Cost and quality-adjusted life year differences in the treatment of active ulcerative colitis using once-daily 4 g or twice-daily 2 g mesalazine dosing

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Abstract

Background: Improved compliance in active ulcerative colitis (UC) is likely to improve healthcare efficiency by reducing time spent in active mild to moderate UC state. To establish whether once daily (OD) mesalazine offers economic advantages over twice daily (BD) dosing in active UC, we evaluated the outcomes and costs of a recently published randomized study. Methods: A cost-effectiveness model with four week Markov cycles was developed to reflect current treatment practices in the Netherlands with OD and BD mesalazine for active UC. The health service perspective of the Netherlands was reflected in the model and considered a 32 week time horizon with 4 weekly Markov cycles. Outcomes evaluated in the model were time spent in active and remission UC and the corresponding health-related quality of life associated with different clinical states. This was then used to derive quality adjusted life-years (QALYs) at each treatment stage.

Results: A greater proportion of subjects on 4 g OD achieved remission at weeks 4 and 8 compared with 2 g BD. After 32 weeks the average costs per patient with active UC were \( \varepsilon3097 \) and \( \varepsilon3548 \) for those treated with OD and BD mesalazine respectively, with an average saving of \( \varepsilon451 \) per patient treated with OD mesalazine. The average costs per QALY for OD and BD mesalazine were \( \varepsilon5433 \) and \( \varepsilon6324 \) for OD and BD, respectively.

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1. Background

Increasing healthcare costs has increased the need for prescribers to optimize treatment outcomes across many different diseases within constrained budgets. The need for improved efficiency has placed increased emphasis on adopting cost saving interventions. Taking into consideration the increasing prevalence of inflammatory bowel disease, the opportunity to optimize treatment with limited budgets would be welcomed considering the likely demand for treatment.

Treatment compliance is important for maintaining and achieving clinical goals, with the added advantage of potentially saving costs. Previous investigations have shown that compliance to ulcerative colitis (UC) maintenance therapy can reduce the frequency of UC flares, which translates into less need for more costly treatment interventions. A retrospective study in the United States evaluated mesalazine medication possession and overall healthcare costs. It was shown that reduced medication possession resulted in elevated gastro-related inpatient care, with treatment persistent patients incurring reduced medical costs.

UC is a chronic inflammatory disease of the colon that is characterized by periods of remission, with unpredictable episodes of relapse causing rectal bleeding, urgent diarrhea, abdominal discomfort and fatigue. Following induction of remission, preventing recurrence of active UC offers benefits for patients and healthcare systems. Consequently, the choice of maintenance therapy is important as it offers opportunity to influence outcomes like patients' quality of life (QoL) and to save costs. Compliance to oral mesalazine treatment in clinical trials is often very high. However, outside of clinical trials, compliance in treatment will be lower resulting in higher relapse rates and longer time to remission in daily practice. Dosing frequency is one mechanism by which physicians can improve patient compliance and outcomes.

Because dosing frequency is an important treatment consideration known to influence compliance and outcomes in treating active UC, we evaluate in this analysis the economic consequences of outcome differences observed in the MOTUS study comparing mesalazine 4 g once daily (OD) versus 2 g twice daily (BD) dosing in combination with 1 g mesalazine enema in patients with active UC.

2. Methods

Previous studies have defined optimal treatment practices for management of active UC to be in combination treatment with oral and topical mesalazine. Based on recently reported evidence, there are variations in outcomes between OD and BD dosing of the oral mesalazine within this regimen. We estimated the cost differences between OD and BD dosing arising from these variations.

2.1. Treatment practices in the Netherlands

The model was designed to take into consideration the current treatment practices for mild to moderate active UC treatment practices in the Netherlands according to national guidelines. In clinical practice a step-up regimen for treatment of active UC is normally used, starting with an escalated treatment of combined oral and topical mesalazine therapy. In patients who do not respond to intensive mesalazine therapy corticosteroids, topically and/or orally are added. An 8-week course of 40 mg tapered prednisolone is mostly used. In selected cases non-response to oral corticosteroids results in admission for intravenous corticosteroids. Finally, escalation to Infliximab is initiated as a rescue therapy if combination of intensive mesalazine and corticosteroids fails to achieve remission. Infliximab is administered in an outpatient setting at weeks 0, 2, and 6 and then every 8 weeks.

