

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Budesonide Extended-Release in Patients With Mild to Moderate Ulcerative Colitis



Asher Kornbluth, MD
Clinical Professor
The Dr Henry D. Janowitz Division of Gastroenterology
Icahn School of Medicine at Mount Sinai
New York, New York



G&H How does budesonide extended-release differ from other oral budesonide formulations, such as controlled ileal-release budesonide capsules?

AK Multimatrix (MMX) budesonide extended-release (Uceris, Salix Pharmaceuticals) is indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis (UC). This drug provides once-daily delivery of budesonide throughout the full length of the colon with extended release for the full 24-hour period via MMX technology, which is also used in MMX mesalamine (Lialda, Shire Pharmaceuticals). Budesonide extended-release dissolves at a pH of 7, so the active drug is “saved” for delivery in the colon and is not released in the ileum.

One difference between budesonide extended-release and controlled ileal-release budesonide capsules (Entocort EC, Prometheus Therapeutics & Diagnostics) is that the latter are indicated for mild to moderate right-sided colitis and terminal ileal disease in Crohn’s disease. Controlled ileal-release budesonide capsules dissolve once the intestinal pH approaches 5.5, so the drug has been released by the time it reaches the general area of the hepatic flexure. Therefore, controlled ileal-release budesonide should not be used in patients with any form of UC, including mild to moderate colitis. Finally, the dosage of controlled ileal-release budesonide consists of three 3-mg capsules, as opposed to one 9-mg tablet for budesonide extended-release.

G&H What studies have been conducted on budesonide extended-release?

AK The CORE I and II studies comprised almost 900 patients with mild to moderate, but not severe, UC who

received 9 mg of budesonide extended-release daily. The primary endpoint was to achieve both clinical remission and endoscopic remission. Clinical remission plus endoscopic remission were achieved in 18% of patients over 8 weeks, compared with 6% of patients who were treated with placebo.

G&H How does budesonide extended-release differ from prednisone, particularly in terms of adverse events?

AK Some people assume that because budesonide is a corticosteroid, it might act as a “distant cousin” of prednisone in terms of corticosteroid-like side effects and the 2 drugs might be similar in this regard. However, budesonide extended-release is not a replacement for prednisone; the former is not indicated for, and has not been studied in, severe UC, as prednisone has.

In addition, budesonide extended-release did not have any corticosteroid-related adverse events compared with placebo during the 8-week study of a 9-mg daily dose. A 12-month study looked at corticosteroid-related adverse events during a safety analysis of a 6-mg budesonide extended-release tablet that is available in Europe, but not in the United States. When all of the adverse events that occurred in more than 2% of patients, including bone density loss, were examined, there was no difference between the 6-mg budesonide group and the placebo group (each of which comprised 250 patients) after 12 months of use except for a decrease in AM cortisol that did not translate into signs of adrenal insufficiency. Budesonide extended-release has first-pass hepatic metabolism, which significantly reduces the systemic bioavailability of the drug. This

accounts for the lack of differences between the drug and placebo in terms of corticosteroid-related adverse events, such as mood changes, sleep changes, insomnia, and acne, as well as cumulative adverse events.

Some patients refuse to take prednisone, even in the setting of severe colitis, because they would rather deal with their disease than with the adverse events of the drug. These patients are typically young adults who are concerned about the adverse events of the drug affecting their social lives. Therefore, it is important for physicians to consider these adverse events when looking at a drug that might have corticosteroid-like side effects.

G&H Can budesonide extended-release be used in patients who are currently on prednisone?

AK It is important that corticosteroids be tapered slowly if patients are being transferred to budesonide extended-release. This drug cannot be used as a quick bridge for rapid weaning from prednisone. In other words, if a patient is on, say, 20 mg of prednisone and is doing well, a physician cannot put the patient on 9 mg of budesonide extended-release and then take prednisone out from under the patient. This is because of the relatively low systemic bioavailability of the budesonide extended-release.

