The Use of Budesonide MMX to Induce Remission in Active, Moderate to Mild Ulcerative Colitis: A Systematic Review

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The Use of Budesonide MMX to Induce Remission in Active, Moderate to Mild Ulcerative Colitis: A Systematic Review

Abstract

Background: Ulcerative colitis (UC), a type of inflammatory bowel disease characterized by diffuse colonic mucosal inflammation, accounts for over 250k physician visits annually with direct medical costs alone exceeding 4 billion dollars annually. The disease, whose etiology is not well understood, can have severe consequences such as colorectal cancer. First-line treatment for mild to moderate disease is topical 5-ASA agents such as mesalamine. Patients refractory to this treatment are candidates for oral steroids, but these can have severe side effects. Budesonide, a second-generation glucocorticoid already used topically for UC, has less systemic effects, but needs an effective delivery mechanism as an oral form to treat areas unreachable via topical solutions. Budesonide multi-matrix (MMX) was just approved January 2013 for treatment. Will it be effective in inducing remission in patients with active, mild to moderate UC?

Methods: An exhaustive literature search using Medline-OVID, CINAHL, EBMR Multifile, and Web of Science using the terms ulcerative colitis and budesonide was conducted. Lists from identified articles were also investigated for further studies. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).

Results: Two study articles were included in the review. CORE 1, a randomized, double-blind, double-dummy study, determined the efficacy of budesonide MMX in inducing remission in ulcerative colitis patients with active disease classified as mild to moderate. The other study was a randomized and double-blind preliminary safety and efficacy study for budesonide MMX. Both studies demonstrated statistically significant rates of remission induction with no increase in side effects.

Conclusion: This systematic review indicates this drug as a viable option for patients with active, mild to moderate UC who are refractory to first line therapies. A recommendation for the use of budesonide MMX as an alternative can be given because of the evidence of efficacy, safety of the drug and the already-established use of its two components.

Degree Type
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Degree Name
Master of Science in Physician Assistant Studies

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The Use of Budesonide MMX to Induce Remission in Active, Moderate to Mild Ulcerative Colitis: A Systematic Review

Terence Potter

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 2013

Faculty Advisor: Robert P. Rosenow, Pharm.D., OD
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Terence Potter is a native of Illinois, who, after a successful career in information technology, made a transition into health care, working as an EMT and a technician’s aide in an MRI clinic before beginning his Physician Assistant Master’s degree at Pacific University. He has a strong interest in family medicine and hopes to join a practice that emphasizes prevention and healthy lifestyles as well as providing effective and modern care to its community.

Abstract

**Background:** Ulcerative colitis (UC), a type of inflammatory bowel disease characterized by diffuse colonic mucosal inflammation, accounts for over 250k physician visits annually with direct medical costs alone exceeding 4 billion dollars annually. The disease, whose etiology is not well understood, can have severe consequences such as colorectal cancer. First-line treatment for mild to moderate disease is topical 5-ASA agents such as mesalamine. Patients refractory to this treatment are candidates for oral steroids, but these can have severe side effects. Budesonide, a second-generation glucocorticoid already used topically for UC, has less systemic effects, but needs an effective delivery mechanism as an oral form to treat areas unreachable via topical solutions. Budesonide multi-matrix (MMX) was just approved January 2013 for treatment. Will it be effective in inducing remission in patients with active, mild to moderate UC?

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**Conclusion:** This systematic review indicates this drug as a viable option for patients with active, mild to moderate UC who are refractory to first line therapies. A recommendation for the use of budesonide MMX as an alternative can be given because of the evidence of efficacy, safety of the drug and the already-established use of its two components.

**Keywords:** Ulcerative colitis, budesonide, MMX
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List of Abbreviations

5-ASA............................................................5-aminosalicylic acid
CAI..............................................................Clinical Activity Index
CRP............................................................C-reactive protein
IBD............................................................Inflammatory Bowel Disease
MMX..........................................................Multi-matrix
NNH.........................................................Number Needed to Harm
NNT.........................................................Number Needed to Treat
UC...........................................................Ulcerative Colitis
UCDAI......................................................Ulcerative Colitis Disease Activity Index
The Use of Budesonide MMX to Induce Remission in Active, Moderate to Mild Ulcerative Colitis: A Systematic Review

