
<td>Previous adverse events to 6-MP (median 7 [IQR 7–8])</td>
<td>Previous history of TB exposure (median 9 [IQR 7.5–9.0])</td>
</tr>
</tbody>
</table>

3.2. Factors influencing the decision to use infliximab

3.2.1. Treatment goals

The panel recognized the importance of going beyond symptom control to achieve additional treatment objectives (Table 2). There was consensus that treatment with infliximab may: improve symptoms/reduce number of flares (median 8 [IQR 7–8]), heal mucosal lesions (median 8 [IQR 7–8]), reduce hospitalisations and surgeries (median 7.5 and 8, respectively [IQR 7.75–8.0]), reduce dependence on steroids (median 8 [IQR 7–8]), and improve patient QoL (median 8 [IQR 8–8]). All of these goals, as well as restoring patient productivity (median 7 [IQR 7–8]) and achieving steroid-free clinical remission (median 8.0 [IQR 7.75–9.0]) were determined to be highly relevant factors in the decision to select infliximab for UC patients.

Table 2  Consensus: treatment goals highly relevant in the decision to use infliximab in patients with ulcerative colitis.

- Achieve fast clinical improvement (median 8 [IQR 7.75–8.0])
- Maintain symptom control (median 8 [IQR 7.75–8.25])
- Achieve mucosal healing (median 7 [IQR 7–8])
- Maintain normal gut function
- Maximize bowel preservation
- Change natural course of disease
- Improve quality of life (median 8 [IQR 7–8])
- Improve feelings of social acceptability
- Reduce physical impact of disease
- Avoid adverse effects of steroids (median 8 [IQR 7–8])
- Avoid surgery (median 8 [IQR 8–8])

3.2.2. Patient selection

Panelists agreed that they would recommend infliximab to candidates ≥16 years old and up to 70 years old (median 8 [IQR 7–9]). However, no consensus was reached on recommending infliximab to patients older than 70 (median 6 [IQR 5.0–6.5]), and the most relevant factor to this decision in this age group was safety (median 8 [IQR 8–9]). Malignancy (median 6 [IQR 4.5–7.5]) and surgical risks (median 7 [IQR 5.5–7.5]) were deemed by some to be relevant to the decision. Experts also were asked about the likelihood they would recommend infliximab to a female candidate with established UC who was pregnant or wished to become pregnant. Consensus was lacking regarding existing pregnancy (median 7 [IQR 6–7]), although the majority were highly likely to recommend infliximab to those planning pregnancy (median 7 [IQR 7–8]). Several other patient- and disease-specific factors also were considered highly influential in the decision to use infliximab (Table 3). Panelists agreed that patients with a previous history of TB exposure (median 9.0 [IQR 7.5–9.0]) or risk of latent TB reactivation (median 8 [IQR 7–9]) have relative contraindications to treatment with infliximab. Panelists agreed with product labeling that those with active infection (median 9 [IQR 8–9]; positive consensus) or congestive heart failure (median 2 [IQR 1–2]; negative consensus) are not candidates for infliximab.

Table 3  Consensus: patient factors highly relevant when initiating infliximab.

- Previous treatment failures:
  - Failed and/or did not tolerate steroids (median 8 [IQR 7.5–8.5])
  - Failed and/or did not tolerate azathioprine and/or 6-MP (median 8 [IQR 8–9])
- Steroid dependence (median 8 [IQR 8.0–8.25])
- Steroid intolerance or resistance (median 8 [IQR 7.5–8.5])
- Severity of current symptoms * (median 8 [IQR 7–8])
- Persistently active disease + laboratory results (median 8 [IQR 7–8])
- Frequent flares (median 8.5 [IQR 8.0–9.0])
- Severe flare at time of office visit (median 7 [IQR 7–8])
- Persistence of mucosal lesions (median 7 [IQR 7–8])
- Presence of extraintestinal manifestations (median 7.0 [IQR 7.0–7.5])
- Nocturnal stooling (median 7.0 [IQR 7.0–7.25])

* Nocturnal stooling, urgency, blood in stool, anemia, incontinence, tenesmus, pain, and malnutrition.
treatment—accurate definitions are essential. There was ac-
cord that the ECCO guidelines provide useful definitions of
these disease states, and the expert panel expanded on
them (Table 4).

3.2.4. Patient quality of life
The expert panel agreed that improvement in patient QoL
is achievable with infliximab in patients with UC (median 8.0
[IQR 7.75–8.0]). Consensus also was reached that restoring
patient QoL is highly relevant in the decision to select inflix-
imab (median 8 [IQR 7–8]).

