DIFFERENTIATING AMONG BIOLOGIC AGENTS IN CROHN’S DISEASE

MAY 17–21, 2008, SAN DIEGO, CA, USA
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Treating CD in 2008: setting new goals

In his introduction to a satellite symposium that focused on the optimal use of biologic therapy, chairman William J. Sandborn (Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA) summarised the current treatment goals in CD. These include primarily the induction and maintenance of clinical response and remission, with steroid sparing and maintenance of fistula closing as additional targets. The current treatment algorithms for CD consist of a stepwise approach. Medical treatment typically starts with 5-aminosalicylic acid (5-ASA), antibiotics or budesonide, escalates to systemic steroids, then to immunosuppressive agents (azathioprine, 6-mercaptopurine and methotrexate), and finally to biologics (infliximab, adalimumab, certolizumab pegol and natalizumab). Natural-history studies have shown, however, that with such step-up strategies the large majority of patients progress from inflammatory disease to stricturing or perforating complications [5]. A Danish study found that the probability of surgical intervention within 15 years after diagnosis was 70% [6].

These observations have led to the new concept of intestinal damage in CD. “At a certain point in time inflammatory lesions go from reversible to irreversible. The result is tissue damage, with fibrosis, strictures and fistulas that eventually will require surgical resection. Medical therapy with steroids, for example, may improve symptoms, but very often there is this chronic inflammation progressing in the background, and patients continue to go on towards bowel damage. The field is now trying to develop an intestinal damage score — which is different from the acute disease activity — to help detect damage at an early stage, when it is potentially reversible,” Prof. Sandborn explained. Future treatment goals in CD will include mucosal healing, delaying of disease progression and reduction of hospitalisations and surgery. Large clinical trials are needed to determine if these goals can be achieved through novel treatment strategies and whether this will change the natural history of the disease.

Anti-TNF therapy improves long-term outcome

Stefan Schreiber (Department of General Internal Medicine, Christian-Albrechts University, Kiel, Germany) reviewed the clinical data on the efficacy of biologic therapies in CD. Approved agents in the European Union are the tumour necrosis factor (TNF) inhibitors infliximab and adalimumab; in the USA, the therapeutic options also include the integrin blocker natalizumab, and since very recently the TNF inhibitor certolizumab pegol. “Certain molecular characteristics differentiate the anti-TNF agents from each other. Adalimumab has the highest degree of similarity to human ‘natural’ immunoglobulin. In addition, these agents differ in their binding affinity for TNF, and in their ability to activate complement and induce immune-cell apoptosis. Yet, none of these features have thus far been shown to correlate with significant differences in clinical benefit,” Prof. Schreiber noted.

The typical induction trial is a short-term (4–10 weeks) study in which patients with moderately to severely active CD are randomised to receive either active drug or placebo at week 0 and at varying intervals thereafter. Primary end points are the rate of response (defined as the proportion of patients experiencing a decline of the CDAI [Crohn’s Disease Activity Index] score of at least 70 points from baseline) and remission (reduction of the CDAI score to less than 150). Prof. Schreiber illustrated that, with regard to their capacity to induce remission at week 4, all three TNF inhibitors show similar results, with remission rates of around 30% across agents [7–9]. For adalimumab there is a
clear dose–response relationship, with the highest short-term remission rate of 37% observed at the highest induction dose (160 mg at week 0, followed by 80 mg at week 2) [7]. In maintenance trials, patients with moderate to severe CD who respond to open-label induction therapy after two to six weeks are randomised to continued active drug therapy or placebo, and then followed for another six or twelve months. End points are usually maintenance of response and remission in these initial responders. Again, in such trials the observed differences between the anti-TNF agents are only minor, with remission rates at week 26–30 ranging from 39% with infliximab 5 mg/kg [10], through 40% with adalimumab 40 mg every other week [1], to 48% with certolizumab pegol 400 mg four-weekly [9].