BACKGROUND

Ulcerative colitis (UC) is a chronic condition that is a type of inflammatory bowel disease (IBD) characterized by diffuse colonic mucosal inflammation. Bloody diarrhea is the hallmark symptom of UC. Tenesmus and rectal urgency are also common symptoms. The clinical course involves flare-ups and remissions, which may occur spontaneously or as a response to treatment. ¹ Serious consequences of UC can include toxic megacolon, massive hemorrhage, perforation, toxic colitis, and strictures. Patients with long standing UC are at increased risk of developing epithelial dysplasia and carcinoma. ² UC is classified by severity as mild, moderate, or severe based on factors such as the number of stools and signs of anemia. ³

The etiology is not clear and it is considered to be multi-factorial. A consensus hypothesis is that in genetically predisposed individuals, both exogenous factors (eg, normal gut flora) and endogenous host factors (eg, intestinal epithelial cell barrier function, innate and adaptive immune function) interact to cause a chronic state of dysregulated mucosal immune function that is further modified by specific environmental factors (e.g., smoking). ² Simply stated, the cause of IBD is currently considered an inappropriate immune response to these factors. ²

The disease accounts for over 250k physician visits annually, 30k hospitalizations, and loss of over a million workdays per year. ⁴ The direct medical costs exceed 4 billion dollars annually, comprising estimated hospital costs of over $960 million ⁵,⁶ and drug costs of $680 million. ⁶ Incidence of the disease is rising or just
beginning to stabilize in the entire world. As many as 1.4 million persons in the United States and 2.2 million persons in Europe suffer from IBD. There is a clear need for effective pharmacotherapy.

The goal of treatment is induction and maintenance of remission, reduction in the need for the long-term use of corticosteroids, and minimization of cancer risk. Treatment is dictated by anatomic location of the disease and severity classification. Patients with mild to moderate UC can be treated with a topical 5-aminosalicylic acid (5-ASA) agent such as mesalamine, oral mesalamine, and topical steroids. Topical mesalamine has traditionally been first line therapy, and is superior to topical corticosteroids. Refractory cases are treated with oral prednisone or infliximab. However, these oral therapies do not have trivial side effect profiles, with prednisone causing cushingoid features (moon face, fat redistribution, striae), suppression of the hypothalamic-pituitary-adrenal axis, and many others. Infusion reactions, abdominal pain, nausea, headache, diarrhea, and infections are the most common adverse events associated with infliximab reported in clinical trials.

Budesonide, a second generation glucocorticoid, has less systemic effects than typical steroids such as prednisone. It has been used for the treatment for UC for more than 10 years, but used as a topical solution. Because of its extensive first-pass metabolism, oral budesonide would be ineffective as the drug would be unavailable to the colon after going through the stomach. And a topical formula would only be effective as far as an enema could deliver the drug. Topical steroids and 5-ASA agents have been in use for the treatment of proctitis (inflammation of the rectum) for many years. A coating, called MMX (multi-matrix), which allows a drug to survive gastric acidity and...
be available in the colon, was added to oral mesalamine and approved in 2007 for use in UC. This, along with topical mesalamine, became an effective treatment combination. But this did not help patients refractory to mesalamine. A similarly effective delivery mechanism for budesonide was needed. A study for oral budesonide MMX was conducted in 2005 on healthy males, demonstrating that this combination is suitable for targeted colonic drug delivery. The next step was to determine efficacy in UC patients. A study took place in 2011 demonstrating efficacy, and, in January of 2013, budesonide MMX for UC was approved by the FDA under the trade name Uceris®. Does the use of budesonide MMX induce remission in active, moderate to mild UC?

METHODS

An exhaustive literature search using Medline-OVID, CINAHL, EBMR Multifile, and the Web of Science using the terms ulcerative colitis and budesonide was conducted. Lists from identified articles were also investigated for further studies. The search was narrowed by using only English language articles, and for studies that involved human subjects. Further narrowing was employed; included were full-text articles with primary data, randomized control trials with the non-control patients having ulcerative colitis, trials with oral formulas only, trials after 2009, and trials whose endpoint was induction of remission. Also, a search was conducted on the National Institute of Health clinical trials site using the term budesonide MMX to reveal all of the trials associated with the therapy. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).
RESULTS

The initial search revealed 152 articles. After duplicates were removed, and the inclusion and exclusion criteria applied, two study articles remained, see Figure I for details on the search. Both studies are randomized control trials comparing budesonide MMX against placebo. Both were sponsored by Santarus, a biopharmaceutical company that produces Uceris®, which is the trade name for budesonide MMX. The study period of comparing budesonide MMX to placebo was 8 weeks in the CORE 1 study, but only 4 weeks in the safety and efficacy study. Also, in the safety and efficacy study, the diagnosis for the patients was specific to left-sided ulcerative colitis, whereas in the CORE 1 study, it was not as specific. See Table I for study details and Table II for a summary of the findings.

