Title:
Once daily oral mesalamine compared to conventional dosing for induction and maintenance of remission in ulcerative colitis: A systematic review and meta-analysis

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Once Daily Oral Mesalamine Compared to Conventional Dosing for Induction and Maintenance of Remission in Ulcerative Colitis: A Systematic Review and Meta-Analysis

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Abstract: We systematically reviewed and compared the efficacy and safety of once daily (OD) mesalamine to conventional dosing for induction and maintenance of remission in ulcerative colitis (UC). A literature search to January 2012 identified all applicable randomized trials. Study quality was evaluated using the Cochrane risk of bias tool. The GRADE criteria were used to assess the overall quality of the evidence. Studies were subgrouped by formulation for meta-analysis. Eleven studies that evaluated 4070 patients were identified. The risk of bias was low for most factors, although five studies were single-blind and one was open-label. No difference was observed between the dosing strategies in the proportion of patients with clinical remission (relative risk [RR] 0.95; 95% confidence interval [CI] 0.82–1.10), clinical improvement (RR 0.87 95% CI 0.68–1.10), or relapse at 6 (RR 1.10; 95% CI 0.83–1.46) or 12 months (RR 0.92; 95% CI 0.83–1.03). Subgroup analyses showed no important differences in efficacy. No significant difference was demonstrated in rates of medication adherence or adverse events between OD and conventional dosing. OD mesalamine appears to be as effective and safe as conventional dosing for both the treatment of mild to moderately active UC and for maintenance of remission in quiescent UC. The failure to demonstrate a superior rate of adherence to OD dosing may be due to the high rate of adherence observed in the clinical trials environment. Future research should assess the value of OD dosing in community settings.

Key Words: ulcerative colitis, mesalamine, meta-analysis, adherence, maintenance and induction of remission

Oral mesalamine formulations are first-line treatments for mild to moderately severe ulcerative colitis (UC) and are also effective for maintenance of remission. However, many patients are nonadherent with conventional multidose (2 or 3 times daily) treatment regimens, which may result in reduced efficacy, poor long-term prognosis, and increased costs of care. Poor adherence may be particularly problematic in quiescent disease, since patients lack continuing symptoms that incentivize them to take medication. Although multiple factors have been shown to influence medication adherence in patients with UC it is commonly believed that a high pill burden and multidose regimens are major determinants. Accordingly, it is reasonable to hypothesize that once daily (OD) dosing of mesalamine might improve both adherence and outcomes.

The efficacy and safety of OD oral dosing of mesalamine for the treatment of UC has been compared to conventional dosing in multiple randomized trials. These studies evaluated the efficacy and safety of OD dosing of various formulations of mesalamine compared to conventional dosing schedules of the same drugs or to different formulations. However, many of the trials had relatively small sample sizes and therefore had limited statistical power to yield definitive conclusions. The main objective of this review was to compare the efficacy and safety of OD dosing of mesalamine for the treatment of UC to conventional multidose regimens. This systematic review is partially based on two recently updated Cochrane systematic reviews.

MATERIALS AND METHODS

Search Strategy

MEDLINE (Ovid SP), EMBASE (Ovid SP), and the Cochrane Library were searched from inception to January 20, 2012. No language or document type restrictions were applied. The multipurpose search command for the Ovid SP interface was used to search both text and database subject heading
fields. Review articles and conference proceedings were also searched to identify additional studies. The search strategies are listed in Table 1.

Eligibility
Randomized controlled clinical trials that compared OD mesalamine treatment to conventional dosing for either induction or maintenance of remission were considered for inclusion. Patients of any age with active mild to moderate UC or quiescent UC as defined by a combination of clinical, radiographic, endoscopic, and histologic criteria (e.g., Truelove and Witts) were considered eligible. The outcome measures of interest were endoscopic, global, or clinical measures of improvement or complete remission and relapse as defined by the authors of each study.

Outcomes
The primary outcomes were: failure to induce global or clinical remission; failure to induce global/clinical remission or improvement; and failure to maintain global/clini
cal remission (relapse). Secondary outcomes included failure to adhere to the medication regimen and adverse events including the proportion of patients who experienced at least one adverse event, a serious adverse event, and withdrawal from therapy due to an adverse event.