A considerable proportion of patients (up to 25%) are able to sustain long-term remission on anti-TNF therapy without the use of additional steroids [10,12]. Both infliximab and adalimumab have shown efficacy in mucosal healing [13,14] and closure of enterocutaneous fistulas [15]; fistula healing can be maintained over time [1]. Anti-TNF agents also reduce the number of hospitalisations and surgery in high-risk populations, thus improving long-term outcome [10,16].

“Further trials are urgently needed to confirm whether anti-TNF therapy reduces the incidence of complications like bowel destruction with fistulas, and to develop post-operative maintenance regimens,” Prof. Schreiber concluded.

How to deal with loss of response?

A major problem with maintenance anti-TNF therapy is the loss of response over time. This phenomenon is particularly observed with episodic therapy (as opposed to scheduled maintenance treatment) [20]. “Induction therapy leads to response in 50% to 60% of patients. Successful maintenance of remission at year 1 is seen in 40% to 50% of responders. However, approximately one third of responders lose their responsiveness in the first 14–18 weeks of therapy. This clearly asks for optimalisation of the current maintenance regimens,” Prof. Schreiber summarised. Various mechanisms of action underlying the loss of response have been suggested, the most important of which appears to be the development of immunogenicity, with formation of neutralising antibodies against the drug. This may be overcome by high-dose induction, by concomitant use of immunosuppressive agents (which have consistently shown to reduce sensitisation rates), and/or by systematic maintenance therapy. Patients who become sensitised may be switched to another TNF inhibitor or to a biologic with another mechanism of action.

Adalimumab in infliximab non-responders

GAIN (Gauging Adalimumab effectiveness in Infliximab Nonresponders) was the first clinical study to prospectively evaluate the efficacy of a TNF inhibitor in CD patients who had responded to another anti-TNF drug and then lost their response or became intolerant to the original agent [2]. This four-week, randomised, double-blind, placebo-controlled trial enrolled 325 patients with moderate to severe disease at baseline, who had symptoms despite receiving infliximab therapy or who could not tolerate infliximab. They were randomised to induction doses of adalimumab (160 mg and 80 mg, at weeks 0 and 2, respectively) or placebo at the same time points. A total of 301 patients completed the study. In the adalimumab group, 21% of patients achieved remission at week 4 — the study’s primary end point — versus 7% in the placebo group (p < 0.001). Treatment with adalimumab also resulted in a significantly higher proportion of patients with CDAI reduction ≥70 (CR-70 response) compared with placebo (52% vs. 34%; p = 0.001) [2].

Study investigator Remo Panaccione (Division of Gastroenterology, University of Calgary, AB, Canada) presented one-year follow-up data from the GAIN trial at this meeting. At week 4, all GAIN patients were eligible to enter an extension phase during which they received open-label adalimumab 40 mg every other week. Patients could switch to weekly dosing in the case of flares or non-response. Post-hoc analyses of maintenance of remission (CDAI <150) and response (decline in CDAI ≥70 or ≥100) were performed in both the intention-to-treat population (all patients entering the open-label extension) and the responder population (patients with CR-70 at week 4 of GAIN). A total of 310 patients enrolled in the extension study, 126 of whom were responders. Remission and response results at week 52 (48 weeks open-label adalimumab in addition to the original four weeks in GAIN) are shown in Table 1. These data demonstrate that maintenance treatment with adalimumab sustains clinical remission and response through one year of therapy in patients who failed prior infliximab therapy. Two thirds of the GAIN responders maintained their response over one year, and 40% achieved clinical remission [4].

**Table 1**

**GAIN: MAINTENANCE OF REMISSION AND CLINICAL RESPONSE AT ONE YEAR**

<table>
<thead>
<tr>
<th>End point</th>
<th>Months since GAIN baseline*</th>
<th>Intention-to-treat n = 310 (%)</th>
<th>Responder n = 126 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>6</td>
<td>107 (35)</td>
<td>72 (57)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>89 (29)</td>
<td>50 (40)</td>
</tr>
<tr>
<td>CR-100</td>
<td>6</td>
<td>157 (51)</td>
<td>94 (75)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>135 (44)</td>
<td>83 (66)</td>
</tr>
<tr>
<td>CR-70</td>
<td>6</td>
<td>187 (60)</td>
<td>116 (92)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>156 (50)</td>
<td>82 (65)</td>
</tr>
</tbody>
</table>

