according to the Oxford Centre for Evidence Based Medicine (http://www.cebm.net/levels_of_evidence.asp#refs).

Conventional induction therapy for IBD

WCOG Statement 1.1
While corticosteroids for IBD provide short-term efficacy, they are associated with a significant number of adverse effects. An evolving concept is therefore, to limit long-term steroid therapy, which can be facilitated by biological therapy. [EL 1b]

Several lines of evidence support efforts to minimize corticosteroid therapy in CD. Although steroids are effective induction agents (14,15,19–21), they fail to maintain remission (22,23) [EL 2a]. Only one in four patients given corticosteroids to induce symptomatic remission will still be in remission after a year (24–26) [EL 2b]. Endoscopic improvement is uncommon after steroid therapy. In a cohort with Crohn's colitis treated with prednisolone only, 29% showed significant endoscopic improvement (27)[EL 2b]. Observational series of patients treated with multiple therapies including steroids and biologics (16,17) show that steroids are associated with a higher risk of infections [EL 2b].

There is, therefore, wide agreement that corticosteroids, even those with low systemic bioavailability, should only be used as induction agents for a limited period. As steroids are ineffective as maintenance therapy, they should not be used for this purpose [EL 1b].

How many patients with IBD need biological therapy?

WCOG Statement 1.2
Not all patients with IBD need biological therapy. [EL 5]

Cohort studies indicate that many patients with CD have a mild course of disease. In an inception cohort of 843 patients (IBSEN, Inflammatory Bowel South-Eastern Norway) diagnosed between 1990 and 1994, only a quarter were treated with immunomodulators and 4% with anti-TNF agents during the first 10 years (28)[EL 2b]. In another cohort from Minnesota, 43% of patients never had steroids (29)[EL 2b]. Among patients treated at private hospitals in Germany, 27% were managed without steroids or immunomodulators (30). Despite widespread availability of biological therapy in most countries, it is estimated that <15% patients with IBD currently receive anti-TNF treatment (http://ibdaudit.rcplondon.ac.uk/2006/).

Identifying the need for biological therapy

WCOG Statement 1.3
Clinical characteristics can be used to select patients with CD who should receive immunosuppression and/or anti-TNF treatment at an early stage of their illness. [EL 2c]

It has proved difficult to identify risk factors that predict a poor disease outcome (31–37). Smoking has an adverse effect on CD. Young patients and those with extensive small bowel CD had a 3–7-fold increase in mortality in a population-based study. Patients with extensive UC had a higher mortality in the year after diagnosis [EL 2b]. As no epidemiological study relates the outcome to the phenotype, none of these factors are sufficiently robust to guide patient selection for biological therapy.

In 2006, a retrospective study of 1,188 patients identified clinical factors associated with a "disabling" course of CD (38) [EL 2c]. This was defined as the need for more than two steroid courses, hospitalization, immunomodulators, or surgery within 5 years of diagnosis. Factors at diagnosis associated with "disabling disease" included age <40 years, initial need for steroid therapy, and the presence of perianal disease. These clinical factors have been independently confirmed (39,40) [EL 2c]. Louis and colleagues (39) defined "severe disease" as complex perianal disease, colonic resection, ≥2 small bowel resections, or a definitive stoma within 5 years of diagnosis. The prevalence of "severe disease" in their cohort was 37%. Having two risk factors (stricturing disease and weight loss at diagnosis) had a 78% predictive value for "severe disease" (39). In 72 patients diagnosed 1983–1996 in Minnesota, 54% had "disabling disease" (40) [EL 2c].

This suggests that patients presenting at a young age, with stricturing disease, needing initial treatment with steroids, and with perianal disease at diagnosis have a poorer prognosis. Such patients may benefit from early introduction of biological or immunomodulator therapy. Genotypic, serological, and immunological factors that may predict an unfavorable disease course are under investigation (41–47).

When to avoid biological therapy

Fibrostenotic CD without inflammatory activity.

WCOG Statement 1.4
Patients with fibrostenotic CD rarely benefit from biologic therapy. [EL 5]

Patients with fibrostenotic CD without objective evidence of active inflammation including an elevated C-reactive protein (CRP), endoscopy, or radiographic assessment usually have a poor response to biological therapy. Strictures are not always a contraindication to anti-TNF therapy. If the stricture is inflammatory, it may well respond, but if there is evidence of pre-stenotic dilatation, a fibrotic component which cannot be reversed by medical therapy is likely (14). A Crohn's disease Clinical trial Evaluating infliximab in a New long term Treatment regimen (ACCENT) I and the the Crohn's Therapy, Resource, Evaluation and Assessment Tool registry indicate that only disease severity or duration, and not treatment with infliximab (IFX), is associated with obstructive episodes (37). In a small study to evaluate the response of strictures to IFX, only two of six patients avoided surgery. The study was discontinued prematurely (48), but it emphasizes that clinical judgment and assessment of inflammatory activity is necessary before anti-TNF therapy for obstructive strictures (49). [EL 1b]

Infections and vaccinations.

WCOG Statement 1.5
Patients with infection should not receive biological therapy until the infection is under control. Any abscess needs effective drainage first. Latent infections (such as tuberculosis, hepatitis B, or immunodeficiency virus) should be excluded or treated before biological therapy starts. Patients who have received live vaccines should not receive biological therapy for 3 months. [EL 5]

WCOG Statement 1.6
Before starting biological therapy latent tuberculosis should be excluded. The vaccination status should be reviewed and updated if necessary. [EL 5]

Screening for tuberculosis should follow local guidelines, and an European Crohn's and Colitis Organization Consensus on vaccination has been published (18). Patients had best see a health-care professional before administration of biologics when new or unexplained symptoms occur and be instructed to contact their doctor promptly should fever, cough, skin rash, or neurological symptoms arise (18).

Malignancy and other relative contraindications.

WCOG Statement 1.7
Patients with a history of malignancy (excluding non-melanoma skin cancer) or lymphoproliferative disorder, severe congestive heart failure, or demyelinating neurologic disease should not be treated with anti-TNF therapy if other options exist. [EL 5]

A meta-analysis of anti-TNF trials in 3,955 patients with CD showed no difference in malignancy rates between anti-TNF and control groups (50). There are few data on the risk of anti-TNF therapy in patients with previous malignancy. In the British Society of Rheumatology Biologics' Register, 6 of 154 patients (4%) who had a malignancy before starting anti-TNF therapy developed a new cancer compared with 158 of 9,844 patients (1.6%) with no previous malignancy (51). In those with an earlier malignancy, the condition was diagnosed >10 years before anti-TNF therapy. In August 2009, the Food and Drug Agency (US) (FDA) updated the "Boxed Warnings" alerting prescribers to an increased risk of lymphoma and malignancies in children or adolescents treated with anti-TNF therapy (http://www.fda.gov), because an FDA analysis identified 48 cases of malignancy in this population. Half of these were lymphomas and 88% had been treated with concomitant immunomodulators. Potential benefits of anti-TNF therapy must be balanced against the potential risks of malignancy (52–54).

Choice of biological therapy

WCOG Statement 1.8
Based on the available evidence on mode of administration, clinical outcomes, quality of life outcomes and economic analyses, the first-line biologic for luminal CD should be tailored to the individual patient, practice and country setting. [EL 2c]

Modes of administration include intravenous (IFX, natalizumab (NAT)) and subcutaneous (CZP, ADA). Intravenous infusion takes longer time to administer than subcutaneous injection [EL 1b], and can lead to serum sickness [EL 4]. Subcutaneous dosing can lead to painful injection-site reactions or prolonged post-injection pain [EL 4], but modes of administration have not been compared head-to-head. Intravenous dosing has the advantage of directly observed patient adherence. A qualitative study of patient preferences of anti-TNF agents in rheumatoid arthritis suggests that younger patients prefer the convenience of subcutaneous dosing, whereas older patients prefer the perceived safety of infusion in a clinic [EL 2c]. The choice should be discussed with individual patients.

WCOG Statement 1.9
Currently, infliximab has the longest and most extensive history of published clinical trial data and clinical experience in CD. Studies with other biologic agents (adalimumab, certolizumab pegol and natalizumab) suggest that they produce generally similar benefits in CD, although the study populations were different. [EL 5]

When to start biological therapy

Luminal CD.

WCOG Statement 1.10
Biological therapy is indicated in steroid-refractory, steroid-dependent and/or immunomodulator-refractory inflammatory bowel disease and in patients intolerant to these conventional therapies. [EL 1b]

Perianal fistulizing CD.

WCOG Statement 1.11
A complex fistula in CD is an indication for biological therapy in conjunction with surgical drainage. [EL 1b]

Despite a detectable effect of antibiotics on fistula drainage, recurrence is common (55–57). AZA has only been assessed in retrospective series, where "healing of fistulas" was reported in a third of patients (58). Given the devastating long-term effect of perianal disease on fecal continence, complex fistulizing CD warrants intervention with anti-TNF therapy. The ACCENT II trial demonstrated that most patients with draining fistulas experienced improvement or cessation of drainage within 8 weeks of starting IFX (7). Combining anti-TNF therapy with ciprofloxacin may improve results, with 73% "fistula response" after 18 weeks' combination treatment vs. 39% on IFX alone (59). Nevertheless, disappearance of fistulas visualized by MRI is unusual (60). Combined medical and surgical strategies have therefore evolved, with drainage of sepsis and insertion of a seton, followed by two doses of anti-TNF therapy, fistula curettage, and then further anti-TNF therapy (61,62).

WCOG Statement 1.12
The efficacy of IFX for induction of fistula closure is better documented than for ADA or CZP [EL 2c]. The relative strength of available data suggests that IFX should be the first line biologic for fistulizing CD until more data become available. [EL 5]

Local sepsis and abscess.