3.3. Factors related to timing of infliximab therapy
Some of the expert panel agreed that initiating infliximab
when disease is not yet severe, earlier in the course of UC,
increases the likelihood of achieving treatment goals, i.e.,
symptom relief, reduced flares, mucosal healing, fewer
complications (hospitalisation and surgeries), and improved
QoL, but there was no consensus. Consensus was reached
only on the statement that using infliximab earlier in the
course of disease increases the likelihood of reducing patient
dependence on steroids (median 8 [IQR 7–8]).

3.4. Issues regarding surgery for ulcerative colitis
Most of the panel agreed that patient fear of the surgical
procedure and patient age >70 were highly relevant in the
decision to use infliximab. Consensus was reached that pa-
tient fears about the consequences of surgery (median 7
[IQR 7–8]) and possible surgical complications (median 7
[IQR 7.0–7.5]), and patient desire to avoid surgery (median
7 [IQR 7–8]) were highly relevant to the decision. Consensus

Table 4 Definitions from ECCO guidelines and definitions produced by the expert panel.

<table>
<thead>
<tr>
<th>Definition</th>
<th>Definitions from ECCO guidelines</th>
<th>Definitions from expert panel consensus</th>
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</thead>
<tbody>
<tr>
<td>Persistent active UC</td>
<td>Persistent symptoms of active UC without a period of remission, i.e., when the pattern of relapse is not infrequent but rather continuous</td>
<td>Symptoms of active UC for 6–9 months out of a 12-month period: • &gt;4 bowel movements per day independent of other symptoms • Elevated inflammatory biomarkers (e.g., CRP) • Blood in stools • Mucosal lesions • Persistence of loose stools with blood and urgency • Steroid-dependent or immunosuppressive-refractory disease • Persistence of any symptom of disease activity • Low QoL • Weight loss, anemia, malnutrition and fatigue</td>
</tr>
<tr>
<td>Steroid-dependent UC</td>
<td>Patients who are either unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting steroids, without recurrent active disease, or who have a relapse within 3 months of stopping steroids</td>
<td>None</td>
</tr>
<tr>
<td>Steroid-refractory UC</td>
<td>UC patients who have active disease despite prednisolone up to 0.75 mg/kg/day over a period of 4 weeks</td>
<td>• Failure to respond to prednisone 40–60 mg or equivalent in 2 to 4 weeks • Failure to achieve remission with prednisone 40–60 mg or equivalent in 4 weeks • Failure to respond to up to 1 mg/kg body weight of prednisone after 4 weeks • Normalisation of bowel function and absence of blood • Cessation of UC symptoms, complete endoscopic and histologic healing • Normal or improved endoscopy, normal fecal calprotectin, disappearance of symptoms that required treatment • Prolonged absence of symptoms off steroids</td>
</tr>
<tr>
<td>Remission</td>
<td>Complete resolution of symptoms and endoscopic mucosal healing: stool frequency ≤ 3/day with no bleeding, and normal or quiescent mucosa at endoscopy</td>
<td></td>
</tr>
</tbody>
</table>
also was reached that use of infliximab results in fewer surgeries (median 8 [IQR 7–8]).

### 3.5. Infliximab as an alternative to surgery

The expert panel stated that they routinely consult with surgeons prior to making treatment decisions in patients suitable for elective colectomy or infliximab therapy. Consensus was reached that infliximab can be used as an alternative to surgery in many patients with acute, severe UC at imminent risk of colectomy (Fig. 2). The expert panel agreed that many patients with moderate to severe, persistently active UC considered at risk of colectomy, or those with severe UC failing intravenous (IV) steroids are candidates for infliximab. The expert panel would use infliximab rather than cyclosporin in patients with severe active or chronic acute UC as an alternative to surgery, because infliximab was considered safer and easier to administer. There was consensus that treating acute UC patients with infliximab prolongs the time to colectomy (median 8 [IQR 7–8]).

The panel reached consensus that mucosal healing can be sustained with infliximab over time (median 8 [IQR 7–8]), and that rapid, sustained mucosal healing leads to clinical remission (median 8 [IQR 7–8]), reduced colectomy risk (median 8 [IQR 7.5–8.25]), better long-term outcomes (median 8 [IQR 8–9]), and improved patient QoL (median 7.5 [IQR 7.0–8.0]).