* Months 6 and 12 represent Weeks 24 and 48 in the open-label extension, in addition to the original 4 weeks in GAIN

GAIN = Gauging Adalimumab effectiveness in Infliximab Nonresponders; CR-100 = drop in Crohn’s Disease Activity Index [CDAI] ≥100; CR-70 = drop in CDAI ≥70

Source: Panaccione R. Gastroenterology 2008;134(Suppl. 1):A-133–A-134

GAIN: MAINTENANCE OF REMISSION

AND CLINICAL RESPONSE AT ONE YEAR
Adalimumab sustains remission through two years of therapy

In a separate DDW oral session Dr. Panaccione reported results from an open-label extension of another pivotal adalimumab trial, CHARM (Crohn’s trial of the fully Human antibody Adalimumab for Remission Maintenance). This trial enrolled 854 patients with moderate to severe CD, who received open-label induction with adalimumab at weeks 0 and 2. At week 4, patients were stratified by the presence or absence of response or flares and randomised to 56 weeks of double-blind treatment with adalimumab 40 mg every other week (EOW), adalimumab 40 mg every week (EW), or placebo. At or after 12 weeks, patients experiencing flare or non-response could receive open-label adalimumab (EOW, and subsequently EW). Both halfway through and at the end of CHARM, the percentage of randomised responders who achieved remission (CDAI < 150) was significantly greater in the adalimumab 40 mg EOW and 40 mg EW groups than in the placebo group: 40% and 47% versus 17%, respectively, at week 26 (p < 0.001); 36% and 41% versus 12%, respectively, at week 56 (p < 0.001). Adalimumab was well tolerated. Less patients receiving adalimumab 40 mg EOW and 40 mg EW discontinued treatment due to an adverse event compared with those receiving placebo (6.9% and 4.7% vs. 13.4%, respectively).

At the end of the CHARM trial, 467 patients enrolled in an open-label extension, in which randomised patients received open-label adalimumab 40 mg EOW, and patients who had already been on open-label adalimumab 40 mg (EOW or EW) continued their regimens. Post-hoc analysis of maintenance of remission was performed for patients initially randomised to adalimumab who were in remission at week 56, both in the intention-to-treat (ITT) and the randomised-responder (CR-70 at week 4) populations; data on patients randomised to placebo in the original study were not evaluated. Table 2 summarises the remission rates two years after CHARM enrolment. Of the ITT patients who had initially been randomised to adalimumab and were in remission at the end of CHARM, 77% remained in remission at year 2. Among the randomised responders 79% maintained remission.

Table 2

<table>
<thead>
<tr>
<th>Population</th>
<th>Months since CHARM baseline</th>
<th>Remission, NRI</th>
<th>Remission, LOCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT (n = 145)</td>
<td>18</td>
<td>111 (78)</td>
<td>118 (81)</td>
</tr>
<tr>
<td>RR (n = 123)</td>
<td>18</td>
<td>99 (80)</td>
<td>103 (84)</td>
</tr>
<tr>
<td>RR (n = 123)</td>
<td>24</td>
<td>97 (79)</td>
<td>107 (87)</td>
</tr>
</tbody>
</table>

CHARM = Crohn’s trial of the fully Human antibody Adalimumab for Remission Maintenance; NRI = non-responder imputation; LOCF = Last observation carried forward; ITT = Intention-to-treat; RR = randomised responder


Critical questions regarding the optimal use of biologics in CD are related to patient selection, optimal dosing and, most importantly, proper timing of the introduction of these agents. “For the last two decades we have been using the typical step-up paradigm, in which biologic therapy is reserved for those who fail steroids and immunosuppressants. Steroids are effective for induction of remission, yet off-treatment relapse is high and immunosuppression is often required. But even in patients who respond well to steroids and immunosuppressants in terms of symptom remission, the disease is often not completely controlled, with persistently low quality of life as a result. Moreover, mucosal healing is not achieved in the majority of cases. In any clinical practice there is a cohort of CD patients who might benefit from earlier use of biologic therapy,” Dr. Panaccione noted.