WCOG Statement 1.13
All septic collections need to be drained before biological therapy is started. [EL 5]

Drainage of a perianal or an intraabdominal abscess is essential before anti-TNF therapy.

Treatment-refractory UC.

WCOG Statement 1.14
Infliximab is effective for treatment-refractory, moderate or severe UC [EL 1b]. IFX can induce or maintain remission and mucosal healing [EL 2c]. It is not known whether oral immunomodulators without IFX will maintain remission. Other drugs may prove as effective, but there is insufficient published evidence. [EL 4]

Outpatients with treatment-refractory, moderately active UC benefit from IFX (1). Patients with UC who are corticosteroid dependent (63) usually receive thiopurines (15), but it remains to be determined whether combination therapy in UC is superior to AZA or IFX alone. Other anti-TNF agents in UC are under study (below). Before initiating treatment with IFX, colectomy and ileoanal pouch formation should at least be discussed as surgery usually becomes necessary if patients fail to respond to IFX. However, IFX appears to halve the risk of colectomy (64) during a year of treatment.

Acute severe UC.

WCOG Statement 1.15
For patients admitted to the hospital with severe UC colitis that is then refractory to intravenous steroids, IFX halves the need for colectomy on that admission [EL 2b]. The efficacy of IFX relative to cyclosporine remains to be determined.

A Scandinavian trial investigated a single dose of IFX 5 mg/kg given to patients with acute severe UC failing intravenous corticosteroids (65). Colectomy within 90 days was avoided in 17 of 24 (71%) after IFX, but in only 7 of 21 (33%) patients given placebo ($P=0.02$). This demonstrates the potential of a rescue strategy, and a comparison between IFX and cyclosporine is under study. Continued treatment with IFX or AZA to reduce the risk of relapse appears sensible, but it is unclear which approach is superior.

Role of immunomodulators when starting biological therapy

WCOG Statement 1.16
When starting biological therapy in patients with CD naïve to thiopurines the combination of IFX and AZA is better for induction of remission and mucosal healing over 1 year [EL 1b]. The optimal maintenance strategy after this induction regimen and whether the same applies to other agents remains unknown.

Only patients with an elevated CRP or mucosal lesions at colonoscopy benefited from combining IFX and AZA in the Study Of biologic and immunomodulator Naive patients In Crohn's disease (SONIC) trial (49). AZA may influence IFX immunogenicity, but other reasons are possible (66). The optimal strategy after 12 months' combination therapy remains unknown, but reducing treatment towards monotherapy may be appropriate, simply to reduce infection risks (17). Whether combination therapy could improve outcomes from other anti-TNF agents is unknown.

Continuing biological therapy for luminal CD

WCOG Statement 1.17
Patients with moderate to severe luminal CD who have responded to an induction regimen with anti-TNF therapy should be considered for scheduled re-treatment with or without concomitant immunomodulators. This strategy is more effective than episodic therapy for maintaining response. NAT for appropriately selected patients is also effective at maintaining response. [EL 1b]

Maintenance with IFX. The pivotal maintenance trial for IFX was ACCENT I. It studied patients with moderate–severe luminal CD refractory to conventional treatment (2) and compared single-dose with three-dose induction, leading to 65 and 52% respective response rates at 10 weeks. Responders at week 2 were randomized to placebo, 5 or 10 mg/kg IFX every 8 weeks. The median time to loss of response was longer in patients who continued IFX (19 weeks on placebo, 38 weeks at 5 mg/kg, >54 weeks at 10 mg/kg; $P=0.0002$). Maintenance therapy with IFX was superior to placebo at week 54 (remission 14% on placebo, 28% at 5 mg/kg, 38 % at 10 mg/kg; $P<0.05$) [EL 1b]. Patients on scheduled therapy had more mucosal healing (9) [EL 2b], fewer hospitalizations and surgery (67) [EL 2b], and a better quality of life (68) [EL 1b].

Maintenance with ADA. The pivotal maintenance trial for ADA was Crohn's trial of the fully Human Antibody adalimumab for Remission Maintenance (CHARM) (4) [EL 1b]. Patients with moderate–severe CD refractory to conventional therapy or IFX received open label ADA 80 mg at week 0 and 40 mg at week 2. Responders were randomized to ADA 40 mg every other week, ADA 40 mg every week or placebo. A total of 60% responded by week 4. Both maintenance doses were effective at weeks 26 and 56. Remission rates at week 26 and 56 were, respectively, 17 and 12% on placebo, 40 and 36% on ADA 40 mg every other week and 47 and 41% on ADA 40 mg every week ($P<0.001$) [EL 1b]. Concomitant immunomodulators or previous anti-TNF therapy did not affect response, remission, or steroid withdrawal. Patients on ADA had fewer hospitalizations and surgery (69).

Maintenance with CZP. The pivotal maintenance trial for CZP was Pegylated antibody fRagment Evaluation in CrOhn's dIsease: Safety and Efficacy (PRECiSE) II (5) [EL 1b]. Patients with moderate–severe CD received open-label CZP 400 mg at 0, 2, and 4 weeks; responders were randomized to continue CZP 400 mg every 4 weeks or placebo. A total of 64% responded for initial induction. At week 26, 63% on CZP maintained response compared with 36% on placebo ($P<0.001$). The proportion maintaining remission was significantly higher with CZP (48 vs. 29%, $P<0.001$) [EL 1b]. Response to CZP was no different for those with an elevated CRP, concomitant immunomodulators, or previous anti-TNF therapy.

Maintenance with NAT. The pivotal maintenance trial for NAT was Efficacy of Natalizumab as Active Crohn's Therapy (ENACT)-2 (70) [EL 1b]. Patients with active CD who had responded to induction therapy with NAT in ENACT-1 were randomized to receive 300 mg NAT or placebo (1:1) every 4 weeks. In all, 61% of NAT-treated patients had a sustained response vs. 28% on placebo ($P<0.001$) at week 36 [EL 1b]. Remission rates were 44% on NAT and 26% on placebo ($P=0.003$). Response and remission rates were significantly better with NAT compared with placebo at every time point beyond week 20. At week 36, 45% on NAT and 22% on placebo were off corticosteroids ($P=0.003$). Serious adverse events occurred in 8% on NAT and 10% on placebo. The risk of progressive multifocal leucoencephalopathy transpired after this study. NAT is approved by the FDA, but not by European Medicines' Evaluation

Agency, as monotherapy for moderate-to-severe CD, for patients with biological evidence of disease activity, who have failed to respond to conventional therapy and at least one anti-TNF agent.

Continuing biological therapy for fistulizing CD

WCOG Statement 1.18
Patients with fistulizing CD who have responded to an induction regimen with anti-TNF therapy, should receive scheduled re-treatment with IFX or ADA, since this is effective for maintaining fistula closure or response [IFX EL 1b; ADA EL 2b]. No controlled data are available for fistula closure with NAT or CZP.

Fistula maintenance with IFX. The pivotal maintenance trial for IFX in fistulizing CD was ACCENT II (7) [EL 1b]. Systematic treatment with IFX 5 mg/kg every 8 weeks was superior to placebo in both improvement and closure of draining fistulas over 54 weeks [EL 1b]. The median time to loss of response was >40 weeks on scheduled treatment with 5 mg/kg every 8 weeks following three-dose induction therapy.

Fistula maintenance with ADA. There is no dedicated maintenance study of ADA for fistulizing CD. Within the CHARM study (8), 117 patients had documented draining fistulas. A third of those given ADA had fistula closure on two consecutive visits. This proportion remained constant [EL 2b]. The results of extended treatment (to 3 years) show that response is maintained (71).

Continuing biological therapy for UC

WCOG Statement 1.19
Patients with UC refractory to conventional therapy which has responded to infliximab should best be considered for continuing therapy, since scheduled re-treatment is effective for maintaining response and reducing the risk of colectomy. [EL 1b]

IFX is the only anti-TNF agent licensed for therapy of moderate-to-severe UC. In the active ulcerative colitis trials (ACT) studies, outpatients with moderate–severe UC who had failed or were intolerant to aminosalicylates (ACT-2), corticosteroids (ACT-1 and -2), or thiopurines (ACT-1) were randomized to IFX (5 or 10 mg/kg) at 0, 2, 6 weeks, or placebo followed by maintenance IFX/placebo every 8 weeks for 46 weeks (ACT-1) or 6 months (ACT-2) (1). At week 8, significantly more patients receiving IFX had a clinical response compared with placebo (62–69% for IFX vs. 37% for placebo, $P<0.001$), which was maintained to week 30 (47–60% for IFX vs. 26–30% for placebo; $P<0.001$) [EL 1b]. Remission defined as a Mayo score <2 was achieved in 39 and 34% in the 5 mg/kg IFX group at weeks 8 and 30, respectively, compared with 15 and 16% on placebo [EL 1b]. Mucosal healing was seen at both IFX doses (59–62% at week 8 and 46–50% at week 30 vs. 34% and 25% for placebo; $P<0.001$). Steroid withdrawal by week 30 was achieved in 19–24% on IFX.

Recently, results were released of a controlled trial with ADA in patients with moderate–severe UC, naïve to anti-TNF agents. Clinical remission at week 8 was attained in 18.5% of patients following induction with 160 mg ADA at week 0, 80 mg ADA at week 2, and 40 mg every other week thereafter ($P=0.031$) vs. 10% following induction with ADA 80 mg/40 mg and 9% with placebo (not significant (NS)) (72) Long-term results of this trial are awaited.