### 4. Discussion

The results of this Delphi survey underscore the potential of biologic therapy to change the disease course in UC. The expert panelists identified speed of clinical improvement, ability to achieve mucosal healing, better QoL, and avoidance of colectomy as critical factors in the decision to recommend biologic therapy to their patients. A variety of other factors also were deemed highly relevant, including previous treatment failures and presence of extraintestinal manifestations. Although the survey included questions about cost and reimbursement, consensus could not be reached due to regional reimbursement rules. Consensus was achieved in many other areas, however (Table 5).

Accurate identification of candidates for biologic therapy is essential—the panel achieved consensus on this point. Therefore, the definitions of “persistently active,” “steroid dependent,” and “steroid resistant” UC and of “remission” are important to ensure appropriate treatment. There was accord among panelists that the ECCO guidelines provide useful definitions, and the panelists expanded them with specific criteria.

The panelists were in consensus that their decisions to use infliximab were based on clinical trial data (median 8 [IQR 7–8]) showing significant clinical response within 8 weeks, ability to achieve clinical remission and discontinue steroids, and stimulation of mucosal healing, as well as on...
Table 5 Summary: consensus areas reached during the Delphi process.

Factors influencing the decision to use biologic therapy

Treatment goals:
- Rapid steroid-free remission (median 8 [IQR 7.75–9.0])
- Complete mucosal healing (median 8 [IQR 7–8])
- Reduction in hospitalizations and surgeries (median 8 [7.75–8.0])
- Improved patient QoL (median 8 [IQR 7–8])

Factors influencing the decision to use infliximab

Candidate characteristics:
- Persistently active, moderate to severe UC (median 8 [IQR 7–9])
- Acute severe UC (median 8 [IQR 7–9])
- Steroid-dependent UC (median 8 [IQR 8.0–8.25])
- Steroid-refractory UC (median 8 [IQR 8–9])

Quality of life issues:
- Symptoms of active UC, i.e., nocturnal stooling, malnutrition, urgency, blood in stool, anemia, incontinence (medians 7–8 [IQRs 7.5–8.25])
- Physical impact of disease on patient (median 8 [IQR 7–8])
- Inability to perform job function (median 8 [IQR 7–8])
- Improvement in QoL desired in majority of patients (median 8 [IQR 7–8])
- Cyclosporine side effects—use infliximab in severe acute (median 8 [IQR 6.5–9.0]) and chronic, active UC (median 8 [IQR 8–9])

Alternative to surgery:
- Acute severe UC (median 8 [IQR 7–9])
- Moderate to severe, persistently active UC at risk for colectomy (median 8 [IQR 7–9])
- Severe UC failing IV steroids (median 7 [IQR 7–7])
- Infliximab prolongs the time to colectomy (median 8 [IQR 7–8])
- Infliximab reduces the likelihood of colectomy (median 7 [IQR 7–8])
- Mucosal healing reduces risk of colectomy (median 8 [IQR 7.5–8.5])
- Infliximab can potentially achieve mucosal healing (median 7 [IQR 7–8])

**Long-term safety data** (median 7.5 [IQR 7–8]) from inflammatory bowel disease (IBD) cohorts and registries. (For example, see.5,14,15.) There was positive consensus that in some patients, infliximab has the potential to: improve symptoms, reduce flares, stimulate mucosal healing, reduce hospitalizations and surgeries, reduce dependence on steroids, improve QoL, restore productivity, and achieve steroid-free clinical remission.

Panelists strongly agreed that restoring QoL is an important treatment goal. The symptoms of active UC (e.g. nocturnal diarrhea, urgency, incontinence, tenesmus and pain) can have a significantly negative effect. The impact must be reduced so that patients can perform at work and enjoy leisure activities, both of which encourage feelings of social acceptability. Also, patients’ stress/anxiety about disease symptoms and long-term effects, and any fears regarding surgery must be addressed. Importantly, perceptions of QoL vary, so interpretations of improvement should be assessed on a patient-by-patient basis. There was strong consensus among panelists that the goal of restoring QoL was highly relevant in the decision to recommend infliximab.