G&H What are the contraindications for budesonide extended-release?

AK This drug is contraindicated in patients who have hypersensitivity to budesonide. Budesonide extended-release is still a corticosteroid, which can result in variable degrees of biosystemic availability. Patients who are going to surgery should receive a stress dose of a corticosteroid. Extra caution should be used when this drug is used in patients who are particularly susceptible to any corticosteroid-like adverse events, including, but not limited to, patients who have diabetes, hypertension, cataracts, glaucoma, active or high risk for infection, or osteoporosis. Because of the first-pass hepatic metabolism of budesonide extended-release, physicians should also be particularly cautious in patients with liver disease, who may have impaired hepatic synthetic or metabolic function. Important drug–drug interactions may also occur in patients who are on drugs that inhibit the cytochrome P450 C4A enzyme (or who drink grapefruit juice) because of competitive drug metabolism.

G&H How should a patient be managed after achieving remission with this drug?

AK This question is probably the most common one that I have received from physicians about budesonide

extended-release. Although there is no maintenance label or indication for this drug, I usually taper it in patients who have been treated with it. After patients receive 8 weeks of 9-mg doses on label, I taper down to the “equivalence” of 6 mg for 4 weeks and then to 3 mg for 4 weeks. Because this drug cannot be crushed or cut into halves or thirds—as this would interfere with its release—I administer the 9-mg dose every day for the first 8 weeks, then taper the dosage by giving the patient a 9-mg tablet every 2 of 3 days and then a 9-mg tablet every 1 of 3 days. I have had many patients come into remission on 9 mg a day, and I find that as I lower the dosage—for example, going from the equivalent of 6 mg a day to 3 mg a day—patients have recurrence. Based upon the 12-month safety data on the 6-mg dose that is available in Europe (but not in the United States), I am reassured that there has been no increase in corticosteroid-like adverse events and no increase in bone density loss, so I feel comfortable leaving patients on the equivalent of 3 mg or 6 mg a day, monitoring them for corticosteroid-like side effects. Again, I stress that this is an off-label manner of using the drug as a maintenance strategy and is not based on any clinical trial or pharmacokinetic data.

At the end of a year, it has been my custom to have patients undergo a measurement of bone density and an ophthalmologic examination for assessment of cataracts and glaucoma. There is no ideal amount of time that should elapse before another 9-mg course. However, if a patient needs 9 mg repeatedly—for example, over the course of a year—I would recommend trying another medication.

G&H Can budesonide extended-release be used concomitantly with a mesalamine compound?

AK In the 2 CORE studies, the subjects could not have been on concomitant 5-aminosalicylic acid (5-ASA) drugs. However, most of the patients who are presenting to gastroenterologists with mild to moderate disease are probably already on 5-ASA therapy and flaring while on it. There is no reason to think that 5-ASA agents and budesonide extended-release cannot be used in combination. There has not yet been a head-to-head comparison trial that has been adequately powered to determine whether budesonide extended-release is more effective than 5-ASA therapy. In one of the 2 CORE trials, there was a 2.4-g daily dose of mesalamine used as an internal control arm. However, the study was not powered to show superiority of the mesalamine or budesonide drug.

On the other hand, if a presenting patient is naive to 5-ASA therapy and has mild to moderate disease, I see no reason not to use budesonide extended-release as first-line therapy.

This column is based on a 2014 ACG presentation sponsored by Salix Pharmaceuticals.

Dr Kornbluth has served as a speaker and on the advisory board for Salix Pharmaceuticals, Shire Pharmaceuticals, and Prometheus Therapeutics & Diagnostics. He has served on the advisory board or as a consultant for Janssen Pharmaceuticals, AbbVie, and Pfizer. He has served on the speakers bureau for Janssen Pharmaceuticals, AbbVie, Prometheus Diagnostics & Therapeutics, Millennium/Takeda, and Salix Pharmaceuticals.

Suggested Reading

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