Role of immunomodulators and continuing biological therapy

WCOG Statement 1.20
Combined treatment with an immunosuppressant and infliximab for patients with moderate-severe CD is more effective than monotherapy for patients naïve to both agents [IFX EL1b, ADA, CZP EL5].
The risks of combination immunosuppression should be considered, especially in children, young adults, or the elderly. It is not known whether the same applies to other anti-TNF agents. Natalizumab should not be combined with an immunosuppressant or prolonged corticosteroids, because this may increase the risk of progressive multifocal leucoencephalopathy.

Influence on efficacy. A key question is whether combination therapy improves efficacy (synergy). This may depend on the patient population. For patients with established, active CD despite immunomodulators, *post-hoc* analyses of the pivotal trials with IFX, ADA, CZP, and NAT have not demonstrated superior efficacy in patients failing immunomodulators (5,73–75) [EL 2b]. An 18-month follow-up study (Infliximab Maintenance Immunosuppressives Discontinuation (IMID)) trial in 80 CD patients who had failed immunomodulators before starting IFX, found no benefit from continuing immunomodulators beyond 6 months (76) [EL 2b]. A total of 60% of patients on continued immunomodulators experienced relapse compared with 55% who discontinued their immunomodulator ($P=$ NS). The major criticism is that the study was underpowered, so cannot definitively demonstrate equivalence between the strategies.

IFX and thiopurines. Lémann *et al.* (77) studied 113 patients with active steroid-dependent CD. In all, 55 were receiving AZA/mercaptopurine (MP) at a stable dose and were continued on this treatment. Patients were randomized to IFX 5 mg/kg or placebo at weeks 0, 2, and 6. Steroid-free remission at week 24 was attained in 57% on IFX vs. 29% on placebo ($P=0.003$). In both patients with and without previous immunomodulators, success rates were significantly higher in the IFX group up to 6 months [EL 2b]. However, this study does not constitute the proof that IFX can be used as a bridge, because long-term follow-up showed that the majority of AZA naïve patients relapsed (73% after 4 years) (78) [El 2b].

The most coherent evidence that combination therapy has a synergistic effect comes from the SONIC trial (49)[EL 1b], which demonstrated that in relatively early CD, the combination of IFX and AZA was superior to either IFX or AZA alone in patients naïve to immunomodulators and biologics. At week 30, 57% on combination therapy with IFX and AZA, 44% on IFX monotherapy, and 31% on AZA monotherapy were in steroid-free remission [EL 1b]. The benefit was dominated by those with endoscopic or biochemical evidence of active inflammation at trial entry. Absence of ulcers at week 30 occurred in 44% on combination therapy, 30% on IFX, and 16% on AZA monotherapy. These differences were maintained through week 50. The decision to use combination therapy cannot

be divorced from the safety implications, which are reviewed in an accompanying paper (79).

IFX and methotrexate. The Combination of Maintenance Methotrexate-Infliximab Trial trial was a randomized placebo-controlled trial comparing methotrexate in combination with IFX against IFX alone in patients who received prednisone induction therapy for active CD (80)[EL 1b]. The primary end point was time-to-treatment failure (success was Crohn's Disease Activity Index < 150 through week 50 and no steroids). There were no differences in steroid-free remission between the two groups (76 and 77% at week 14; 56 and 57% at week 50). Although this can be interpreted as a failure of methotrexate to offer additional benefit to IFX, the very high rate of steroid-free remission (twice that seen in the pivotal studies) is notable. Whether this is due to the induction regimen that included steroids, or the mandated withdrawal of steroids, is unclear.

Predicting response to biological therapy

Identifying factors that influence response or failure could help select the most appropriate biological regimen for individual patients.

Clinical predictors. **Tables 1** and **2** list the studies that have examined predictive factors for successful anti-TNF therapy in CD. Most are *post-hoc* or retrospective analyses, therefore, the levels of evidence are low. Comparable data in UC are scarce.

Predictors of response in luminal CD.

WCOG Statement 1.21
Patients with early luminal CD have a higher chance of response to anti-TNF therapy than those with longstanding disease. [EL 3]

Several analyses have convincingly shown that anti-TNF therapy is more effective in patients with a short disease history. In the CHARM trial with ADA, remission rates approached 60% in patients who had CD for <2 years compared with 40% ($P<0.05$) in those with a longer duration of disease (4). The same applies to CZP (5,6). In all, 90% of patients given IFX as first-line treatment had a clinical response (12). The most compelling evidence in favor of early intervention comes from a pilot trial in postoperative CD: 10 of 11 (91%) patients treated with IFX after ileocolic resection had no endoscopic recurrence after 1 year compared with 2 of 13 (15%, $P=0.0006$) given placebo (81).

Patients with isolated colonic disease (77,82,83) and those with no previous abdominal surgery (26,31,40) are also more likely to respond to anti-TNF therapy. Young patients (77,82,83) and nonsmokers (82–84) have a better response in some studies, but not all (85). Patients with endoscopic evidence of ileocolonic ulcers at baseline had a better response (49), whereas those with stricturing disease are less likely to respond (37,47).

Predictors of response in fistulizing CD. In an open study from Calgary, the presence of a rectovaginal fistula predicted a poor response IFX (86), but this was not confirmed in the ACCENT II study (10).

Predictors of response in UC. Few studies have examined predictors of (non-)response to anti-TNF therapy in UC (87,88). Factors associated with short-term response include young age and absence of perinuclear anti-neutrophil cytoplasmic antibodies (89). For long-term outcome, independent predictors for colectomy include absence of a short-term clinical response, a baseline CRP >5 mg/l, and previous intravenous treatment with corticosteroids or cyclosporine (90).

Biological predictors.

WCOG Statement 1.22
Patients with a high CRP have a higher chance of achieving and maintaining response to biological therapy than patients with a low or normal CRP. [EL 1b]

CRP is a marker of inflammation that generally correlates well with disease activity in CD (91). Not surprisingly, patients with an increased CRP have the best chance of responding to anti-TNF therapy. A baseline CRP >5 mg/l before the start of IFX was associated with higher response (76%) compared with patients with normal CRP (46%, $P=0.004$) (92). In the SONIC study (49), a CRP >8 mg/l at baseline also predicted clinical response. Similar findings have been reported for CZP, ADA, and the anti-adhesion molecules (6,70,93). In ENACT-1, patients with a raised CRP showed significant benefit of NAT over placebo (70). In the Leuven cohort, a return to normal of an elevated CRP after the initiation of IFX was associated with a better outcome (94). However, up to 46% of patients with a normal or low CRP did show response in another Belgian study (92). So restricting the biological therapy to patients with an increased CRP would deny treatment to a substantial proportion of patients who might benefit.

Anti-*Saccharomyces cerevisiae* and perinuclear anti-neutrophil cytoplasmic antibodies are serological markers associated with IBD (91). Despite initial reports (95), a large study showed that neither anti-*Saccharomyces cerevisiae* nor perinuclear anti-neutrophil cytoplasmic antibodies alone or in combination could predict response to anti-TNF therapy (96). Expanding the panel of serological markers has not yet improved the predictive value with regard to response to biological therapy.

Trough drug concentrations.

WCOG Statement 1.23
High trough concentrations of IFX have been associated with more durable maintenance of clinical response [EL 2b] and low trough concentrations with potential loss of response.

A Belgian study showed that patients with luminal CD who received episodic IFX treatment and developed antibodies to IFX (antibodies to infliximab (ATIs)) during follow-up, had lower IFX trough concentrations 4 weeks after the first infusion compared with patients who never developed ATIs (97). Trough concentrations 4 weeks after the first infusion were lowest in the patients with ATIs >8 μg/ml compared with patients with no or low ATIs or inconclusive ATI concentrations (97). The Toronto group (88,98) reported that clinical and endoscopic remission rates were

Table 1. Clinical predictors of response to anti-TNF therapy from randomised controlled trials