Panelists strongly agreed that using infliximab earlier in the course of disease may improve the likelihood of achieving treatment goals. Currently, infliximab tends to be used in patients with more severe disease. Although there is strong evidence in Crohn’s disease (CD) showing benefits of initiating infliximab early, the data in UC is scant. Some experts recommend considering use of infliximab in patients with moderately severe UC who are steroid-dependent or steroid-refractory. Our expert panel reached positive consensus in agreeing with this recommendation (median 8 [IQRs 7–8 and 8–9, respectively]). Interestingly, data for use of infliximab in patients with moderate disease is building. In a cohort of 115 patients receiving infliximab, those with moderately severe compared with severe UC had a higher rate of clinical response (70% vs. 41%, P = 0.004) and clinical remission (41% vs. 17%, P = 0.015). A posthoc analysis of data from the Active Controlled Ulcerative Colitis Trial (ACT) 1 and 2 showed that infliximab patients who had mucosal healing at week 8 (Mayo endoscopic subscore classification 0 — normal or 1 — mild) were less likely to progress to colectomy at week 54 (P = 0.0004). Note that 63.8% of these patients (309/484) had moderate disease at baseline.

UC SUCCESS, a 16-week trial in biologic-naïve patients with moderately severe UC, is now complete. Patients were failing corticosteroids and either naïve to AZA or had stopped AZA ≥ 3 months before entry. Combination therapy with infliximab and AZA was found to be superior to both AZA (P < 0.05) and IFX (nominal P < 0.05) monotherapy in inducing steroid-free remission in patients with moderately severe UC. Also, patients treated with an IFX-based strategy were more likely to achieve response and mucosal healing than those treated with AZA monotherapy. A full report of this trial has not yet been published, but the data have been orally presented at ECCO 2011. The results must be extended and investigated further.

Some patients have a more progressive form of UC that is associated with poor outcomes (e.g., increased hospitalizations and colectomy and mortality rates). Predictive factors of poor prognosis in UC have been identified. A subanalysis of ACT 1 and 2 revealed that steroid dependency, high (≥ 2 mg/dL) baseline C-reactive protein (CRP), high disease severity (Mayo 10–12), and moderate to severe, active UC of short disease duration (≤ 3 years) were significantly associated with increased risk of colectomy. In a retrospective single-center analysis, independent predictors of colectomy included absence of short-term clinical response, baseline CRP ≥ 5 mg/dL, and previous intravenous treatment with cyclosporine and/or corticosteroids. A multicenter study had similar results, with the addition of a diagnosis of acute severe colitis. In routine clinical practice, physicians have to decide when to initiate infliximab therapy and for which patients. Currently, there are limited published data from large RCTs on selecting patients with these identifying factors for treatment with infliximab before rapid progression.
Patients with moderate to severe, active UC may require surgery for refractoriness to conventional treatments or for complications of their disease. The ACT trials showed that infliximab significantly reduces the risk of UC-related hospitalisations and surgeries. Importantly, infliximab is an effective rescue therapy in patients with severe or moderately severe UC not responding to conventional therapy. Cyclosporin also is effective initially for rescue therapy, but many patients will require colectomy in the long term. Patients with 6-MP/AZA failure who subsequently receive cyclosporin are especially at risk of colectomy. Moreover, the necessity of frequent monitoring and the toxicity risk associated with cyclosporin tend to make infliximab more appealing to gastroenterologists. An RCT comparing infliximab and cyclosporine has not been published, but preliminary data suggest equal efficacy in 111 patients failing IV steroids.

In a recent retrospective survey of 86 patients with steroid-refractory UC or indeterminate colitis, 65 had failed to respond to cyclosporine and were treated with infliximab as the second-line rescue therapy (CYS-IFX), and 21 had failed to respond to infliximab and were treated with cyclosporine second-line (IFX-CYS). Median follow-up was 22.6 ± 7.0 months. At month 3, 25% of patients (16/65) in the CYS-IFX subgroup and 14% of patients (3/21) in the IFX-CYS subgroup were in remission without steroids. (Three additional were in remission but with steroids.) Among the 65 patients treated with CYS-IFX, 35 (54%) were operated. Among the 21 patients treated with IFX-CYS, 14 (67%) were operated. The colectomy rate was similar whatever agent was used. The colectomy rate was similar whatever agent was used. The colectomy rate was similar whatever agent was used.

The relevance of disease status in choosing to use infliximab also was an area of non-consensus in our Delphi. This area, which arose due to lack of data, included prescribing infliximab to pregnant patients or to those >70 years old. Age >70 was considered highly relevant in the decision to use infliximab if the other option was surgery. A recent Austrian (non-Delphi) consensus on safety issues related to use of infliximab in IBD noted, as does infliximab product labeling, that no studies have focused on the safety of infliximab in the elderly. Sparse data constrained these experts, who issued 1 statement pertaining to this demographic: "Close monitoring for infectious complications is mandatory in IBD patients with higher age."