Methods of the Review
Relevant studies were selected for analysis on the basis of the listed inclusion criteria. The reasons for exclusion were indicated for each study deemed ineligible. The Cochrane risk of bias tool was used to assess the methodological quality of the included studies. Factors assessed were the methods used for sequence generation and allocation concealment, blinding, potential problems with incomplete outcome data, and selective outcome reporting. These items were rated as low (e.g., adequate methods were used for blinding), high (e.g., blinding was not used), or unclear risk of bias (e.g., procedures for blinding were not adequately described). The overall quality of the primary outcomes was assessed using the criteria of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group. This instrument rates outcomes on a scale ranging from high quality to very low quality based on risk of bias, consistency, directness, imprecision, and reporting bias.

Statistical Analysis
Data were analyzed using the Cochrane Collaboration software Review Manager (RevMan 5.1). Raw data for each outcome were extracted and converted into individual 2 × 2 tables (OD vs. conventional dosing). The tables were further subgrouped according to the formulation of mesalamine evaluated. The relative risk (RR) and 95% confidence intervals (95% CI) derived from each 2 × 2 table were individually calculated and plotted. The results for each comparison group were pooled to determine the RR and 95% CI for each outcome resulting from OD dosing relative to conventional dosing. A fixed-effect model was used to calculate the RR. The definitions of treatment success, remission, clinical improvement, and relapse were set by the authors of each article, and the data were combined for analysis only if these definitions were sufficiently similar. Results were recorded on an intention-to-treat (ITT) basis, regardless of whether or not the original authors had performed such an analysis. As such, dropouts or withdrawals before completion of the studies were considered treatment failures.

The presence of heterogeneity among studies was assessed using the chi-square test. As the chi-square test has low statistical power when trials have a small sample size or are few in number, \( P = 0.10 \) was regarded as statistically significant. The \( I^2 \) statistic was used to assess the degree of inconsistency between the trials. This measure describes the percentage of total variation across studies that is due to

### TABLE 1. Search Strategies

<table>
<thead>
<tr>
<th>MEDLINE Search Strategy:</th>
<th>EMBASE Search Strategy:</th>
<th>Cochrane Library Search Strategy:</th>
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</tbody>
</table>
heterogeneity rather than chance. A value of 50% is considered moderate heterogeneity. Whenever statistically significant heterogeneity was detected, a random-effects model was used to calculate the RR. Sensitivity analyses were performed to investigate statistically significant heterogeneity. These analyses included the use of a different statistic model (i.e., random-effects model) and repeating the analysis excluding specified studies (e.g., outliers).

RESULTS

Description of Studies

A literature search conducted on January 20, 2012 identified 9259 studies. After duplicates were removed a total of 6895 studies remained for review of titles and abstracts. Two authors independently reviewed the titles and abstracts of these studies and 25 trials that assessed the efficacy of OD mesalazine for induction or maintenance treatment of UC were retrieved for further evaluation (Fig. 1). Kane et al\textsuperscript{13} and Hussain et al\textsuperscript{14} were excluded since they were not randomized controlled trials. Ten studies were excluded because the treatment evaluated was OD topical mesalamine (suppository or enema) rather than oral treatment.\textsuperscript{15–24} Gross et al\textsuperscript{25} was excluded because the study compared OD mesalamine treatment (Salofalk) with OD budesonide. D’Haens et al\textsuperscript{26} was excluded because the study investigated the efficacy of OD MMX mesalamine (SPD476) at three different doses (1.2, 2.4, or 4.8 g) without a conventional dosing regimen comparison group.

Eleven randomized studies that met the inclusion criteria were identified. Three studies were induction of remission studies,\textsuperscript{3,27,28} and eight studies assessed maintenance of remission.\textsuperscript{29–36} The Kamm et al\textsuperscript{27} trial also compared two different doses of OD MMX mesalamine (2.4 g and 4.8 g per day) for treatment of active UC. Kruis et al\textsuperscript{35} investigated two different doses of OD mesalamine (3 g and 1.5 g Salofalk granules) for maintenance treatment. Three of the included studies were designed as noninferiority studies,\textsuperscript{3,32,34} whereas the others were designed as superiority studies. The characteristics of the included studies are described in Table 2.