Author	Year	No. of randomized patients (initial population)	Anti-TNF	Duration (weeks)	Randomized patients	Factors possibly associated with a better efficacy	Factors not associated with a better efficacy
Targan *et al.* (117)	1997	108 (108)	IFX single infusion 5, 10, 20 mg/kg or placebo	12	Patients with active CD	None	Disease location Concomitant medication
Rutgeerts *et al.* (118)	1999	73 (73)	IFX 10 mg/kg per 8 week	44	Responders to an initial IFX treatment	Concomitant thiopurine therapy	NR
Present *et al.* (119)	1999	94 (94)	IFX 5 or 10 mg/kg vs. placebo	34	Patients with CD who had draining abdominal or perianal fistulas	None	Concomitant medication Single or multiple fistulae
Hanauer *et al.* (2)	2002	335 (573)	IFX 5 mg/kg per 8 week 10 mg/kg per 8 week	54	Responders at week 2 to open-label IFX (single infusion of 5 mg/kg)	None	NR
Sands *et al.* (120)	2004	282 (306)	IFX 5 mg/kg per 8 week or placebo	54	Patients with CD who had draining abdominal or perianal fistulas Responders and non responders after 3 IFX infusion at weeks 0 and 14 were randomized	None	All baseline characteristics
Schreiber *et al.* (93)	2005	292	CZP 100, 200, 400 mg or placebo at weeks 0, 4, 8	12	Patients with active CD	CRP >10 mg/l	NR
Lémann *et al.* (77) (GETAID)	2006	112 (113)	AZA+IFX (3 infusions) AZA+placebo	52	Steroid-dependent patients Stratified as AZA naïve or AZA failure	Low CDAI at baseline Young age Absence of small bowel involvement Long duration of steroids	All other baseline characteristics including sex, previous surgery, steroid dose, CDEIS, CRP
Hanauer *et al.* (3) (CLASSIC I)	2006	299 (299)	ADA 40/20 mg, 80/40 mg, 160/80 mg or placebo at weeks 0, 2	4	Patients with active CD	None	CRP >10 mg/l, concomitant immunosuppressive therapy
Colombel *et al.* (4) Schreiber *et al.* (11)(CHARM)	2007	499 (854)	ADA 40 mg eow 40 mg/wk	56	Responders to open-label ADA (80 mg/40 mg) at week 4	No previous IFX therapy Early disease	CRP >10 mg/l, concomitant immunosuppressive therapy
Sandborn *et al.* (121)	2007	55 (276)	ADA 40 mg eow 40 mg per week	56	Patients from an induction RCT then received open-label ADA 40 mg at week 0 and 2. Remitters at week 4 enrolled	None	Concomitant immunosuppressive therapy
Sandborn *et al.* (102) (GAIN)	2007	325 (325)	ADA 160/80 mg or placebo	4	Patients with active CD previously treated with IFX	Corticosteroids at baseline[1]	Previous loss of response or intolerance of IFX, CRP, concomitant immunosuppressive therapy, presence of ATI
Schreiber *et al.* (5) Sandborn (122) (PRECISE 2)	2007 2006	428 (668)	CZP 400 mg per 4 week	26	Responders to open-label induction with CZP 400 mg at weeks 0, 2, 4	No previous IFX therapy Recent disease onset	CRP >10 mg/l, Concomitant steroids or immunosuppressive therapy, smoking status, BMI
Sandborn *et al.* (6) (PRECISE 1)	2007	662 (662)	CZP 400 mg per 4 week	26	Patients with active disease (induction then maintenance)	No previous IFX therapy	CRP >10 mg/l, concomitant steroids or immunosuppressive therapy
Colombel *et al.* (49) In press	2008	508 (508)	IFX 5 mg/kg IFX+AZA AZA	26	Patients with active disease and no previous exposure to biological agents and immunosuppressive agents (induction then maintenance)	Concomitant azathioprine, CRP, and presence of endoscopic lesions at baseline	NR

ADA, adalimumab; AZA, azathioprine/mercaptopurine; BMI, body mass index; CD, Crohn's disease; CDEIS, Crohn's disease endoscopic index of severity; CRP, C-reactive protein concentration; CZP, certolizumab pegol; IFX, infliximab; NR, not reported; RCT, randomized controlled trial; TNF, tumor necrosis factor.

Table 2. Clinical predictors of response to anti-TNF therapy from cohort studies

Author	Year	No. of patients	Prospective or retrospective	Anti-TNF	Episodic/ scheduled	Follow-up (months)	Characteristics of patients	Factors associated with a better outcome	Factors not associated with a better outcome
Farrell *et al.* (123)	2000	100	Prospective	IFX	E	6	L/F	None	Concomitant IS or CS
Cohen *et al.* (124)	2000	129	Prospective	IFX	E	12	L/F	Concomitant IS	NR
Ricart *et al.* (125)	2001	100	Retrospective	IFX	E/S	7 (median)	L/F	None	NR
Parsi *et al.* (84)	2002	100	Retrospective	IFX	Induction only	>3	L/F	Concomitant IS (L only) Non-smoking status	Colonic involvement, age, concomitant CS
Vermeire *et al.* (82)	2002	240	Prospective	IFX	Induction only	4	L/F	Young age Isolated colitis No previous surgery Concomitant IS CRP level	Age, gender, disease duration, concomitant CS, smoking status
Kinney *et al.* (126)	2003	122	Retrospective	IFX	E	—	L/F	Concomitant IS (trend)	NR
Arnott *et al.* (83)	2003	74	Prospective	IFX	Induction only	12	L/F	Isolated colitis Non-smoking status Concomitant IS	Age, previous surgery
Fefferman *et al.* (85)	2004	200	Prospective	IFX	Induction only	>6	L/F	None	Concomitant IS or CS, smoking status, age, gender, disease duration, previous surgery
Luna-Chadid *et al.* (127)	2004	108	Prospective	IFX	Induction only	3	L/F	None	Concomitant IS
Laharie *et al.* (128)	2005	44	Retrospective	IFX	Induction only	2	L	Isolated colitis Concomitant IS Non-stricturing disease Young age of CD onset	CRP, age, gender, smoking status, CDAI, steroids
Orlando *et al.* (129)	2005	573	Retrospective	IFX	Induction only	3	L/F	Multiple infusions vs. single infusion (L) No previous surgery (L)	Age, gender, location, smoking status, concomitant IS
Poupardin *et al.* (130)	2006	137	Retrospective	IFX	E/S	15	L/F	NR	Concomitant IS
Pacault *et al.* (131)	2006	137	Retrospective	IFX	E only	35	L/F	Continuous concomitant IS No previous use of IS Non-smoking status	Age, gender, location, disease duration, luminal or fistulizing CD
Allez *et al.* (104)	2009	67	Retrospective	CZP	S	6 (median)	L/F Previous failure of ADA and IFX	None	Age, gender, disease duration, concomitant CS or IS, location, behavior
Rudolph *et al.* (35)	2008	198	Retrospective	IFX	S only	30 (median)	L/F	Concomitant IS started >3 months before IFX Non-smoking status	Gender, age, disease duration, location, previous surgery, induction dosing
Karmiris *et al.* (99)	2009	168	Prospective	ADA	S only	~24 (median)	L/F	Decrease in elevated CRP to normal value after induction	Concomitant IS or CS
Schnitzler *et al.* (94)	2009	614	Prospective	IFX	E/S	55 (median)	L/F	Decrease in elevated CRP to normal value after induction	Concomitant IS or CS at baseline, disease duration, previous surgery CRP level at baseline Luminal or fistulizing CD
Gonzaga *et al.* (133)	2009	153	Retrospective	IFX	S only	~48 (mean)	L/F	No previous episodic exposure Concomitant methotrexate (trend)	Concomitant IS Previous failure of IS
Cohen *et al.* (134)	2009	75	Retrospective	ADA	S only	53 (median)	Previous IFX therapy in 69%	Female Non-smoking status Non-isolated colitis[a]	—

ADA, adalimumab; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein concentration; CS, corticosteroids; CZP, certolizumab pegol; NR, not reported; IFX, infliximab; IS, immunosuppressive therapy including thiopurines and methotrexate; F, fistulising, L, luminal Crohn's disease; E, episodic, S, scheduled treatment strategy; TNF, tumor necrosis factor.
[a]Predictive factors of dose increase with ADA.

higher in patients with detectable trough serum IFX. The value of measuring trough drug levels (66,99) was confirmed by retrospective data from the Mayo clinic, but ATI concentrations were not consistently associated with outcome (100).

Genetic predictors. Several genetic factors have been studied with regard to response to IFX (47). They need to be confirmed in different cohorts of patients, as most studies are retrospective analyses of single-center cohorts with modest sample sizes.

WCOG Statement 1.24
Despite attempts to link genetic factors to the clinical response to anti-TNF therapy, no definitive result can currently be translated into clinical practice. [EL 2c]

Therapeutic strategies

Bridging from biological therapy to immunomodulators in CD.

WCOG Statement 1.25
Bridge therapy to an oral immunomodulator has been shown to be associated with a higher rate of clinical relapse than scheduled re-treatment for patients with moderate-severe luminal CD who have responded to induction biological therapy. [EL 2b]

There still appears to be a group of patients who can have remission induced by anti-TNF therapy and maintenance with an immunomodulator, but there are no predictive factors to identify such patients (77).

Bridging from biological therapy to immunomodulators in UC.

WCOG Statement 1.26
Hospitalized patients with UC refractory to intravenous steroids who have responded to IFX can have a prolonged response to an oral immunomodulator without scheduled re-treatment, although more data are needed. [EL 2b]

At 2 years after the trial of IFX in hospitalized patients (65), only 4 of 24 patients had required additional IFX (101). In all, 13 of 15 IFX responders received AZA through the 2-year follow-up. It is possible that patients with acute severe UC have a prolonged response to IFX followed by AZA, but difficult to think of a biological reason that UC should differ from CD in this respect.

Managing loss of response to biological therapy. Randomized controlled trials have shown that anti-TNFs initially fail in 10–30% of patients. These are classified as "primary failures." Those who show initial benefit, but lose response over time are termed "secondary failures." Central to the evaluation is whether lack of response is due to factors unrelated to the drug. This includes absence of active inflammation, concurrent infection, or septic complications. A key question is the time point defining non-response. Most agree that primary non-response should not be determined before 8–12 weeks. This translates into induction dosing with IFX at weeks 0, 2, and 6 before determining response, although few respond to a third dose of IFX if they have not already responded. For ADA, some respond out to week 12, so patients should receive additional doses beyond 160 mg/80 mg "induction" dosing. Similar time lines exist for CZP. Data from the registration trials for ADA and CZP show that patients who have lost response to one anti-TNF agent have a lesser response to a second agent compared with anti-TNF naïve patients (4,5,102,103). A retrospective series of 67 patients from France who had received all three anti-TNF agents suggests that primary non-responders to one anti-TNF may still show response to a second or a third agent (104,105).