CORE 1 Study

This was a randomized, double-blind, double-dummy, placebo-controlled, 8-week trial to determine the efficacy of budesonide MMX in inducing remission in ulcerative colitis patients with active disease classified as mild to moderate. It was a multi-center study conducted at 108 centers in North America and India between August 2008 and May 2010. This was the phase three trial for the drug. The trial had 509 patients who were up to 75 years old with active, mild-to-moderate ulcerative colitis for at least 6 months and with an ulcerative colitis disease activity index (UCDAI) score of 4-10 points. The UCDAI is a composite score of four items (stool frequency, rectal bleeding, mucosal appearance, and physician’s rating of disease activity). Concurrent therapy for UC was not permitted during the study. Patients receiving oral mesalamine or other oral 5-aminosalicyclic medications at the screening visit were required to wash out of their
medication at least 2 days before randomization. Exclusion criteria included diagnosis of severe UC (UCDAI >10 points); evidence or history of toxic megacolon; disease limited to the rectum (proctitis extending from the anal verge up to 15 cm); presence of infectious colitis; presence of severe anemia, leukopenia, or granulocytopenia; verified, presumed, or expected pregnancy or ongoing lactation; presence of cirrhosis or evident hepatic or renal disease or insufficiency; presence of severe diseases in other organs and systems; local or systemic complications or other pathological states requiring therapy with corticosteroids and/or immunosuppressive agents; type 1 diabetes; glaucoma; or known infection with hepatitis B or C or with human immunodeficiency virus.  

The primary endpoint was combined clinical and endoscopic remission at week eight. Secondary endpoints were clinical improvement, endoscopic improvement, histologic healing and symptom resolution. Patients were randomized to one of four treatments at a 1:1:1:1 ratio using a block size of 4. As each new patient was randomized via the interactive voice response system, he or she was given the next available randomization number that was associated with a study drug. Patients were followed up through week 10. A follow-up safety visit was to be conducted two weeks after the final visit (week 8 or early withdrawal). The interactive voice response system was used to centrally randomize patients to study drug. A double-dummy procedure was used to maintain blinding, with patients in each treatment group receiving their blinded study drug 3 times daily. The four treatment groups in the 8-week trial were: 9mg budesonide MMX each day, 6mg budesonide MMX each day, 1.2 grams of mesalamine each day, and placebo. The main study drug and focus of this systematic review was 9mg budesonide. The 6-mg dose strength was included as an additional treatment arm, at the
request of regulatory authorities, to establish the lowest effective dose for budesonide MMX in inducing remission in active mild to moderate UC. A non-powered reference arm using Asacol (mesalamine) 2.4 g was also included as active control and internal reference. The 9mg budesonide MMX group had 123 patients and the placebo group had 121 patients. 

Budesonide MMX significantly increased the rate of combined endoscopic and clinical remission (relative risk (RR)=2.40, number needed to treat (NNT)=10), clinical improvement (RR=1.32, NNT=13), endoscopic improvement (RR=1.20, NNT=13), and symptom resolution (RR=1.65, NNT=9). However, there was not a significant increase in histologic healing, in fact, treatment favored placebo. (RR=0.62, number needed to harm (NNH)=40). See Table III for study end points.

Treatment with budesonide MMX was generally well tolerated with an overall safety profile similar to placebo. The percentage of patients with severe AEs was highest in the placebo group. There was no evidence of any increase in glucocorticoid effects in the budesonide MMX groups when compared to the placebo group. There was a decrease in mean morning plasma cortisol levels at weeks two four for the budesonide MMX groups, but the levels gradually increased toward baseline values by the final visit. See Figure 2 for details of the glucocorticoid effects across the treatment groups.