Most of the included studies were of high methodological quality (Table 3). One study was open-label,\textsuperscript{31} and five studies were single-blind.\textsuperscript{29,30,32,34,36} Outcomes were assessed by a blinded investigator in the single-blind studies. However, the open-label study\textsuperscript{31} and three of five single-blind studies\textsuperscript{30,32,36} used investigator-performed endoscopy as an endpoint, which may protect against bias. Nine studies used adequate methods of allocation concealment.\textsuperscript{27–35} Two studies did not describe the methods used for allocation concealment and were rated as unclear.\textsuperscript{3,36} Five studies used adequate methods for randomization (e.g., computer-generated or table of random numbers).\textsuperscript{3,29,30,33,35} Six studies did not describe the methods used for randomization and these studies were rated as unclear for this item.\textsuperscript{27,28,31,32,34,36}
## TABLE 2. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Country, No. of Centers</th>
<th>Interventions</th>
<th>Duration of Therapy</th>
<th>Methods</th>
</tr>
</thead>
</table>
| Kruis et al, 2009<sup>1</sup> | 380                | 13 countries, 54 centers | 3 g mesalazine (Salofalk) OD (n=191)  
1 g mesalazine TID (n=189) | 8 weeks | Double-blind, Double-dummy, Non-inferiority |
| Kamm et al, 2007<sup>1</sup> | 341                | 10 countries, 49 centers | 2.4 g MMX mesalamine OD (n=84)  
4.8 g MMX OD (n=85)  
800 mg (Asacol) TID (n=86)  
placebo (n=86) | 8 weeks | Double-blind, Double-dummy |
| Lichtenstein et al, 2007<sup>1</sup> | 280                | 8 countries, 52 centers | 4.8 g MMX mesalamine OD (n=94)  
2.4 g MMX BID (n=93)  
placebo (n=93) | 8 weeks | Double-blind, Double-dummy |
| Kruis et al, 2011<sup>2</sup> | 647                | 13 countries, 65 centers | 3 g mesalazine (Salofalk) OD (n=217)  
1.5 g mesalamine OD (n=212)  
500 mg mesalamine TID (n=218) | 1 year | Double-blind, Double-dummy |
| Hawthorne et al, 2011<sup>2</sup> | 213                | 1 country, 32 centers | 2.4 g mesalazine (Asacol) OD (n=103)  
2.4 g mesalazine (Asacol) divided TID (n=110) | 12 months | Investigator-blinded, Non-inferiority |
| Sandborn et al, 2010<sup>2</sup> | 1023               | 3 centers, 193 centers | 1.6 to 2.4 g mesalamine (Asacol) OD (n=512)  
1.6 to 2.4 g mesalamine divided BID (n=511) | 12 months | Investigator-blinded, Non-inferiority |
| Dignass et al, 2009<sup>2</sup> | 362                | 8 countries, 68 centers | 2.0 g mesalamine (Pentasa) OD (n=175)  
2.0 g mesalamine divided BID (n=187) | 12 months | Investigator-blinded, Non-inferiority |
| Prantera et al, 2009<sup>2</sup> | 331                | 3 countries, 47 centers | 2.4 g MMX mesalazine OD (n=162)  
1.2 g mesalazine (Asacol) BID (n=169) | 12 months | Double-blind, Double-dummy |
| Kamm et al, 2008<sup>2</sup> | 451                | 19 countries, 101 centers | 2.4 g MMX mesalazine OD (n=219)  
1.2 g MMX BID (n=232) | 12 months | Open-label |
| Kane et al, 2008<sup>2</sup> | 20                 | 1 country, 2 centers | 2.4 g mesalamine (Asacol) OD<sup>3</sup> (n=12)  
2.4 g/day Asacol BID or TID<sup>3</sup> (n=8) | 12 months | Investigator-blinded |
| Kane et al, 2003<sup>2</sup> | 22                 | 1 country, 1 center | 2.5 g mesalamine (Asacol) OD<sup>3</sup> (n=12)  
2.7 g/day Asacol BID or TID<sup>3</sup> (n=10) | 6 months | Investigator-blinded |

OD, once daily; TID, three times daily; BID, twice daily.
<sup>1</sup>Induction of remission study.
<sup>2</sup>Maintenance of remission study.
<sup>3</sup>Mean dose per day.
Meta-analysis: OD Mesalamine Versus Conventional Dosing

**Failure to Induce Global/Clinical Remission**

The pooled analysis of the ITT population included 738 patients and three trials. Overall, 42.0% (327/780) of patients in the OD dosing group failed to enter remission compared to 44.3% (328/750) of patients in the conventional dosing group. The pooled RR was 0.95 (95% CI 0.82–1.10), showing no statistically significant difference between OD dosing and conventional dosing for induction of remission ($P = 0.49$; Fig. 2). No statistically significant heterogeneity was detected for this comparison ($\chi^2 = 1.98$, degrees of freedom [df] = 2, $P = 0.37$, $I^2 = 0$). None of the subgroup comparisons by formulation showed any differences in efficacy between OD dosing and conventional dosing. However, only three formulations were evaluated in this pooled analysis.