WCOG Statement 1.27
A diminished or suboptimal response to IFX can be managed by:
i. shortening the interval between dosing [EL 2b]
ii. increasing the dose to 10 mg/kg [EL 1b]
A diminished or suboptimal response to ADA can be managed by weekly dosing. [EL 1b] A diminished or suboptimal response to CZP can be managed by a supplemental dose [EL 2b]. Patients who continue to have a diminished or loss of response after increasing the dose may benefit from switching to a different anti-TNF agent. [EL 1b]

WCOG Statement 1.28
Patients losing response to one anti-TNF have a lower chance of responding to a second anti-TNF agent. [EL 5]

Secondary non-response affects 30–40% of patients during the first year of therapy (2,4,5). It is unclear whether there are differences between anti-TNF agents. Secondary non-response may also be due to disease-related factors (above) or drug-related factors including neutralizing antibodies, altered clearance of drug, or possibly biological escape mechanisms. Dosing is best "optimized" by increasing the dose or shortening the interval before switching to another anti-TNF agent (106). In the ACCENT I trial, 88% who had initially responded to IFX but lost response during maintenance therapy, regained response by increasing the dose to 10 mg/kg (107). With loss of response to ADA 40 mg every other week, shortening the interval to 40 mg every week re-establishes response in ~75% (108). The optimal strategy for loss of response to CZP is unclear. Data from a small group of patients who lost response during PRECiSE 2 suggest that a single re-induction dose with CZP 400 mg may re-establish response (109).

When anti-TNF agents fail, switching treatment to an agent with a different mechanism of action is logical. The only other biologic currently available is NAT (70,110). In the Efficacy of Natalizumab in CrOhn's disease Response and rEmission trial trial evaluating NAT induction therapy in CD, subgroup analysis demonstrated that NAT was as effective for patients who had failed to respond to anti-TNF therapy as those who were anti-TNF naïve (111).

Managing intolerance to biological therapy.

WCOG Statement 1.29
Patients with CD who have intolerance to one anti-TNF therapy may achieve a therapeutic response to a different anti-TNF agent. Careful consideration should be given to the reasons for intolerance. [IFX EL 1b, ADA/CZP EL 2b]

Patients who develop intolerance to IFX are reasonably switched to treatment with a second anti-TNF agent. Most experience

comes from switching IFX to ADA (102,112–114) [EL 2b]. Sub-analysis of the CHARM trial showed a response to ADA after IFX (4) [EL 2b]. Similar data exist for CZP (5) [EL 2b]. It is sensible to ensure that the dose and interval of the first agent are optimized, to avoid a precipitate switch that limits future options. The Gauging Adalimumab efficacy in IFX Non-responders trial trial investigated the effect of ADA after secondary non-response or intolerance to IFX (102) [EL 1b]. Patients were randomized to receive ADA 160 mg/80 mg at weeks 0 and 2 or placebo. In the ADA group, 21% (vs. 7% on placebo) entered remission and 52% (vs. 34%) had a response at week 4 ($P < 0.05$). Efficacy of ADA was similar whether patients were intolerant to or had lost response to IFX at study entry. In an open-label extension, 57% of responders at week 4 achieved remission by week 24 (114), consistent with a benefit from ADA beyond a 4-week induction period.

Evidence for CZP after intolerance or secondary loss of response to IFX comes from the 26 Week open label trial Evaluating certo Lizumab pegol induCtiOn and Maintenance trial (103,115). Patients were treated with CZP 400 mg at weeks 0, 2, and 4. At week 6, 62% achieved response, 39% achieved remission, and benefit was sustained over 18 months.

WCOG Statement 1.30
The unique risks of natalizumab, while rare, and its current approved labeling as a second-line biologic agent in some countries, will lead many practitioners to choose an anti-TNF agent as first-line and make natalizumab a second- or even third-line agent (after a second attempt at anti-TNF therapy). [EL 5]

Stopping biological therapy

WCOG Statement 1.31
In patients with UC or CD who have responded to a year of anti-TNF therapy, the benefits of continuing therapy should be weighed against the risks of discontinuation. Withdrawal of therapy is possible in patients with CD who have both complete mucosal healing and no biological evidence of inflammation [EL 2b]. The previous pattern of disease and response to different therapies are essential considerations. There are no data for UC.

As a rule, most patients who start biological therapy should continue treatment for the foreseeable future. Local policy, patient preference, or reimbursement may dictate stopping. Unfortunately, there are still insufficient data to make recommendations on when to stop anti-TNF therapy. Preliminary evidence suggests that for patients in clinical remission for >1 year, with a normal CRP and mucosal healing, an appreciable proportion will remain in remission during the year after stopping treatment. In a cohort study from Leuven, 20% of patients who had responded to IFX were able to stop therapy over a variable amount of time (94) [EL 2b]. The Infliximab diSconTinuation in CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressor study recruited 115 patients in steroid-free remission on IFX+AZA for >1 year and discontinued IFX. The relapse rate was 57% in the first year. Predictors of relapse included smoking, previous steroid use, elevated fecal calprotectin, or elevated CRP (116). Randomized controlled data are required to confirm these observations. Whether the behavior of disease is altered in the longer term remains unknown. Potential consequences of discontinuation (relapse, lower response to re-induction, and risk of infusion reactions) should be discussed with individual patients.

REVIEW

Conclusions

Biological therapy has altered the approach to IBD. There are clear criteria for starting treatment in those with steroid-dependent, steroid-refractory, or complex fistulizing disease, or those failing immunomodulators. Clinical predictors of a poor outcome at diagnosis need to be considered. Biological therapy is best started at an early stage in such patients. All anti-TNF agents appear similarly effective, although there are more data on IFX than ADA or CZP. Treatment is best continued in those who respond. Combination with AZA is appropriate when starting treatment with IFX in immunomodulator-naive CD patients. Loss of response or intolerance to anti-TNF therapy can be managed by optimizing dosing regimens, switching anti-TNF agents, or switching class. It is unclear whether these approaches are similarly effective. It is also unclear when treatment can be stopped.

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CONFLICT OF INTEREST

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Comparison of QD and TID Oral Mesalazine for Maintenance of Remission in Quiescent Ulcerative Colitis: A Double-blind, Double-dummy, Randomized Multicenter Study

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Background: Mesalazine preparations are widely used to treat mild to moderately severe ulcerative colitis (UC). We compared once-daily administration of oral mesalazine in patients with quiescent UC with the established 3-times-daily prescription, assessing the efficacy and safety of each method in maintaining remission for 52 weeks.

Methods: This was a double-blind, double-dummy, randomized, multicenter noninferiority study in which 301 patients with quiescent UC were randomly assigned to treatment groups and administered prolonged-release oral mesalazine at doses of 1.5 to 2.25 g/d once daily (QD) or 3 times daily (TID) for 52 weeks. The primary endpoint was whether remission was maintained after 52 weeks of administration or until the time of discontinuation, as represented by the Ulcerative Colitis Disease Activity Index score.

Results: The proportion of patients still in remission after 52 weeks of administration was 79.4% in the QD group and 71.6% in the TID group. The between-group difference was 7.8% (2-tailed 95% confidence interval [CI]: −2.2% to 17.8%), and the noninferiority of QD administration to TID administration was verified with a noninferiority margin of −10%. In the safety analysis, the incidence of adverse events in each group was 72.4% for the QD group and 76.5% for the TID group, showing no statistically significant difference between the 2 groups ($P = 0.4305$).

Conclusions: This double-blind parallel-group comparison verified for the first time the noninferiority of QD administration of oral mesalazine 1.5 to 2.25 g/d to TID administration in terms of maintaining remission in patients with UC.

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Key Words: mesalazine, ulcerative colitis, maintenance, double-blind, double-dummy

Ulcerative colitis (UC) is a debilitating disease presenting with the primary symptoms of frequent bowel movements, rectal bleeding, and abdominal pain; it often alternates between active periods of inflammation and quiescent remission periods when the symptoms disappear.[1] Complete cures are rare, and this disease typically becomes chronic in many patients.[2,3]

Oral preparations of mesalazine are often used for treating UC, and they are administered not only during active periods but also during remission periods.[4–6] Mesalazine is effective at a dose of over 0.8 g/d for maintenance of remission, although a clear dose-response effect has yet to be established.[7–11]

The problem with treatment during the remission period is that adherence often deteriorates since the patient needs to continue with therapy despite having no symptoms, to prevent the disease from flaring up again. Factors affecting adherence reportedly include aspects of self-regulation, such as irregular meals, forgetting to take the medication during active daytime hours, or not taking the drug because it is considered to be unnecessary or out of concern regarding side effects.[12,13] The connection between adherence and the remission maintenance effect of mesalazine preparations in UC has been studied, and adherence has been confirmed to be an extremely important factor in the remission maintenance effect of this drug.[14,15] Therefore, it is important to investigate the dosage/administration and methods of taking mesalazine that can potentially contribute to better adherence to the treatment regimen.

Efficacy in maintaining remission and the safety of long-term administration have already been investigated for various types of oral mesalazine preparations administered once daily (QD) or in a multiple daily dose (MDD) regimen, and the efficacy and safety of QD administration have been reported to not differ

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from those for MDD, with findings supported by meta-analyses.[16] However, because these studies included adherence among the endpoints, they represent single-blind clinical studies. We present here the results of the first double-blind, randomized parallel-group study in which the remission maintenance effect of QD administration of a prolonged-release oral preparation (Pentasa; Kyorin Pharmaceutical Co., Ltd., Tokyo, Japan) of mesalazine was assessed and was compared against the efficacy of the established 3 times daily (TID) prescription, with evaluation of safety within the same study.

MATERIALS AND METHODS

This phase 3, double-blind, double-dummy, randomized, multicenter noninferiority study was conducted at 53 medical institutions in Japan from December 2009 through June 2011. A prolonged-release oral preparation of mesalazine was administered to patients with quiescent UC, at 1.5 g QD or 500 mg TID (total dose, 1.5 g) and at 2.25 g QD or 750 mg TID (total dose, 2.25 g). The efficacy of QD administration was compared with that of TID administration to verify its noninferiority in terms of the proportion of patients still in remission at 52 weeks. The safety of the 2 dosing patterns was also compared.