A subsequent subanalysis demonstrated harmful effects in the elderly. Comparison between a prospectively recruited study group of 95 patients >65 years old treated with infliximab or adalimumab and retrospective matched controls (190 patients ≤65 years old treated with both biologics plus 190 patients >65 years old treated with other drugs) showed that those >65 years old and treated with TNF inhibitors (TNFI) had a high rate of infections and mortality compared with younger patients, or same-age patients who did not receive TNFI. However, these results must be viewed with caution due to several study limitations (e.g., retrospective controls, uncertainty about whether disease severity was greater in biologically treated control patients, innate higher risk of infection in elderly due to comorbidities, mortality already higher in elderly with IBD). Therefore the message reiterates product labeling in recommending that particular attention be paid to treatment of the elderly.

Similarly, our Austrian colleagues could make no recommendation to continue or initiate infliximab during pregnancy. The product label recommends against it. However, ECCO has rated infliximab as "probably safe" during pregnancy and lactation, with the following official statements:

- Use of 5-ASA derivatives, corticosteroids and biologics is not significantly associated with malformations or adverse outcomes in pregnant IBD patients and their offspring.
- All anti-TNFs are likely to be excreted in the breast milk in very small amounts. However, no adverse effects have been reported in the small number of infants breastfed by mothers on this therapy.
- Infliximab is of low risk in pregnancy, both for the early and late outcomes, and does not seem to be a teratogenic.

The World Congress of Gastroenterology has taken a nearly identical position. However available data are mostly observational only. Moreover, outcomes of 130 pregnancies in the U.K. British Society for Rheumatology Biologics Register (BSRBR) led researchers to conclude that no firm conclusions can be drawn about use of TNF in pregnancy, and such treatment during conception may even be associated with increased risk of spontaneous abortion. Since our Delphi was conducted, conflicting evidence has accumulated for both a lack of infliximab-associated adverse pregnancy outcomes and cause for concern—sometimes in the same article. There is general agreement, however, that infliximab should be stopped during the last trimester of pregnancy.

Conflict of interest

R. Befrits has worked as a paid consultant for Schering-Plough.

G. D’Haens has been a consultant and speaker and has developed educational presentations for MSD; and has received grants and travel reimbursement for projects unrelated to this paper from MSD.
S. Ghosh has been a speaker and consultant for Abbott, Merck, and Shire, and has received research grants from Abbott and Merck.

P. Michetti has been a consultant for Abbott, Ferring, Merck-Serrano, MSD, and UCB; a board member for Abbott, AstraZeneca, MSD, Nycomed, and UCB; and a speaker for Abbott, MSD, and UCB; and has received grants from MSD and UCB.

T. Ochsenkühn has been a consultant and speaker and has developed educational presentations for Abbott and MSD; and has received travel reimbursement from Abbott.

R. Panaccione has been a speaker and consultant for Abbott, Schering-Plough (SP), Centocor, and Elan; has received research grants from Abbott, SP, Centocor, Millenium, Elan, Proctor & Gamble, and BMS Canada; and has served on advisory boards for Ferring, Abbott, SP, Elan, and UCB.

J. Panes has been a board member at Abbott, MSD, and Pfizer and a consultant for Roche and Novartis; has received grants from Abbott and MSD; has received payment for lectures from Abbott, MSD, Tilotts, Shire, and Ferring; and has developed educational presentations for Abbott, MSD, and Shire.

W. Reinisch has been a consultant for Abbott, Aesca, AstraZeneca, Biogen, Centocor, Ferring, Elan, Genentech, MSD, Millenium, Novartis, Schering-Plough, Shire, Takeda, UCB, Vifor, and 4SC; has provided unpaid expert testimony for Centocor; has received payment for lectures from Abbott, Aesca, Centocor, Ferring, Essex, MSD, Pharmacosmos, Schering-Plough, Shire, UCB, and 4SC; and has received travel reimbursement from all of these companies.

D. Sorrentino has been a board member for Centocor; a consultant for Centocor, Schering-Plough, Abbott, MSD, AstraZeneca, Giuliani, and Hoffmann-LaRoche; and has developed educational presentations and been a speaker for Centocor, Schering-Plough, Abbott, MSD, and Hoffmann-LaRoche.

G. van Assche has received grant support and speaker’s fees from Abbott, Schering-Plough, Centocor, and UCB.

S. Vermeire has received a grant (paid to his institution) from UCB and has been a consultant for Abbott, Centocor, MSD, and UCB.

W. Connell, CJ van der Woude, S Schreiber, and M Silverberg have nothing to disclose.

References