**Preliminary Safety and Efficacy Study**

This was a European pilot multicenter efficacy study conducted in 2009 that was a randomized, double-blind, placebo-controlled 4-week trial to determine if budesonide 9mg MMX could induce clinical remission and improvement in patients with active moderate left-sided ulcerative colitis, while other ulcerative colitis therapies were
kept stable such as 5-ASA. An additional 4-week period of open-label treatment was conducted in which all of the study participants received active treatment.  

After screening 56 patients, 36 patients were enrolled in the study. The original intent was to have 40 patients, but the trial was interrupted before reaching the planned sample of 40 subjects. Also, not all 36 patients completed four weeks in the trial. Because of worsening disease, after two weeks, five patients switched from placebo to open-label active treatment.  

Patients were males and females with a diagnosis of active, left-sided ulcerative colitis (up to the splenic flexure) with a clinical activity index (CAI) < 14, which would exclude severe disease. CAI is a validated instrument to reflect the severity of ulcerative colitis, which was defined by a clinical activity grading system. The index is composed of the number of weekly stools, weekly average of blood in stool, abdominal pain/cramps, among others. These patients were on stable treatment with oral 5-ASA at a dose between 0 and 3 grams a day for at least two months before the study. Exclusion criteria: distal proctitis (<15 cm above the anal verge from the pectineal line), severe left-sided ulcerative colitis (CAI N14), extensive colitis proximal to the splenic flexure, and infections as a cause of relapse. Also, patients, who had been using oral or topical steroids in the last 4 weeks, could not participate. The use of immunosuppressive medication was disallowed with the exception of 6-mercaptopurine and azathioprine. Other reasons for exclusion were prior treatment with anti-TNF agents, use of NSAIDs or drugs affecting the colonic motility including antidiarrheal and drugs altering the pH of the intestinal content. Pregnancy and severe concomitant diseases also represented exclusion criteria. 

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The primary endpoint was achieving a relevant clinical improvement that was defined as either remission (which means a CAI $\leq 4$), or a reduction of CAI by 50% from the baseline value. Further objectives of the trial were the evaluation of reduction in clinical symptoms after eight weeks of treatment, evaluation of endoscopic and histological changes, and c-reactive protein (CRP) level after four and eight weeks of treatment.\textsuperscript{12}

The study population average age was 44.5±12.6, body weight averaged 72.7±15 kg, and height averaged 171.7±9.5 cm. The placebo group was 9 males and 9 females, while the treatment group was 12 males and 6 females. The mean duration of ulcerative colitis from diagnosis to the start of the study varied from 0 to 35 years in both groups; in the budesonide group it was nine years and in the placebo group it was 10 years. \textsuperscript{12}

Budesonide MMX significantly increased the rate of achieving clinical improvement (meaning either remission, defined as a CAI $\leq 4$ or a CAI reduction by at least 50% of the baseline value) after four weeks of treatment (RR=1.42, NNT=7). Reduction in endoscopic index from baseline for budesonide MMX was 6.44 (±3.27) from 9.06 (±1.79) and for placebo it was 6.33 (±2.64) from 8.53 (±2.10). Reduction in histologic index from baseline for budesonide MMX was 1.69 (±0.70) from 1.82 (±0.53). Histologic index actually increased for placebo to 1.8 (±0.77) from 1.67 (±1.05). Figure III shows CRP changes from baseline levels. After four weeks the budesonide MMX group CRP level fell from 1.09 (±1.23) mg/dL (CI 0-4.80) to 0.47 (±0.5) mg/dL (CI 0-1.66); a smaller decrease was measured for placebo after four weeks but the actual number was not given.\textsuperscript{12}
DISCUSSION

UC is a disease that severely impacts one’s lifestyle, can have deadly consequences, and is a significant worldwide problem. There is an array of treatment options, of which topical mesalamine is first line. Oral mesalamine was developed for disease unreachable by topical therapy, and special coatings were developed to allow the oral drug to remain intact long enough to reach all areas of the colon. For patients refractory to mesalamine, corticosteroids and infliximab have been used but with significant side effects. Budesonide, a steroid that undergoes significant first-pass metabolism, was used for UC patients unresponsive to mesalamine, but similarly to first generations of oral mesalamine, getting the drug to the colon intact was a challenge. The MMX coating, first used successfully in oral mesalamine, was combined with budesonide and approved by the FDA in January 2013.9

The goal of this review was to determine the efficacy and safety of budesonide MMX by critically appraising applicable drug studies and making a recommendation for clinical practicality if the evidence supports it. Two studies were analyzed and both show statistically significant improvement in both patient-important outcomes and surrogate outcomes, establishing Budesonide MMX as an alternative therapy to mesalamine for UC patients. However, both studies have their limitations and potential for bias.