For evaluation of efficacy, we used the Ulcerative Colitis Disease Activity Index (UC-DAI) score representing the total of the scores for 4 items: stool frequency, rectal bleeding, mucosal friability (sigmoidoscopy), and physician's global assessment.[17,18] Remission was defined as UC-DAI score of 2 or less and a rectal bleeding score of 0. The primary endpoint was whether remission was maintained after 52 weeks of administration or until the time of discontinuation of therapy, and the secondary endpoints were the duration of remission maintenance in the period up to 52 weeks of administration and the UC-DAI score at the time of the final assessment.

Inclusion/Exclusion Criteria

Male and female patients who were aged 15 to 64 years and had a documented diagnosis of UC were enrolled. All patients were in remission (defined as UC-DAI score ≤2 and rectal bleeding score of 0) at study entry, had experienced clinical relapse during the previous 1 year, and were receiving ≤2.25 g of mesalazine or ≤4.5 g of salazosulfapyridine. Patients with significant hepatic, renal, respiratory, cardiovascular, blood, or pancreatic diseases and/or malignancy were excluded. Eligible patients had not received oral or topical corticosteroid treatment for ≤30 days, immunosuppressant treatment for ≤90 days, infliximab treatment for ≤60 days, mesalazine enema and suppository treatment for ≤30 days, and >2.25 g of mesalazine or >4.5 g of salazosulfapyridine for ≤30 days before entry into the study (see Table, Supplemental Digital Content 1, http://links.lww.com/IBD/A162). Each subject was given a full explanation of the nature of the study, and written informed consent was provided by each subject of their own free will before entry into the study. If the subject was a minor, written consent was also obtained from a parent or other legal guardian.

Study Procedures

Patients meeting the inclusion criteria and not meeting any of the exclusion criteria were assigned to the 1.5 g/d group if the dosage they had received before starting the study was oral mesalazine 1.5 g/d (oral salazosulfapyridine 3 g/d) or less and to the 2.25 g/d group if the dosage they had been taking before the start of the study was more than 1.5 g/d but not more than 2.25 g/d (salazosulfapyridine 3–4.5 g/d). They were then randomly assigned to a QD group or a TID group at their respective dose levels (see Fig., Supplemental Digital Content 2, http://links.lww.com/IBD/A163). At this time, dynamic allocation was used to assure the uniformity of assignment to each dosage/administration group, and the extent of lesions in the past and the study center were used as factors for determining this allocation.

After being assigned to the groups, the subjects visited the study center once every 4 weeks until week 52 of administration. At the time of each study visit, the stool frequency score, rectal bleeding score, physician's global assessment score, and adherence status were checked. Sigmoidoscopy was performed at the time of the initial administration of the test drug and again at week 52 or at the time of discontinuation of therapy. Clinical laboratory tests and vital sign assessment were performed at the start of drug administration and at weeks 4, 8, 12, 20, 28, 36, 44, and 52 or at the time of discontinuation. In addition, the subjects were assessed for the presence of adverse events throughout the study period.

Concomitant Treatments

Use of the following drugs and therapies for the purpose of treating UC was not allowed during the entire study period: salazosulfapyridine preparations, mesalazine preparations other than the study drug, corticosteroids (oral formulations, enema agents, suppositories, or injections or enema administration of ointments), adrenocorticotropic hormone preparations, immunosuppressants, infliximab preparations, metronidazole, surgical therapy for the primary disease, and blood component removal. Moreover, patients were prohibited from using antidiarrheal drugs and therapeutic agents for irritable bowel syndrome for 3 days immediately before each visit because these agents affect the frequency of bowl movements.

Statistical Assessment

The main analysis set for the evaluation of efficacy was the Per Protocol Set, which was analyzed together with the intention-to-treat set. The analysis method for the primary endpoint was to calculate the percentage of subjects who did not relapse after 52 weeks of treatment or by the time of discontinuation (proportion of patients still in remission) for both the QD and the TID groups, the between-group difference (QD group − TID group), and the 2-tailed confidence interval (CI) of the between-group difference to verify the noninferiority of the QD group to the TID group, with the noninferiority margin set as −10%.

For secondary analysis of the primary endpoint, we calculated the percentage of subjects who did not relapse after 52 weeks of treatment (proportion of patients still in remission) and the proportion of patients still in remission after 52 weeks of treatment (Kaplan–Meier estimates) for both the QD and the TID groups to verify the noninferiority of the QD group to the TID group, as described above.

The method for analyzing the secondary endpoints involved calculating the mean of the Kaplan–Meier estimate and performing a between-group comparison using the log-rank test for the duration of remission maintenance until week 52 of treatment. Moreover, descriptive statistics were calculated for the UC-DAI score and the score for each item at the time of final evaluation.

The analysis set for the safety evaluation consisted of the set of subjects who had received the study drug and undergone the safety evaluations; the subjects who had not been administered to the study drug at all and those who had not been evaluated for safety were omitted from the total group of registered subjects. The subjects in the safety analysis set were divided into groups on the basis of the frequency of adverse events and compared in terms of duration of treatment, with the use of an exact test.

Ethical Considerations

This study strictly abided by the ethical principles based on the Declaration of Helsinki and Good Clinical Practice (GCP) and other related rules and regulations. Approval from the institutional review board of each study center was also obtained before the study was started. This study has been registered at the clinical study web site (JapicCTI-090967(ja)).

RESULTS

Flow of Participants

A total of 301 subjects were randomly assigned to the QD group (152 subjects) or the TID group (149 subjects). After 52 weeks, 215 subjects had taken the study drug for the entire period (114 and 101 in each group), whereas 86 subjects had discontinued therapy (38 and 48 in each group). For the analysis of efficacy, all 301 subjects were adopted as the intention-to-treat set, and 282 subjects (excluding 19 subjects who did not follow the protocol) were adopted as the Per Protocol Set (QD group, 141 subjects; TID group, 141 subjects) (Fig. 1).

Baseline Data

A between-group test of uniformity (2-tailed level of significance, 15%) was performed for evaluating the demographic characteristics of dosage, sex, age, height, weight, duration of UC, duration of the most recently used therapy for maintaining remission, extent of past lesions, presence/absence of complications, and presence/absence of smoking. There were no significant between-group differences for any of these items, and no nonuniformity was observed (Table 1).

Adherence

The adherence status was investigated at the time of each study visit from the initiation of treatment to week 52 or discontinuation, and the cumulative adherence rate was calculated. The adherence for both the QD and the TID groups was 90% or higher (Table 2).

Efficacy

Primary Endpoints

Per Protocol Set analysis showed that the proportion of patients still in remission—calculated as the percentage of subjects in the QD and TID groups who did not relapse after 52 weeks of treatment or until the time of discontinuation—was 79.4% in the QD group and 71.6% in the TID group, with a between-group difference of 7.8% (2-tailed 95% CI, −2.2% to 17.8%) (Table 3). Moreover, the proportion of patients still in remission—calculated as the percentage of subjects who did not relapse after 52 weeks of treatment—was 77.3% for the QD group and 68.1% for the TID group, with a between-group difference of 9.2% (2-tailed 95% CI, −1.1% to 19.6%) (Table 3). Moreover, the proportion of patients still in remission according to the Kaplan–Meier estimate was 79.1% for the QD group and 71.0% for the TID group, with a between-group difference of 8.1% (2-tailed 95% CI, −2.1% to 18.3%). The noninferiority of the QD group to the TID group was verified by a noninferiority margin higher than −10% being exhibited in the CI for each of the groups (Fig. 2).

In the analysis of the intention-to-treat, the proportion of patients still in remission—calculated as the percentage of subjects who did not relapse after 52 weeks of treatment or until the time of discontinuation—was 75.0% in the QD group and 69.1% in the TID group, with a between-group difference of 5.9% (2-tailed 95% CI, −4.2% to 16.0%). Moreover, the proportion of patients still in remission—calculated as the percentage of subjects who did not relapse by week 52—was 72.4% in the QD group and 65.8% in the TID group, with a between-group difference of 6.6% (2-tailed 95% CI, −3.8% to 17.0%). The proportion of patients still in remission according to the Kaplan–Meier estimate was 74.5% in the QD group and 68.5% in the TID group, with a between-group difference of 6.0% (2-tailed 95% CI, −4.3% to 16.3%). The noninferiority of the QD group to the TID group was verified by a noninferiority margin higher than −10% being exhibited in the CI for each of the groups.

In addition, the proportion of patients still in remission—calculated as the percentage of subjects in the QD group and in the TID group who did not relapse after 52 weeks of treatment or until the time of discontinuation—was analyzed at their respective dose levels of 1.5 and 2.25 g/d. The noninferiority of the QD group to the TID group was also verified for each of the groups (Table 3).