<table>
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<th>Study</th>
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<td>High risk$^8$</td>
<td>Low risk$^4$</td>
<td>Low risk$^3$</td>
</tr>
</tbody>
</table>

$^1$Computer-generated; $^2$Not described; $^3$Double-blind, double-dummy; $^4$Drop-outs balanced across intervention groups with similar reasons for withdrawal; $^5$All expected outcomes reported; $^6$Centralized randomization; $^7$Higher number of withdrawals in placebo group due to lack of efficacy; $^8$Investigator-blinded; $^9$Open-label; $^{10}$Opaque sealed envelopes; $^{11}$One patient in the OD group died; $^{12}$Random-numbers table.

**FIGURE 2.** Once daily mesalamine versus conventional dosing: failure to induce global/clinical remission.
Failure to Induce Global/Clinical Remission or Improvement

The pooled analysis of the ITT population included 358 patients (two studies). Overall, 39.7% (141/358) of patients in the OD dosing group failed to improve clinically compared to 45.8% (165/358) of patients in the conventional dosing group. The pooled RR was 0.87 (95% CI 0.68–1.10), showing no statistically significant difference between OD dosing and conventional dosing (P = 0.24). No statistically significant heterogeneity was detected for this comparison (χ² = 1.44, df = 1, P = 0.23).

Failure to Maintain Global/Clinical Remission at 6 Months

The pooled analysis of the ITT population included 1013 patients (two studies). Overall, 9.1% (92/1013) patients who received OD dosing group relapsed compared to 14.8% (156/1013) patients in the conventional dosing group. The pooled RR was 0.61 (95% CI 0.47–0.80), showing no statistically significant difference between OD dosing and conventional dosing for relapse at 6 months (P = 0.10). No statistically significant heterogeneity was detected for this comparison (χ² = 2.81, df = 1, P = 0.09).

Failure to Maintain Global/Clinical Remission at 12 Months

The pooled analysis of the ITT population included 2797 patients (seven studies). Overall, 16.2% (447/2797) patients who received OD dosing group relapsed compared to 31.1% (893/2826) patients in the conventional dosing group. The pooled RR was 0.52 (95% CI 0.41–0.66), showing no statistically significant difference between OD dosing and conventional dosing for relapse at 12 months (P = 0.01). No statistically significant heterogeneity was detected for this comparison (χ² = 2.32, df = 1, P = 0.13).
showing no statistically significant difference between OD dosing and conventional dosing for relapse at 12 months (\( P = 0.17 \); Fig. 3). No statistically significant heterogeneity was detected for this comparison (\( \chi^2 = 6.76, df = 6, P = 0.21, I^2 = 28\% \)). The subgroup comparison for Pentasa showed a statistically significant difference in favor of OD dosing compared to conventional twice-daily dosing (RR 0.70; 95% CI 0.52–0.94) None of the other subgroup comparisons by formulation showed any differences in efficacy between OD dosing and conventional dosing.

