Budesonide is a second generation corticosteroid with very high affinity for the cortisol receptor, and active first pass hepatic metabolism through the cytochrome p450-3CA4 pathway. With a 90% first pass hepatic metabolism of budesonide, systemic corticosteroid side effects are minimized, while targeted end organ release can maximize corticosteroid benefit. The use of targeted release forms of budesonide for allergic disorders of the nasopharynx, esophagus, and respiratory tract are now considered standard of care over oral corticosteroids. Budesonide MMX (multi-matrix system, Cosmo Pharmaceuticals SpA, Lainte, Italy) utilizes a unique pH dependent drug release process to deliver and release budesonide throughout the colon, see Figure 1. This pharmacology theoretically maximizes drug delivery to the colon and minimizes systemic corticosteroid side effects.

In this edition of VHJOE, I will review the important findings of two Phase III pharmaceutical studies that confirm the efficacy of Budesonide MMX (Uceris® Santarus, Inc., now Salix Pharmaceuticals, Inc/ Santarus Inc. all rights reserved, Raleigh, NC USA) for the treatment of mild-moderate ulcerative colitis (UC). The first study, CORE I (Colonic Release Budesonide I) conducted by Sandborn, et al, examined the efficacy of Budesonide MMX (9 mg or 6 mg/day), Mesalamine (5-ASA, 2.4 gm/day, as reference standard) or Placebo as mono-therapy for mild-moderate UC. The CORE II study by Travis, et al, examined the efficacy of Budesonide MMX (9 and 6 mg/day), Budesonide-EC (3 mg, tid, as reference standard) or Placebo as mono-therapy for mild-moderate UC. The CORE I study was conducted in North America and India, while the CORE II study was conducted in Europe, Australia, Russia, and Israel.

The study participants in the CORE I and II studies were required to meet strict colonoscopy and histology criteria consistent with UC and exclusion of infectious causes of colitis. Disease severity was defined by a UCDAI score, see Figure 2.
These two studies included over 900 eligible patients aged 18 to 75 yrs. with active, mild-moderate UC for at least 6 months duration and a UCDAI score of 4 to 10 points (mild to moderate). Study candidates with ≤ 15 cm of colitis (ulcerative proctitis) were not enrolled in either study. No additional concurrent therapy for UC was allowed during the study. Patients receiving treatment with oral 5-ASA required a 2 day washout before enrollment. Those study patients receiving rectal 5-ASA and oral or rectal corticosteroids, immunosuppressive agents, and Anti-TNFα agents were required to be off these medications for 4 wk, 8 wk and 12 wk prior to enrollment, respectively. Clinical evaluations and blood tests were conducted every two weeks and full colonoscopy and biopsies were performed at time of enrollment and final evaluation. Morning cortisol levels were obtained at enrollment and final evaluation.

Both the CORE I and CORE II studies used the same stiff primary endpoint defined as combined clinical and endoscopic remission after 8 weeks of therapy. The criteria used to define “combined remission” included UCDAI score ≤ 1, with rectal bleeding score of 0, stool frequency score of 0, no mucosal friability on colonoscopy, and a ≥ 1 point reduction in baseline endoscopy index (EI). Secondary study end points included clinical improvement, endoscopic improvement and histologic healing. Both studies used a 1:1:1:1 randomization with a double-blind, double-dummy, placebo-controlled, parallel-group design. The CORE I and CORE II studies differed only in the region from where patients were recruited and the type of “active” arm utilized in the study (Mesalamine, 5-ASA, 2.4 gm/day in CORE I and Budesonide-EC 9mg/day in CORE II).

Study subjects were approximately 40 yrs. of age and evenly split by gender. Most of the subjects were Caucasians, with left sided colitis or proctosigmoiditis of less than 5 years disease duration. The median UCDAI score for CORE II study participants was 6.5, while the mean UCDAI score for CORE I study participants was 6.8. Prior 5-ASA prescription was evident in 2/3rd of the participants from both CORE I and CORE II studies, see Figure 3.