The CORE 1 study9 is a study of moderate quality that shows statistically significant improvement vs. placebo in remission induction, clinical improvement, endoscopic improvement, and symptom resolution for the budesonide treatment group. The study does not have any major limitations in methodology, it was a randomized, double-blind, and double-dummy study, there were no patients lost to follow-up, and
there were no increases in medicine adverse effects. There were no serious
inconsistencies in the study as the study and placebo groups were mostly prognostically
balanced except for gender. The percentage of male/female patients in the budesonide
MMX and placebo groups were 62.6/46 and 56.2/53 respectively. However, this isn’t
significant, as gender has not been proven to affect prognosis in UC. The study does not
have serious indirectness; the primary outcome is not a surrogate outcome and it is the
outcome of interest in the study. However, there is a high probability of a risk of
publication bias, as Santarus, the company that produces Uceris®, funded the study. This
downgraded the quality of the study from high to moderate.

The preliminary safety and efficacy study\textsuperscript{12} is a study of low quality that shows
statistically significant improvement vs. placebo in relevant clinical improvement, a
reduction in clinical symptoms, improvement in endoscopic and histological changes, as
well as a reduction in CRP. The study does not have any major limitations in
methodology. It was a randomized, double-blind study and there were no patients lost to
follow-up. Also, there were no increases in medicine side effects. There were no serious
inconsistencies; the study and placebo groups were mostly prognostically balanced
except for gender; the number of male/female patients in the budesonide MMX and
placebo groups were 12/6 and 9/9, respectively. Again, this doesn’t impact prognosis.
The study has serious imprecision as the sample size is small. There is a high probability
of a risk of publication bias; similarly to CORE 1, Santarus funded this study. These
items caused the quality of the study to be graded as low.

For researchers, there are two other areas of research that need to be investigated:
A comparison of efficacy of budesonide MMX to mesalamine MMX in remission
induction and an evaluation of the efficacy of budesonide MMX in maintaining remission. The remission maintenance study was completed in 2012. No papers have been published detailing the results, but the study involves patients from the CORE 1 study who remained in remission and were treated and followed for 12 months. 

CONCLUSION

Budesonide MMX is a drug newly approved in January of 2013 for use in UC that is a combination of two established pharmaceuticals. This systematic review indicates this drug as a viable option for inducing remission in UC patients who are refractory to treatments that are established and considered first-line. The evidence shows statistically significant improvement in outcomes. While the studies have their limitations based on the GRADE criteria, given the low incidence of side effects and the high incidence and devastating impact of this disease, a clinician would need to consider this as an alternative therapy for UC patients who are refractory to other treatments. A recommendation for the use of budesonide MMX can be given.
References


15. Extension Study of Budesonide MMX™ 6mg in Maintenance Of Remission In Patients With Ulcerative Colitis. Available at:

Table I. Characteristics of Reviewed Studies

<table>
<thead>
<tr>
<th>Study Design Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Inconsistency</th>
<th>Publication bias likely</th>
<th>Quality</th>
<th>Importance</th>
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</thead>
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<tr>
<td>Combined clinical and endoscopic remission (primary endpoint)</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>No serious inconsistencies</td>
<td>Industry funded, bias likely</td>
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<td>Relevant clinical improvement (remission as defined by CAI &lt;= 4 or a CAI reduction &gt;= 50% of baseline); (primary endpoint)</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>Information size small</td>
<td>No serious inconsistencies</td>
<td>Industry funded, bias likely</td>
<td>Low</td>
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<tr>
<td>CAI Improvement (secondary endpoint)</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>Information size small</td>
<td>Gender differences between treatment and placebo group</td>
<td>Industry funded, bias likely</td>
<td>Very low</td>
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<td>Clinical improvement (secondary endpoint)</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>No serious inconsistencies</td>
<td>Industry funded, bias likely</td>
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<td>Endoscopic improvement (secondary endpoint)</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>No serious inconsistencies</td>
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<td>Moderate</td>
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<tr>
<td>Histologic Healing (secondary endpoint)</td>
<td>No serious limitations</td>
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<td>Symptom Resolution (secondary endpoint)</td>
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<td>No serious imprecision</td>
<td>No serious inconsistencies</td>
<td>Industry funded, bias likely</td>
<td>Moderate</td>
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Table II. Summary of Findings