2.2. Model description

The economic evaluation described here is based on the ability to achieve remission in mild-to-moderate active UC based on changes from baseline in the ulcerative colitis disease activity instrument (UCDAI). Because active UC significantly affects costs in the healthcare system and patient's QoL, a cost-utility analysis (CUA) was used to express the cost and QoL burden associated with active disease.

The clinical data on which the economic model is based was obtained from the multicenter, controlled, randomized, investigator-blinded study comparing OD with BD mesalazine for active mild-to-moderate UC. The investigators reported a significant difference in the time to remission at 4 weeks with a trend towards improved clinical remission at 8 weeks. For the purposes of the model described here and aligned with treatment practices in the Netherlands, we used the Flourié et al. data reported treatment outcomes at 4 weeks.

A Markov model was constructed based on previously reported cost-effectiveness analyses of active UC to evaluate differences in costs and health outcomes in terms of quality-adjusted life year (QALY) over time. The health service perspective was reflected in the model and considered 32-weeks of treatment with 4 weekly treatment cycles (Markov cycles). The model comprised of five health states: (1) mesalazine active UC (treated with OD or BD mesalazine); (2) mesalazine-refractory active UC (treated with prednisolone); (3) steroid-refractory active UC (treated with Infliximab); (4) continuous Infliximab active UC; and (5) remission. A description of the model is shown in the figure below (Fig. 1).
3. Modelled outcomes

As stated, UC is known to impact patients' QoL, therefore the primary outcome of interest in the two economic models was the change in average QALY from the intention-to-treat population reported by Flourié et al. The use of QALYs is also the accepted outcome metric recommended by the Dutch authorities for making responsible budgetary and resource allocation decisions.

The QALYs were derived from previously reported UC health state utilities for remission and active UC of 0.84 and 0.78, respectively, and applied to for the time spent in each health state. Outcomes evaluated in the model were average cost of treatment over all Markov cycles for OD and BD mesalazine, the costs per QALY for both interventions and the incremental cost per QALY between both treatment options. The number of individuals in active and remission at each stage were also derived from the model. Because the time horizon considered in both models was less than one year, discount of costs and outcomes was not performed (Table 2).

4. Costs

The model was constructed from resource items in the Netherlands. Resource use costs for consultation (e.g. specialist, general practitioner, IBD nurse) and follow-up visits were derived from the Dutch guideline for conducting costing research comprising of standardized prices. Furthermore, unit costs for diagnosis (e.g. laboratory tests, endoscopy, X-ray), mesalazine and other treatments (e.g. beclometasone, prednisolone, azathioprine, Infliximab) were derived from official Dutch tariffs. All costs were expressed in Euros for the year 2012.

5. Sensitivity analysis

Variations in treatment outcomes were evaluated using probabilistic sensitivity analysis (PSA). PSA evaluates parameter uncertainty by simultaneous sampling values from the parameter probability distributions. In the Netherlands, PSA is also referred to as second-order analysis, and is recommended by the national body that evaluates new medicines. The point estimates and distributions assessed in the PSA for the maintenance and active UC states in the models are shown in Table 1.

6. Results

After 32 weeks the average costs per patient with active UC were €3097 and €3548 for those treated with OD and BD
mesalazine respectively, with an average saving of €451 per patient treated with OD mesalazine. The accumulated QALYs were 0.57 and 0.56 for OD and BD mesalazine respectively, resulting in a small QALY gain of 0.01 for OD treatment and an average cost per QALY of €5433 and €6324 for OD and BD mesalazine respectively. Treatment with OD mesalazine is dominant, because it results in lower costs and increases QALYs.