Earlier initiation of biologic therapy may be particularly beneficial to patients with poor prognostic factors, who are likely to have a disabling disease course within the first five years of diagnosis. These are the patients aged less than 40 years, with only small bowel involvement, perianal lesions at diagnosis, and requiring steroids for the first flare, as well as patients with severe endoscopic lesions, who are at increased risk of surgery. The positive predictive value for poor prognosis increases with each factor. Experts in the field are currently developing new treatment algorithms for these types of patients. An example is ‘time-bound step-up,’ an accelerated step-up strategy in which pharmacokinetics play an important role: moderate CD patients who do not respond to prednisone within the first 2–4 weeks are unlikely to respond later on and therefore receive early induction with an anti-TNF agent. Prednisone-treated patients who become steroid-dependent in the first 8–12 weeks are put on methotrexate or azathioprine. The ultimate paradigm change would be a step-down approach, in which anti-TNF agents are used as initial therapy (Figure 1).
Several clinical studies have already shown promising results from such an approach. Early introduction has been associated with higher response and remission rates for all anti-TNF agents. In the course of this chronic progressive disease there appears to be a window of opportunity where we can make a real difference with treatment. Instead of just slowing down disease progression, as we are doing with our traditional non-biologic strategies, we may be able to halt the disease with anti-TNF therapy if we choose the right point in time. The ideal would of course be to pinpoint the moment where treatment would reverse structural bowel damage, which is considered the ‘holy grail’ of CD treatment,” Dr. Panaccione concluded. He emphasised that not every patient is a candidate for biologic therapy. Before starting treatment, physicians should properly assess the disease state and rule out contraindications (such as fibrostenosis) and complications.

An issue of debate is the question whether biologics should best be used in combination with other agents or as monotherapy. For a long time combination therapy has been considered preferable, based on the rheumatology experience, the reported risk of immunogenicity with monotherapy, and the potential synergy between different agents. This point of view is rapidly changing. Analyses of trial data from the clinical development programs of anti-TNF agents demonstrated no significant difference in outcome (response and remission rates, dosing changes and treatment discontinuation) between patients on maintenance anti-TNF therapy with and without concomitant immunosuppressants. This was confirmed by a late-breaking abstract at this meeting that showed that the addition of methotrexate to infliximab provided no additional benefit over infliximab alone, in terms of response and prednisone requirement at week 14 and relapse through week 50.

The benefit–risk ratio of therapy

“Optimal treatment choices cannot be made without considering the benefit–risk equation. This asks for open and effective communication between doctor and patient,” said Bruce E. Sands (Gastrointestinal Unit, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA). All effective CD therapies possess both risks and benefits. Given the negative impact of the disease on quality of life most patients are willing to accept some risk in exchange for benefit. Prof. Sands: “It is a challenging task to make sense of the sometimes conflicting data on the most worrisome side effects from CD treatment, which include infections and lymphoma. Although estimates remain uncertain, the available data suggest that the absolute risks of immune suppression with biologic therapies are small, however.”

Siegel and coworkers presented a large meta-analysis of reported adverse events from 26 studies at this meeting, including 8,843 CD patients who had been treated with infliximab, adalimumab or certolizumab pegol (more than 18,000 patient years). Ten cases of non-Hodgkin lymphoma (NHL) were reported in anti-TNF-treated patients, at a rate of 5.5 per 10,000 patient years. This translates into an elevated risk of NHL in these patients compared to both the expected NHL rate in the general population (incidence rate ratio [IRR]: 2.88) as well as to the observed rate in CD patients treated with immunomodulators alone (IRR: 1.50). Yet, the absolute event rate was low.

“As more data become available, it should become possible to minimise the risk of complications, by avoiding treating patients with the highest risk, and choosing patients who are most likely to benefit from biologic therapy. The advantages outweigh the risks when treatment is indicated,” Dr. Sands concluded. Meanwhile, adequate information supply and dialogue with the patient remain the basis for shared decision making. Best practice in risk communication suggests that absolute risks may be better understood when presented visually, by way of a risk grid or risk ladder.
References