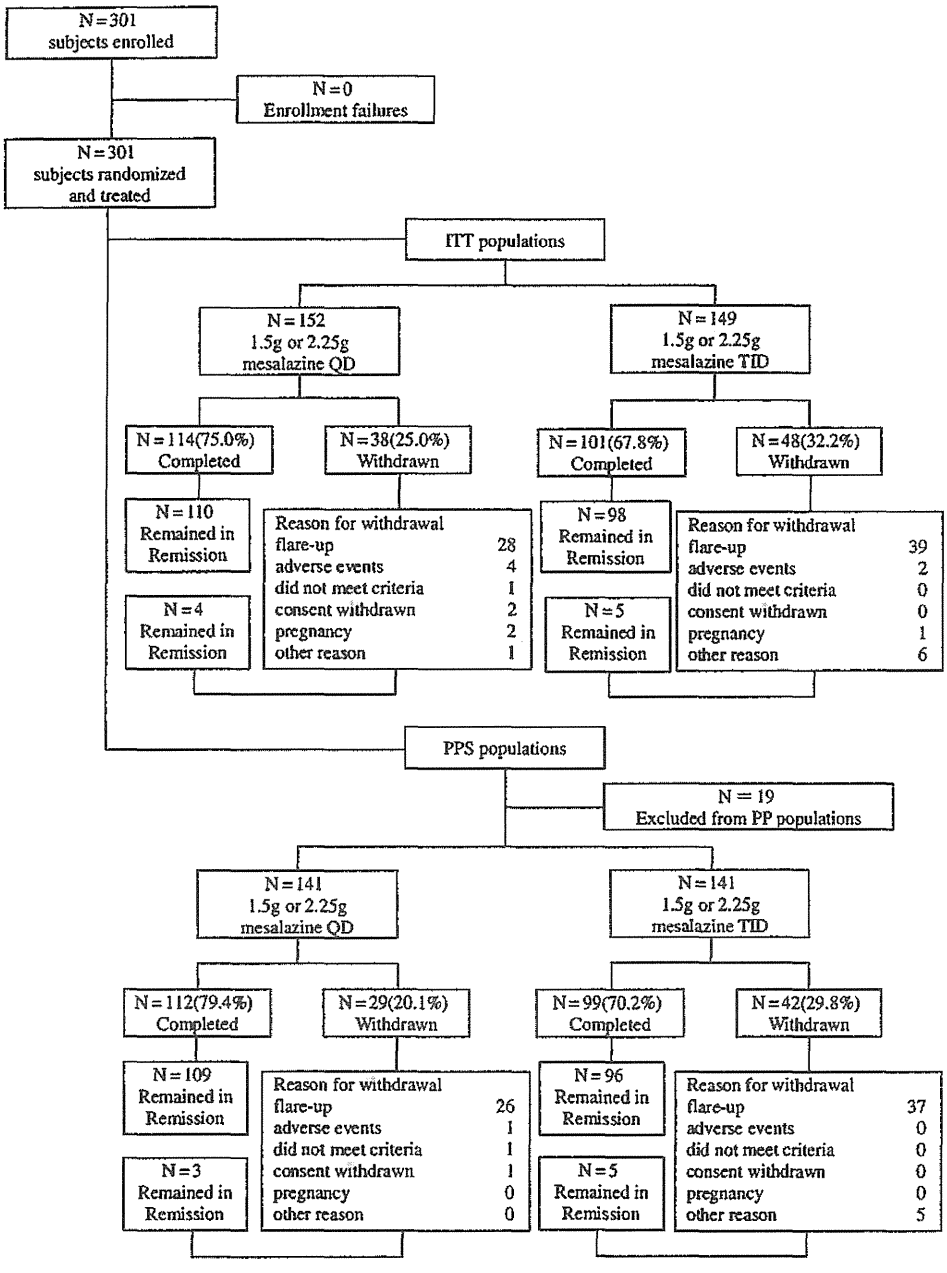

FIGURE 1. Disposition of patients.

Secondary Endpoints

No significant between-group differences were found in the duration of remission maintenance up to week 52 of treatment in the between-group comparison of the QD and TID groups performed by calculating the mean of the Kaplan–Meier estimate and using a log-sum test. The change in the Kaplan–Meier curve showed that the QD group maintained a higher value than the TID group for the rate of remission maintenance for 85-day or longer remission maintenance periods (Fig. 2).

However, since the QD group showed lower values than the TID group in terms of the mean score for each item at the time of final evaluation (stool frequency, rectal bleeding, mucosal friability, and physician's global assessment), the mean UC-DAI score was 1.6 (141 subjects) for the QD group and 2.0 (141 subjects) for the TID group (Table 4).

Moreover, the percentage of subjects with UC-DAI score of 2 or lower at the time of final evaluation was 82.2% for the QD group (116 of 141 subjects) and 73.0% for the TID group (103 of 141 subjects), and the percentage showing a score of 0 for rectal bleeding was 83.7% in the QD group (118 of 141 subjects) and 77.3% in the TID group (109 of 141 subjects), with both percentages being higher in the QD than in the TID group. This demonstrated that the state of remission was better maintained in the QD group than in the TID group.

TABLE 1. Patient Baseline Characteristics (Efficacy Analysis Population: ITT)

Characteristic	Classification	QD n	QD %	TID n	TID %	Test[a]	
No. patients		152		149			
Dose at enrollment	1,500 mg/d	47	30.9	45	30.2	$P = 0.9011$	1
	2,250 mg/d	105	69.1	104	69.8		
Gender	Male	79	52.0	81	54.4	$P = 0.7293$	1
	Female	73	48.0	68	45.6		
Age, yr	<30	26	17.1	23	15.4		
	30–40	42	27.6	46	30.9		
	40–50	39	25.7	43	28.9		
	50–60	27	17.8	26	17.4		
	≥60	18	11.8	11	7.4		
	Mean	42.3		41.1		$t = 0.858$	2
	SD	12.1		11.2		$P = 0.3915$	
	Minimum	17		18			
	Median	41.0		40.0			
	Maximum	64		63			
Height, cm	Mean	164.21		164.99		$t = -0.775$	2
	SD	8.28		9.15		$P = 0.4388$	
	Minimum	144.3		146.0			
	Median	164.05		165.60			
	Maximum	184.0		184.5			
Weight, kg	Mean	60.24		60.76		$t = -0.409$	2
	SD	10.70		11.37		$P = 0.6829$	
	Minimum	41.2		38.8			
	Median	58.10		60.00			
	Maximum	99.7		110.2			
BMI, kg/m^2[b]	<22.0	84	55.3	77	51.7		
	≥22.0	68	44.7	72	48.3		
	Mean	22.22		22.24			
	SD	2.73		3.22			
	Minimum	16.5		15.5			
	Median	21.67		21.80			
	Maximum	30.1		37.0			
Duration of disease, yr	<1	5	3.3	9	6.0		
	1–5	64	42.1	60	40.3		
	5–10	35	23.0	36	24.2		
	≥10	48	31.6	44	29.5		
	Mean	8.6		7.9		$z = -0.595$	3
	SD	7.9		7.2		$P = 0.5516$	
	Minimum	1		0			
	Median	5.9		5.4			
	Maximum	40		41			

TABLE 1 (*Continued*)

Characteristic	Classification	QD n	QD %	TID n	TID %	Test[a]	
Time from start of current remission phase until day 0, d	≤30	26	17.1	25	16.8		
	30–90	64	42.1	59	39.6		
	90–180	28	18.4	31	20.8		
	>180	34	22.4	34	22.8		
	Mean	104.3		108.8		$z = 0.620$	3
	SD	89.2		88.3		$P = 0.5353$	
	Minimum	1		1			
	Median	68.5		78.0			
	Maximum	357		324			
Disease extent	Pancolitis	66	43.4	65	43.6	$P = 0.9307$	1
	Left-sided colitis	29	19.1	32	21.5		
	Rectum sigmoid	26	17.1	22	14.8		
	Proctitis	31	20.4	30	20.1		
Complications[c]	Absent	27	17.8	26	17.4	$P = 1.0000$	1
	Present	125	82.2	123	82.6		
Smoking history	Current nonsmoker	129	84.9	133	89.3	$P = 0.3042$	1
	Current smoker	23	15.1	16	10.7		
Stool frequency score[c]	0	150	98.7	142	95.3		
	1	2	1.3	7	4.7		
	2	0	0.0	0	0.0		
Rectal bleeding score[c]	0	152	100.0	149	100.0		
Mucosal appearance score[c]	0	57	37.5	73	49.0		
	1	85	55.9	62	41.6		
	2	10	6.6	14	9.4		
Physician's global assessment score[c]	0	134	88.2	132	88.6		
	1	18	11.8	17	11.4		
	2	0	0.0	0	0.0		
UC-DAI score[c]	0	54	35.5	65	43.6		
	1	71	46.7	54	36.2		
	2	27	17.8	30	20.1		
	Mean	0.8		0.8			
	SD	0.7		0.8			
	Minimum	0		0			
	Median	1.0		1.0			
	Maximum	2		2			

% = (number of patients ÷ number of patients in each group) ×100.
Numbers in the "Test" column represent the following: 1, Fisher's exact probability test; 2, Student's *t* test; and 3, Wilcoxon rank sum test.
[a]2-sided 15% significance level.
[b]BMI (body mass index) = weight (kg) ÷ height (m^2).
[c]Baseline.

Safety

The incidence of adverse events was 72.4% in the QD group (110 of 152 subjects) and 76.5% in the TID group (114 of 149 subjects), with no statistically significant difference between the 2 groups (Fisher's exact probability test, $P = 0.4305$). Moreover, no difference in adverse event type, severity, or frequency of occurrence was observed between the QD and the TID groups.

The adverse events that occurred at relatively high frequencies (incidence of 3.0% or higher) in the QD group were nasopharyngitis (38.2%), inflammation of the upper respiratory tract (7.9%), diarrhea (6.6%), eczema (3.9%), and dental caries (3.3%). In the TID group, the most commonly occurred adverse events were nasopharyngitis (38.9%), diarrhea (4.0%), gastroenteritis (4.0%), and abdominal pain (3.4%) (see Table,

TABLE 2. Cumulative Adherence Rate

	Cumulative Adherence Rate (%)		
	QD	TID	Test[a]
PPS	98.3 ± 2.7	98.8 ± 1.8	$P = 0.1622$
ITT	98.2 ± 2.8	98.8 ± 1.8	$P = 0.1267$

[a]Fisher's exact probability test (2-sided 10% significance level).
ITT, intention-to-treat; PPS, Per Protocol Set.