More patients treated with OD mesalazine achieved clinical remission by week 4 (39.6% versus BD 27.7%) in the MOTUS study.9 According to treatment guidelines in the Netherlands, patients that do not achieve remission within 4 weeks of intensive mesalazine treatment are switched to other treatment. We therefore modeled the consecutive efficacy of OD and BD treatment, which showed that 80% of patients on OD treatment would be in remission versus 76% on BD treatment based on consecutive efficacy modeled. By week 12 the percent of patients in remission based on the modeled evaluation the likelihood of being in remission was nearly identical for OD and BD (Fig. 2).

Mesalazine treatment costs, consisting of 4 g oral and 1 g topical mesalazine for patients with active disease, and 2 g mesalazine for patients in remission, represented 23% (€722) and 21% (€738) of all treatment costs for OD and BD mesalazine respectively within the 32 weeks estimated in the model.

7. Discussion

In the aforementioned economic analysis described here we demonstrated that 4 g OD dosing is dominant compared to 2 g BD dosing in active UC because it is cost-saving. The cost savings were achieved by limiting the need for intensive rescue therapy. The major cost driver for achieving remission was ancillary treatment costs which included intravenous prednisolone and high cost biological agents. Furthermore, a small increase in QALYs was observed based on the shorter duration of time spent in active disease for patients treated with OD mesalazine compared with BD mesalazine during the first 8 weeks of treatment as outcomes were nearly equivalent in later time periods. Because the QALY gain was Limited over this period (i.e. 0.01), the cost-saving achieved is likely of more interest to clinicians and decision-makers.

Recent estimates of IBD epidemiology suggest an increasing incidence of UC over the past few decades.20 Considering the increasing incidence and continued demand to lower costs within healthcare systems, low cost interventions that can prevent the need for more expensive therapies are likely to increase in importance. The findings shown here reinforce the value of low cost interventions such as mesalazine for first-line intervention to alleviate active UC. In particular we find that OD mesalazine can offer cost savings of €451 compared with BD mesalazine for managing active UC in the Netherlands. We also demonstrated that mesalazine oral and enema costs represent a minor proportion of the overall treatment costs associated with achieving remission in patients with active UC representing less than 25% of all costs.

Shortening the time required to achieve remission in active UC can offer both economic and clinical advantages. Symptoms associated with active UC systematically are known to affect a person’s quality of life compared to remission.21 Furthermore, UC can also influence social activity and work productivity.22 Moreover, the use of intensive immunomodulator therapy

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**Table 1** Remission rates used to construct model and variation applied in PSA.

<table>
<thead>
<tr>
<th>Efficacy period in model</th>
<th>Model parameter</th>
<th>Remission rates (transition probability and variance a)</th>
<th>Distribution</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 0–4</td>
<td>OD 4 g mesalazine</td>
<td>0.396 (0.30–0.50)</td>
<td>Beta</td>
<td>9</td>
</tr>
<tr>
<td>Weeks 0–4</td>
<td>BD 2 g mesalazine</td>
<td>0.277 (0.19–0.38)</td>
<td>Beta</td>
<td>9</td>
</tr>
<tr>
<td>Weeks 5–8</td>
<td>Prednisolone</td>
<td>0.68 (0.43–0.87)</td>
<td>Beta</td>
<td>18</td>
</tr>
<tr>
<td>Weeks 9–32</td>
<td>Infliximab</td>
<td>0.39 (0.30–0.48)</td>
<td>Beta</td>
<td>19</td>
</tr>
</tbody>
</table>

a Variance defined by 95% confidence interval (CI).

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**Table 2** Comparative cost and outcomes for OD and BD mesalazine a.