**Failure to Adhere to Study Medication Regimen at Study Endpoint**

Nine studies provided data regarding adherence.\(^{27–33,35,36}\) Induction and maintenance studies were not pooled together for meta-analysis as it was felt that factors affecting adherence may differ between short-term and long-term studies. The pooled analysis of the ITT population for two induction studies included 358 patients.\(^{27,28}\) Overall, 8.4% (15/179) of patients in the OD group failed to adhere to their medication regimen compared to 6.1% (11/179) of patients in the conventional dosing group. The pooled RR was 1.36 (95% CI 0.64–2.86), showing no statistically significant difference in medication adherence between OD dosing and conventional dosing at 8 weeks (\( P = 0.42 \)). No statistically significant heterogeneity was detected for this comparison (\( \chi^2 = 1.51, df = 1, P = 0.22, I^2 = 34\% \)). The pooled analysis of the ITT population for seven maintenance studies included 1825 patients.\(^{29–33,35,36}\)
Overall, 10.8% (98/909) of patients in the OD group failed to adhere to their medication regimen compared to 8.5% (78/916) of patients in the conventional dosing group. The pooled RR using a random-effects model was 1.17 (95% CI 0.65–2.09), showing no statistically significant difference in medication adherence between OD dosing and conventional dosing at study endpoint (6 months for Kane et al.13 22 and 12 months for the other studies in the pooled analysis; \( P = 0.61 \)). Statistically significant heterogeneity was detected for this comparison (\( \chi^2 = 18.68, \text{df} = 6, P = 0.005, I^2 = 68\% \)). The heterogeneity appears to be a result of the inclusion of two specific trials.31,36 Kamm et al31 reported a significantly higher compliance rate of 99.6% in the twice-daily dosing group compared to 93.3% in the OD group. The Hawthorne et al36 study reported a significantly higher compliance rate of 97.1% in the OD dosing group compared to 85.5% in the three times daily dosing group. To investigate if these studies were the source of the heterogeneity the analysis was repeated excluding these trials. The pooled analysis of the ITT population now included 1161 patients (five studies).29,30,32,33,36 Overall, 13.6% (80/587) of patients in the OD group failed to adhere to their medication regimen compared to 10.6% (61/574) of patients in the conventional dosing group. The pooled RR using a fixed-effect model was 1.21 (95% CI 0.90–1.63), showing no statistically significant difference in medication adherence between OD dosing and conventional dosing at study endpoint (\( P = 0.20 \)). No statistically significant heterogeneity was detected for this comparison (\( \chi^2 = 3.94, \text{df} = 4; P = 0.41; I^2 = 0\% \)).

Adverse Events

Three studies did not report adverse events as an outcome.29,30,36 Six studies reported on the proportion of patients who experienced at least one adverse event.3,28,31–33,35 The most common adverse events included gastrointestinal disorders (e.g., flatulence, abdominal pain, nausea, and diarrhea), headache, and worsening UC. The pooled analysis of the ITT population now included 2154 patients. Overall, 41.2% (437/1064) of patients who received OD mesalamine reported at least one adverse event compared to 42.5% (463/1090) of patients who received conventional dosing of mesalamine. There was no statistically significant difference in the incidence of adverse events (RR 0.97; 95% CI 0.88–1.07; \( P = 0.52 \)). Eight studies reported on the incidence of serious adverse events.3,27,28,31–35 The pooled analysis of the ITT population for the eight studies included 3348 patients. The proportion of patients who experienced a serious adverse event in the OD group was 3.2% (53/1661) compared to 2.3% in the conventional dosing group (39/1687). Meta-analysis detected no statistically significant difference in the incidence of serious adverse events between patients who were treated OD compared to conventional dosing (RR 1.38; 95% CI 0.92–2.07; \( P = 0.12 \)). Eight studies reported the proportion of patients who withdrew due to adverse events.3,27,28,31–35 The pooled analysis of the ITT population for the eight studies included 3348 patients. A similar proportion withdrew due to adverse events from the OD group (28/1661, 1.7%) compared to the conventional dosing group (30/1687, 1.8%). There was no statistically significant difference in the proportion of patients who withdrew due to adverse events (RR 0.96; 95% CI 0.58–1.58; \( P = 0.86 \)).

The GRADE criteria were used to assess the overall quality of the evidence reported (Table 4). The outcomes induction of remission and clinical improvement were downgraded to moderate due to sparse data (i.e., less than 400 events). The outcome failure to maintain remission at 12 months was downgraded to moderate quality due to a high risk of bias in six of the studies in the pooled analysis. One of the studies was not blinded (open-label) and the other five were single-blinded (investigator blinded). The outcome failure to adhere to study medication at study endpoint (12 months) was rated as moderate due to sparse data.

Discussion

This meta-analysis indicates that mesalamine administered OD is as effective as conventional dosing (twice or three times daily) for induction therapy in mild to moderately active UC. The pooled analyses of induction trials showed no significant differences between OD and conventional dosing for induction of remission (RR 0.95; 95% CI 0.82–1.10; \( P = 0.49 \)) or clinical improvement (RR 0.87; 95% CI 0.68–1.10; \( P = 0.24 \)). Furthermore, subgroup analyses by drug formulation showed no differences in efficacy between OD and conventional dosing for induction of remission. However, the latter results should be interpreted cautiously since only three formulations were evaluated in this analysis.