Supplemental Digital Content 3, http://links.lww.com/IBD/A164). Serious adverse events were observed in 12 subjects, but a causal relationship with the study drug was ruled out for all of them.

DISCUSSION

UC is a chronic disease that often presents with alternating active and quiescent phases. To improve the prognosis for patients with this disease, it is extremely important to maintain the state of remission and prevent relapses. One of the important therapies for preventing relapse is the continued administration of a drug such as mesalazine even during remissions. Particularly, mesalazine agents may help maintain acceptable quality of life and possibly reduce colorectal cancer risk, with European Crohn's and Colitis Organisation guidelines also recommending the continued use of mesalazine.[6,19]

Shintoh et al[20] conducted a questionnaire survey of 346 outpatients and found that approximately 28% did not take their medications properly, the main reason being that the daily dosing frequency was considered too high. In addition, Kane et al,[14] who studied adherence in 99 patients with UC who maintained remission for 6 months or more on mesalazine, found that in 50% of the patients with poor adherence, the reason was forgetting to take the doses. Similarly, when the relationship between adherence and the remission maintenance effect was investigated, the proportion of patients still in remission after 1 year was found to be significantly higher ($P = 0.001$) in patients with good adherence (those who took at least 80% of the prescribed medication) than in those with poor adherence, being 89% in the former versus 39% in the latter, an observation indicating that adherence is important for the remission maintenance effect.[14]

A meta-analysis of clinical studies that investigated the remission maintenance effect of QD administration of oral mesalazine in patients with quiescent UC as compared with an MDD regimen found that the remission maintenance effect obtained with a QD dosing regimen was similar to that for MDD for the same preparation; moreover, the results suggested that the incidence of adverse events was also approximately the same.[16]

In an open study on 459 patients with quiescent UC, Kamm et al[21] investigated the proportion of patients who had received QD and twice-daily (BID) administrations of mesalazine 2.4 g/d, administered as a Multi Matrix System preparation of oral mesalazine (Lialda; Shire Pharmaceuticals, Wayne, PA), and were still in remission. They found the proportion of patients still in remission after 12 months to be 64.4% and 68.5% for the QD and BID groups, respectively, showing roughly equivalent proportions of patients still in remission for both groups. Dignass et al[22] investigated the

TABLE 3. UC-DAI Remission Rate

			QD		TID		Difference Between
			No. Subjects	Remission Rates (%)	No. Subjects	Remission Rates (%)	Groups (95% CI)[a]
1,500 and 2,250 mg	End of study[b]	PPS	112/141	79.4	101/141	71.6	7.8 (−2.2 to 17.8)
		ITT	114/152	75.0	103/149	69.1	5.9 (−4.2 to 16.0)
	52 wk[c]	PPS	109/141	77.3	96/141	68.1	9.2 (−1.1 to 19.6)
		ITT	110/152	72.4	98/149	65.8	6.6 (−3.8 to 17.0)
1,500 mg	End of study[b]	PPS	39/44	88.6	32/44	72.7	15.9 (−0.2 to 32.1)
		ITT	39/47	83.0	32/45	71.1	11.9 (−5.2 to 28.9)
	52 wk[c]	PPS	37/44	84.1	30/44	68.2	15.9 (−1.6 to 33.4)
		ITT	37/47	78.7	30/45	66.7	12.1 (−6.0 to 30.1)
2,250 mg	End of study[b]	PPS	73/97	75.3	69/97	71.1	4.1 (−8.3 to 16.6)
		ITT	75/105	71.4	71/104	68.3	3.2 (−9.3 to 15.6)
	52 wk[c]	PPS	72/97	74.2	66/97	68.0	6.2 (−6.5 to 18.9)
		ITT	73/105	69.5	68/104	65.4	4.1 (−8.6 to 16.8)

[a]Noninferiority margin: −10%.
[b]After 52 weeks of treatment or until the time of discontinuation.
[c]After 52 weeks of treatment.
ITT, intention-to-treat; PPS, Per Protocol Set.

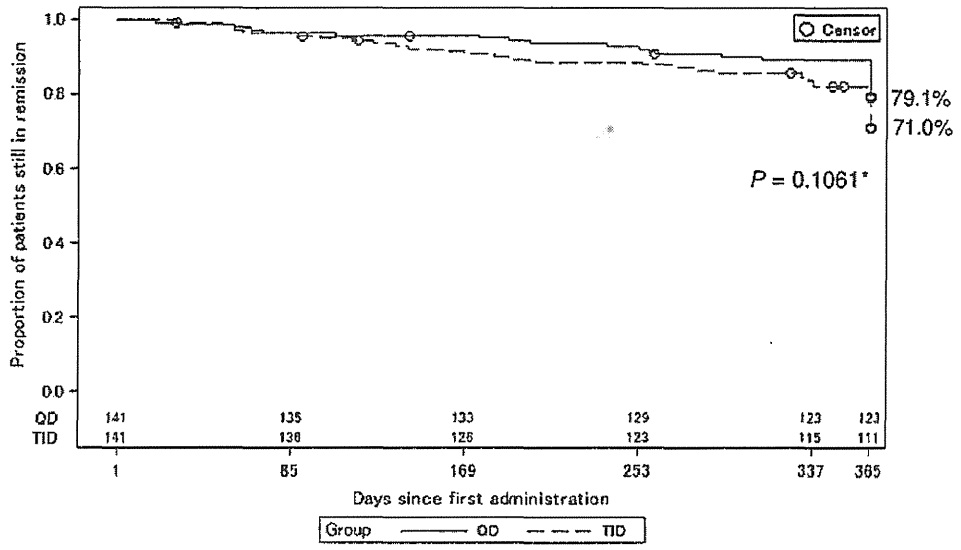

FIGURE 2. Kaplan–Meier estimated UC-DAI remission. Remission is defined as UC-DAI total score ≤2 and rectal bleeding score = 0 (PPS). *Log-rank test (significance level: 2-sided 5%).

proportion of patients still in remission for QD and BID administrations of mesalazine 2 g/d in the form of prolonged-release oral mesalazine (Pentasa; Ferring Pharmaceuticals, Saint-Prex, Switzerland) from 362 patients with quiescent UC in a single-blind study. They found the proportion of patients still in remission after 12 months to be 70.9% and 58.9% in the QD and BID groups, respectively, showing that the proportion of patients still in remission in the QD group was significantly higher ($P = 0.024$). Sandborn et al[23] evaluated the proportion of patients still in remission for QD and BID administrations of mesalazine at 1.6 to 2.4 g/d, in the form of pH-dependent, delayed-release oral mesalazine (Asacol; Procter & Gamble Pharmaceuticals, Manson, OH) in 1,023 patients with quiescent UC in a single-blind study. They demonstrated the proportion of patients still in remission after 12 months to be 85.4% and 85.4% for the QD and BID groups, respectively, confirming the noninferiority of QD to BID administration.[23] In contrast, Kruis et al,[24] who assessed the proportion of patients still in remission for QD and TID administrations of mesalazine 1.5 g/d, in the form of pH-dependent, delayed-release oral mesalazine (Salofalk; Dr. Falk Pharma GmbH, Freiburg, Germany) in 430 patients with quiescent UC in a dose–response study conducted as a double-blind parallel-group comparison, found the proportion of patients still in remission after 52 weeks to be 61% and 69% for the QD and TID groups, respectively. Thus, the noninferiority of QD administration to TID administration was not verified in their study.

The present study—the first of its kind to use a randomized, double-blind, parallel-group comparison method—investigated the proportion of patients still in remission for QD and TID administrations of mesalazine 1.5 and 2.25 g/d, in the form of prolonged-release oral mesalazine (Pentasa tablets) in 301 patients with quiescent UC. The proportions of patients still in remission after 52 weeks or until the time of discontinuation were 79.4% and 71.6% for the QD and TID groups, respectively, and the noninferiority of QD to TID administration was verified. The proportion of patients still in remission—calculated as the percentage of subjects in the QD and TID groups who did not relapse after 52 weeks of treatment or until the time of discontinuation—was analyzed at their respective dose levels of 1.5 and 2.25 g/d. The proportions of patients still in remission after 52 weeks or until the time of discontinuation were 88.6% and 72.7% for the QD and TID groups receiving mesalazine 1.5 g/d, respectively, and 75.3% and 71.1% for the QD and TID groups receiving mesalazine 2.25 g/d, respectively. The noninferiority of QD to TID administration of mesalazine was also verified for both dose levels.

These results demonstrated that the prolonged-release oral preparation of mesalazine has comparable remission maintenance effects for patients with quiescent UC with both QD and TID administration of mesalazine at 1.5 and 2.25 g/d, with no differences in the safety profiles of the QD and TID groups.

The adherence rates for the QD group and the TID group were 98.2% and 98.8%, respectively. Therefore, the effect obtained in the QD group was suggested to have been approximately identical to that in the TID group owing to the high adherence rate, which was accurately reflected as the therapeutic effect of mesalazine.

The prolonged-release oral mesalazine preparations consist of ethyl cellulose–coated mesalazine granules (granules containing mesalazine) formed into tablets, which rapidly disintegrate in the stomach after oral administration, gradually releasing mesalazine from the granules as they move through the intestines without being influenced by intestinal pH, ultimately being excreted along with feces.[25] Higaki et al[26] demonstrated that QD and TID dosing of prolonged-release oral mesalazine preparations results in comparable pharmacokinetic properties in healthy volunteers, while Mitsuyama et al[27] showed that pharmacokinetic parameters for QD dosing of prolonged-release oral mesalazine preparations