<table>
<thead>
<tr>
<th>OD 4 g Oral mesalazine</th>
<th>BD 2 g Oral mesalazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average treatment costs b</td>
<td>€3097</td>
</tr>
<tr>
<td>Incremental treatment costs QALYs</td>
<td>0.57</td>
</tr>
<tr>
<td>Incremental QALYs</td>
<td>0.01</td>
</tr>
<tr>
<td>Average cost-effectiveness ratios</td>
<td>€5433</td>
</tr>
<tr>
<td>Incremental cost-effectiveness ratio OD dominant (i.e. better outcomes, less cost)</td>
<td></td>
</tr>
</tbody>
</table>

a Based on Monte Carlo simulation derived from 10,000 samplings.
b Cost of all medical interventions, procedures and drug costs (including 4 weeks of concomitant treatment with 1 g topical mesalazine in both treatment groups).

Figure 2 Percentage of patients in remission at different time during treatment (modeled results).
exposes patients with UC to potential side effects, e.g. the risks of opportunistic infections.23

The precise mechanism why OD dosing may improve outcomes has not been established to date. One of the most likely causes of improved outcome could be attributed to improved compliance with an OD treatment as dosing frequency in maintenance therapy has been shown to influence compliance in UC.24 The reported compliance obtained from the clinical trial on which the economic analysis described here was based did not suggest any differences in compliance between OD and BD. Alternative suggestions as posited by, Kruis et al., note that OD dosing could lead to a higher peak luminal concentration and higher mucosal concentration of mesalazine compared with divided dosing of the same total daily dose.25 The improved rate of mucosal healing in patients with OD dosing compared with BD achieved in the MOTUS study, namely 87.5% versus 71.1% would be consistent with this hypothesis.9

Modeling treatment outcomes and costs can help to fill a void in the application of evidence based medicine. Because clinical trials often investigate only a single treatment or intervention applied over a defined period of time, they do not consider consecutive treatments and the cumulative efficacy results for those that do not respond to initial interventions. Modeling can help to fill this void in evidence and demonstrate cumulative clinical efficacy of consecutive interventions that follow established treatment guidelines. In the evaluation described here efficacy for weeks 0–4 was based on the study reported by Flourié et al.9 The model then allowed non-responders to progress to subsequent therapy based on treatment practices in the Netherlands and efficacy defined by Lennard-Jones et al. for weeks 5–8 and Rutgeerts et al. during weeks 9–32.18,19 Modeling consecutive treatment options allow healthcare systems and clinicians the opportunity to compare current practice with new treatment paradigms in terms of cost and patient outcomes within established norms. Although clinical populations represent idealized patient populations, real world evidence can also be integrated into models to reflect these variations.

While modeling is a necessary measure in many instances to understand cumulative practices, it carries many weaknesses that are worth considering. Despite the strength of the clinical evidence on which the model is based, there can be uncertainty regarding the external validity of our modeled results in real world practice. This can arise from differences in patient populations recruited into clinical trials in contrast with the variation in patients observed in clinical practice. This is particularly relevant as the key efficacy observation that OD is more effective than BD mesalazine was obtained from a single randomized clinical study.9 Furthermore, compliance is an important factor in achieving clinical remission and can often be elevated in clinical trials compared with real world practice. Consequently, the manner by which poor compliance could influence our results is unknown as well as the cost impact associated with poor compliance.

Author contributions

MPC model development, deriving costs, results generation, manuscript preparation
JPK medical input, identify costs, review results, manuscript preparation
MJP review model design, critical appraisal results and manuscript writing
SKN model development and design, critical appraisal manuscript and writing.

Disclosures

• Mark Connolly was paid as a research analyst in relation to this work. He holds no financial interests in the sponsor organization and declares no financial interest in the sale of mesalazine products.
• Sandy Nielsen is an employee of Ferring Pharmaceuticals. He holds no shares in the privately held company of Ferring.
• Prof. Maarten J. Postma received no grant, honorarium or stipend in relation to this study. However, he has received grants, honoraria and travel stipends from various pharmaceutical companies.
• Johan P. Kuyvenhoven received no funding in relation to his contributions for this work. In the past he received honorarium from Ferring for analysis of clinical data.

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References