Importantly, our results also showed that OD mesalamine is as effective as conventional dosing for maintenance therapy. The pooled analyses showed no significant differences between OD and conventional dosing for maintenance of remission at 6 months (RR 1.10; 95% CI 0.83–1.46; \( P = 0.51 \)) or 12 months (RR 0.92; 95% CI 0.83–1.03; \( P = 0.17 \)). With the exception of Pentasa, subgroup analyses by drug formulation showed no significant differences in efficacy between OD and conventional dosing for maintenance of remission. Dignass et al12 found that 2 g of Pentasa dosed OD was superior to 1 g Pentasa dosed twice daily for maintenance of remission at 12 months. A plausible biological explanation for this finding is not readily apparent to us.

Furthermore, no differences between OD and conventionally dosed mesalamine were observed for safety outcomes including the overall incidence of adverse events, serious
adverse events, or withdrawal from treatment due to an adverse event. In keeping with the well-established safety profile of mesalamine, most of the adverse events reported in the studies were mild to moderate in intensity. Common adverse events were gastrointestinal disorders (e.g., flatulence, abdominal pain, nausea, and diarrhea), headache, and worsening UC.

We believe that the methodological basis for these conclusions is relatively sound. The quality of the individual trials was assessed using the Cochrane risk of bias tool and the possibility of bias was judged to be low for most items assessed. However, a concern exists regarding blinding. One open-label study and five studies that were single-blind (investigator-blind) were rated as having a high risk of bias. However, the open-label study and three of the five single-blind studies included endoscopy as an endpoint, which may protect against performance and detection bias. The overall quality of the evidence using the GRADE approach was rated as moderate for the selected primary and secondary outcomes of interest due to sparse data or high risk of bias (due to blinding) in the pooled analyses.

Important patient preference and adherence differences may exist between dosing regimens. In the only two studies that measured patient preference the majority of patients preferred OD dosing to conventional dosing. Although it is generally believed that administration of fewer tablets and less frequent dosing improves both efficacy and adherence, we could not demonstrate the superiority of OD dosing for either of these outcomes. Several possible explanations exist for these observations; however, the most plausible one concerns the unique aspects of the clinical trial environment. It is noteworthy that adherence with medication was remarkably high in the studies evaluated. The pooled adherence rate for the maintenance of remission studies was 89% for the OD dosing group compared to 91% for the conventional dosing group. These rates likely reflect the highly supervised environment in which the studies were conducted. Adherence with medication in clinical trials is generally greater than in clinical practice since participants are highly selected volunteers who are more likely, in general, to be adherent to drug regimens. In addition, adherence is continuously reinforced during the clinical trial process. Thus, it may be difficult to detect differences in adherence between OD and multiple dose regimens in this setting.

Accordingly, a need exists to compare dosing regimens in large-scale community-based studies. In this regard, reported adherence rates in community-based studies range from 40%–60% and are especially poor among patients in remission. However, whether OD dosing regimens improve adherence in the community remains unknown. Although Kane et al demonstrated significantly higher adherence among patients receiving OD dosing compared to conventional dosing at 3 months, no significant differences were found at 6 months. This time-dependent effect has recently been confirmed in a larger study. Sandborn et al found significantly higher adherence among patients using OD dosing compared to conventional dosing at 3 months. However, no statistically significant difference in adherence was found at 6 and 12 months.

Experience from other indications suggest that factors other than the dosing regimen are important for long-term compliance. Long-term observations in UC patients as well as in other indications indicate that patient and physician behaviors play a dominant role in adherence. The patient–physician relationship should reinforce adherence through education, open communication, and mutual agreement regarding the value of treatment. To ensure continued adherence in a community-based setting, Sandborn et al emphasized the importance of healthcare providers evaluating and reinforcing compliance with patients after 3 months of maintenance therapy.

In conclusion, the results of this meta-analysis demonstrate that OD oral dosing of mesalamine is as effective and safe as conventional dosing for the treatment of mild to moderately active UC and for maintenance of remission in quiescent UC. Patient adherence does not appear to be enhanced by OD dosing in the clinical trial setting. Future research should reevaluate the determinants of adherence in large-scale community-based studies.

REFERENCES