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<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Placebo or no treatment (total)</th>
<th>Combined clinical and endoscopic remission</th>
<th>Relevant clinical improvement (remission as defined by CAI (\leqslant 4) or a CAI reduction (\geq 50%) of baseline)</th>
<th>Clinical improvement</th>
<th>Endoscopic improvement</th>
<th>Histologic Healing</th>
<th>Symptom Resolution</th>
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<tr>
<td>CORE 1</td>
<td>123</td>
<td>121</td>
<td>RR=2.40, NNT=10</td>
<td>RR=1.3, NNT=13</td>
<td>RR=0.57, NNT=3</td>
<td>RR=1.65, NNT=9</td>
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<td>Preliminary safety and efficacy</td>
<td>17</td>
<td>15</td>
<td>RR=1.4, NNT=7</td>
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Table III. CORE 1 Study Primary and Secondary End Points

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Placebo (n=121)</th>
<th>Budesonide MMX 9mg (n=123)</th>
<th>Budesonide MMX 6mg (n=121)</th>
<th>Asacol 2.4g (n=124)Com</th>
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<tbody>
<tr>
<td>Combined clinical and endoscopic remission, n (%)</td>
<td>9 (7.4)</td>
<td>22 (17.9)</td>
<td>16 (13.2)</td>
<td>15 (12.1)</td>
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<td>95% CI</td>
<td>2.8 to 12.1</td>
<td>11.1 to 24.7</td>
<td>7.2 to 19.3</td>
<td>6.4 to 17.8</td>
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<td>Clinical improvement</td>
<td>30 (24.8)</td>
<td>41 (33.3)</td>
<td>37 (30.6)</td>
<td>42 (33.9)</td>
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<td>Endoscopic improvement</td>
<td>40 (33.1)</td>
<td>51 (41.5)</td>
<td>43 (35.5)</td>
<td>41 (33.1)</td>
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<td>Histologic healing</td>
<td>8 (6.6)</td>
<td>5 (4.1)</td>
<td>9 (7.4)</td>
<td>14 (11.3)</td>
</tr>
<tr>
<td>Symptom resolution</td>
<td>20 (16.5)</td>
<td>35 (28.5)</td>
<td>35 (28.9)</td>
<td>31 (25.0)</td>
</tr>
</tbody>
</table>
Figure I. Search Methodology

PRISMA 2009 Flow Diagram

- Records identified through database searches (n = 152)
- Additional records identified through other sources (n = 9)
- Records after duplicates, non-human, and non-English removed (n = 103)
- Records screened (n = 30)
- Records excluded (n = 73)
- Full-text articles assessed for eligibility (n = 6)
- Full-text articles excluded, with reasons (n = 24)
- Studies included in systematic review (n = 2)
Figure II. CORE 1 Study Glucocorticoid Effects and Plasma Cortisol Levels

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Budesonide 9 mg</th>
<th>MMX 9 mg</th>
<th>MMX 6 mg</th>
<th>MMX 3 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Potential Glucocorticoid Effect</td>
<td>13 (10.1)</td>
<td>15 (11.5)</td>
<td>7 (5.6)</td>
<td>10 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Mood</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Discrete</td>
<td>2 (1.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>6 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Fluid retention</td>
<td>1 (0.8)</td>
<td>2 (1.6)</td>
<td>2 (1.6)</td>
<td>1 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Mood changes</td>
<td>3 (2.3)</td>
<td>5 (4.4)</td>
<td>5 (4.4)</td>
<td>2 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Sleep changes</td>
<td>2 (1.6)</td>
<td>4 (3.2)</td>
<td>3 (2.4)</td>
<td>1 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>8 (6.4)</td>
<td>5 (4.6)</td>
<td>3 (2.4)</td>
<td>2 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>3 (2.3)</td>
<td>3 (2.4)</td>
<td>2 (1.6)</td>
<td>4 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Hair loss</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

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Figure III. Safety and Efficacy Study Mean CRP Levels

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