Results from each of the CORE I and CORE II studies showed that Budesonide-MMX 9mg/day is significantly more effective than placebo for the induction of combined clinical and endoscopic remission of mild to moderate UC at 8 week. The CORE I study showed that B-MMX 9 mg/day was significantly more effective in inducing combined clinical and endoscopic remission than placebo (19.9% vs. 7.4%, p = 0.0143), while B-MMX 6 mg/day and 5-ASA 2.4 g/day were not more effective in induction of remission than placebo, Figure 4. Secondary endpoints of clinical improvement, endoscopic improvement, histologic healing and symptom resolution were numerically higher in the B-MMX 9 mg/day group versus placebo, but statistical significance was only seen for symptom resolution 28.5% vs. 16.5%, p = 0.258. Budesonide-MMX 6 mg/day showed only statistically significant improvement in symptom resolution compared to placebo, 28.9% vs. 16.5%, p = 0.0214), while 5-ASA 2.4 g/day did not show statistically significant improvement in any of the primary or secondary end points examined.
The CORE II study showed that B-MMX 9mg/day was significantly more effective in inducing combined clinical and endoscopic remission than placebo (17.4% vs. 4.5%; OR 4.49; 95% CI 1.47 to 13.72; p = 0.0047), while B-MMX 6 mg/day was not more effective than placebo, Figure 5. Interestingly, B-EC 9 mg/day was significantly more effective in inducing combined clinical and endoscopic remission than placebo (12.6% vs. 4.5%, p=0.048). The CORE II study was not significantly powered to evaluate for a statistical difference in combined clinical and endoscopic remission between B-MMX 9 mg/day and B-EC 9mg/day, 17.4% vs 12.6%, respectively. Secondary endpoints of clinical improvement, endoscopic improvement, histologic healing and symptom resolution were numerically higher in the B-MMX 9 mg/day group versus placebo, but statistical significance was only seen for histologic healing (16.5% vs. 6.7%, p < 0.05) and symptom resolution (23.9% vs 11.2%, p < 0.05).

Pooled safety data for CORE I & II showed similar adverse effects for placebo and all of the study treatment groups, Figure 6. The pooled study related, treatment emergent adverse events (TEAEs) and serious TEAEs were also similar across all treatment groups. The most common TEAEs in all groups were UC relapse and headache. Morning plasma cortisol levels were measured at enrollment and at week 8. Cortisol levels remained within the normal range for all study groups, but the mean level of morning cortisol did show a significant decrease from baseline in the Budesonide groups.

Conclusions:

The CORE I and II studies evaluated a new drug delivery system of a second generation corticosteroid, B-MMX, designed to maximized targeted colonic benefit in mild to moderate UC and minimize systemic corticosteroid side effects with 8 weeks of treatment. The results of both studies clearly indicate significant clinical benefit from B-MMX 9 mg/day mono-therapy.
that clinicians will supplement treatment for mild-moderate UC patients that are 5-ASA non-responders or 5-ASA relapsers with an 8 week “pulse” dose of B-MMX 9mg/day, instead of corticosteroids. Moreover, UC patients on immunomodulator drugs or Anti-TNF α experiencing a mild flare or exhibiting rising fecal calprotectin levels may benefit from an 8 week “pulse” dose of B-MMX 9 mg/day. The efficacy of such clinical practices remains to be determined, but the benefit of avoiding corticosteroid side effects appears to be obvious.

The CORE I and II post study follow up at week 10, gives only a 2 wk, post treatment follow up and little insight into the durability of B-MMX 9 mg/day to sustain remission of disease. In defense of the investigators, many study subjects were enrolled into an open-label 12 month extended use study evaluating the safety and benefit of long-term B-MMX 6 mg/day.11,12,13 These long-term B-MMX 6mg/day treatment and safety studies indicate no clinically significant differences between B-MMX 6 mg/day versus placebo on bone mineral density, hypothalamic-pituitary-adrenal axis impairment or other potential corticosteroid effects. However, B-MMX 6 mg is not manufactured in the U.S. and the 6 mg dosage does not have FDA approval for short or long term use in the treatment of UC.

In conclusion, mono-therapy with Budesonide-MMX 9mg/day appears to be safe and effective new treatment for the 8 week induction for remission of mild-moderate UC.

References:


