Recent Advances in Pharmacotherapy of Ulcerative Colitis


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ABSTRACT

Ulcerative colitis is a form of chronic inflammatory bowel disease (IBD) that produces inflammation and ulcers along the inside of the colon, which can interfere with the normal function of the colon. The disease typically starts to manifest in patients as young adults. Ulcerative colitis is an intermittent disease with periods of exacerbated symptoms, or flares, and periods that are relatively symptom-free. According to the Cohn’s and Colitis Foundation of America, several millions people suffer from ulcerative colitis worldwide. Current therapeutic approaches for ulcerative colitis are partially successful despite advances in GIT research. A significant proportion of patients with ulcerative colitis undergo colectomy. Nearly 50% patients do not achieve sustained remission, leading to impairment of physical and mental health, social life, employment issues and sexual activity. Budesonide is an oral, extended release synthetic corticosteroid that is recently approved for UC. Enteric-coated budesonide formulations resist gastric-acid degradation, delivering active drug to the small intestine and proximal colon. Budesonide is specifically indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis. Budesonide has a high first-pass metabolism with minimal systemic absorption. This review describes recent advances in the pharmacotherapy of ulcerative colitis and outlines why future studies targeting sustained suppression of inflammation could have an enormous impact on the natural course of the disease. Ulcerative colitis needs intense therapy and it should be maintained until sustained remission and mucosal healing has been reached.

KEYWORDS: Ulcerative colitis; budesonide; remission; inflammation; IBD; corticosteroids

Introduction

According to the Crohn’s and Colitis Foundation of America, inflammatory bowel conditions affect thousands of people in the U.S. Several million people suffer from ulcerative colitis all over the world. Ulcerative colitis (UC) is a chronic inflammatory bowel disorder of the gastrointestinal tract characterized by mucosal inflammation of the rectum that extends proximally through the colon, in a continuous fashion, but to a variable extent. It is considered as an autoimmune disease. The disorder is characterized by a relapsing and remitting course of variable severity. The majority of patients present with left-sided or distal disease of mild-to-moderate severity. Most remain in remission for long periods with maintenance medical therapy (Farmer et al., 1993; Solberg et al., 2008).

Although most patients present with mild-to-moderate UC, 10% of patients initially present with severe disease. Additionally, approximately 15% of patients will develop a severe flare during the course of their lifetime. Acute severe UC can be defined according to the original criteria set forth by Truelove and Witts: six or more stools per day, with either a body temperature of more than 37.8 °C, a pulse rate of more than 90 bpm, large amounts of blood per stool, a hemoglobin level of less than 10.5 g/dl or an erythrocyte sedimentation rate of more than 30 mm/h (Truelove and Witts, 1955). Ulcerative colitis can occur in both sexes and in any age group but most often begins in people between 15 and 30 years of age.

In the West, the incidence and prevalence of inflammatory bowel diseases has increased in the past 50 years, up to 8–14/100,000 and 120–200/100,000 persons for ulcerative colitis (UC). Studies of migrant populations and populations of developing countries demonstrated a recent, slow increase in the incidence of ulcerative colitis, In patients with UC, the lesions usually remain superficial and extend proximally; colectomy is required for 10%–30% of patients. Prognosis is difficult to determine. The mortality of patients with UC is not greater than that of the population; the peak age for UC is 30–40 years. Some studies have reported that a second peak occurs at 60–70 years, but this observation has not been confirmed. Pediatric IBD accounts for 7% to 20% of all IBD cases, based on varying results from population based studies UC occurs slightly more frequently in men (60%). In the past 50 years, the incidence of UC first increased then stabilized or even decreased; during the stabilization phase, the prevalence of UC in the Punjabi population has been reported to be 44/100,000, and its incidence is 6.0/100,000.

Pathophysiology

The lower gastrointestinal tract may be divided into the cecum, the ascending colon, the transverse colon, the descending colon, the sigmoid colon and the rectum
(Fig.1). The large intestine (colorectum) begins at the cecum, which is a pouch approximately 2-3 inches long. Ileal contents empty into the cecum through the ileocecal valve. The appendix extends from the base of the cecum. The ascending colon rises from the cecum along the right posterior wall of the abdomen, under the ribs to the under surface of the liver. At this point it turns toward the midline (hepatic flexure), becoming the transverse colon. The transverse portion crosses the abdominal cavity toward the spleen, goes high up into the chest under the ribs, and turns downward at the splenic flexure. Continuing along the left side of the abdominal wall to the rim of the pelvis, the descending colon turns medially and inferiorly to form the S-shaped sigmoid (sigma-like) colon. The rectum extends from the sigmoid colon to the pelvic floor muscles, where it continues as the anal canal terminating at the anus. The anal canal is approximately 4 cm long.

In addition to the extent of involvement, people may also be characterized by the severity of their disease:

1. Mild disease correlates with fewer than four stools daily, with or without blood, no systemic signs of toxicity, and a normal erythrocyte sedimentation rate (ESR). There may be mild abdominal pain or cramping.
2. Moderate disease correlates with more than four stools daily, but with minimal signs of toxicity. Patients may display anemia (not requiring transfusions), moderate abdominal pain.
3. Severe disease, correlates with more than six bloody stools a day or observable massive and significant bloody bowel movement, and evidence of toxicity as demonstrated by fever, tachycardia, anemia or an elevated ESR.
4. Fulminant disease correlates with more than ten bowel movements daily, continuous bleeding, toxicity, abdominal tenderness and distension, blood transfusion requirement and colonic dilation (Kornbluth and Sachar, 2004).

**Types of ulcerative colitis**

**Ulcerative proctitis**: Ulcerative proctitis is defined by inflammation that is located in the rectum, most commonly the last 6 inches or less. For about 30% of patients, their UC starts in this form. Symptoms include diarrhea, bloody stool, rectal pain, and an urgent need to move the bowels (tenesmus). With the inflammation limited to a smaller area than in the other forms of UC, ulcerative proctitis is considered a milder type of UC, with fewer incidences of complications.

**Proctosigmoiditis**: When inflammation is located in the rectum and sigmoid colon (the last section of the colon), it is known as proctosigmoiditis. Symptoms include diarrhea, bloody diarrhea, crampy pain, tenesmus, and pain on the left side of the abdomen. This type of UC may be treated with topical medications in the form of suppositories, enemas, and foam. Enemas can reach further up into the colon, making them more effective in treating inflammation higher in the sigmoid. This form of UC may also be treated with a 5-ASA (5-aminosalicylic acid) drug or sulfasalazine, which are given orally and used for long-term maintenance and continuation of remission. An oral corticosteroid may also be used as a short-term therapy during a flare up.

**Left-sided colitis**: As the name suggests, inflammation extends from the rectum up through the sigmoid and descending colon, which are located in the upper left part of the abdomen. Also known as limited or distal colitis, left-sided colitis is when inflammation is in the left side of the colon (the rectum, sigmoid colon, and descending colon). Symptoms include left-sided abdominal cramping and pain, bloody diarrhea, and weight loss. This type of UC may be treated with a combination of topical medication (suppositories, enemas, or foam) as well as a 5-ASA drug, sulfasalazine, or a corticosteroid.

**Pancolitis**: Inflammation affecting the entire colon (right, left, transverse, and rectum). Most patients require oral medications once inflammation extends above the sigmoid colon. Some patients may also benefit from combined treatment with oral and topical preparations. Patients with moderate to severe symptoms may require temporary treatment with a steroid drug (usually with prednisone), either as an outpatient or given intravenously in the hospital. Remission can be achieved in most patients. Once remission is achieved, patients are typically maintained on one of the oral mesalazine drugs. Symptoms include abdominal pain and cramps, bloody diarrhea, fatigue, fever, night sweats, and weight loss.

**Causes, symptoms and risk factors**

The main symptoms of UC include bloody diarrhoea, high fever, watery diarrhoea, and chronic loss of blood from the GIT leading to increased rates of anaemia (Hanauer et al., 1996). While the exact cause is unknown, scientists no longer believe stress or diet to be
the primary causes. The following factors are thought to contribute to the onset of ulcerative colitis. A genetic susceptibility may trigger an abnormal response to the bacterium in some people, leading to ulcerative colitis onset. Viruses may also be responsible for ulcerative colitis.

The following risk factors have been documented for UC:

- **Age**: Ulcerative colitis occurs in all age groups, but normally starts between fifteen and thirty.
- **Ethnicity**: Ulcerative colitis occurs in all groups, but whites are at the highest risk. Those of Jewish heritage are at an even higher risk.
- **Gender**: Ulcerative colitis affects men and women almost equally, but ulcerative colitis is slightly more common in males.

The following main causes have been implicated in UC:

1. **Genetics**: Inheritance on a polygenetic basis seems to play a role in the etiology of ulcerative colitis in about 12-15% of cases. The most firmly established and quantitatively greatest risk factor for developing ulcerative colitis is a family history. A genetic component to the etiology of ulcerative colitis can be hypothesized based on the following (Orholm et al., 2000):
   - Aggregation of ulcerative colitis in families.
   - Identical twin concordance rate of 10% and dizygotic twin concordance rate of 3% (Tysk et al., 1988).
   - Ethnic differences in incidence and prevalence.

2. **Environmental**: Environmental factors that may potentiate the onset of ulcerative colitis are currently under investigation. Such risk factors include diet, breast-feeding and other perinatal events, occupation and social class, oral contraceptive use, and, most impressively, the cessation of cigarette smoking. There have been conflicting reports of the protection of breastfeeding in the development of inflammatory bowel disease. One Italian study showed a potential protective effect (Corrao et al., 1998).

3. **Autoimmune disease**: Some sources list ulcerative colitis as an autoimmune disease, (Baumgart and Sandborn, 2007), a disease in which the immune system malfunctions, attacking some part of the body. In contrast to Crohn's disease, which can affect areas of the gastrointestinal tract outside of the colon, ulcerative colitis usually involves the rectum and is confined to the colon, with occasional involvement of the ileum. This so-called “backwash ileitis” can occur in 10-20% of patients with pancolitis and is believed to be of little clinical significance (Fauci et al. 2008).

The pathogenesis of ulcerative colitis remains unknown. Several theories have been proposed that implicate vascular impairment, autoimmune mechanisms, bacterial-immunological interactions, and allergic or hypersensitivity reactions.

Recent literature on inflammatory bowel disease (IBD), Crohn’s disease, and ulcerative colitis reports an intensive search for the antigens that trigger the immune response in inflammatory bowel disease. There are three major hypotheses as to these antigenic triggers. One hypothesis is that these triggers are microbial pathogens, as yet unidentified. According to this theory, the immune response in IBD is an appropriate but ineffective response to these pathogens. The second hypothesis as to the antigenic trigger in IBD is that there is some common dietary antigen or non-pathogenic microbial agent to which the patient mounts an abnormal immune response. It has been hypothesized that patients with IBD are genetically programmed to mount an intense immune response to some common luminal antigen (dietary or microbial) to which most people do not respond.

Diet is a major source of antigens in the intestinal lumen. Dietary antigens are capable of triggering immune responses. One of the foods implicated in the pathogenesis of IBD is cow’s milk. Patients with IBD and Crohn’s disease demonstrate an increased incidence of antibodies to cow’s milk protein. In patients with IBD, cow’s milk proteins and other dietary antigens have abnormal access to the lamina propria because of the defect in the epithelial cell monolayer caused by inflammation. Normally, the intestinal epithelium is a barrier between the immune cells of the lamina propria and luminal antigens; however, in IBD, the immune cells of the lamina propria are exposed to numerous luminal antigens. These luminal antigens are capable of triggering immune responses. As a result, specific immune responses to the etiological agent may be overwhelmed by immune responses to thousands of luminal antigens that pass through the damaged epithelium. The third hypothesis relating to antigenic triggers postulates that an antigen is expressed on the patient’s own cells, particularly on intestinal epithelial cells. Theoretically, the patient mounts an appropriate immune response against some luminal antigen; but because of similarities between proteins on the epithelial cells and the lumen antigen, the patient’s immune system also attacks the epithelial cells. Under this autoimmune theory, the immune response is directed toward the epithelial cells, and the cells are destroyed by one of two immune effector mechanisms—either antibody-dependent cellular cytotoxicity or direct cell-mediated cytotoxicity.
**Pharmacotherapy of Ulcerative Colitis**

**Non-pharmacological approaches**

In general, physicians recommend that a patient with UC shouldn't use non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen or naproxen. These medicines may cause flare-ups. But some people may be more likely to have flare-ups from NSAIDs than others. Talk to your doctor about whether to avoid these medicines. Change in diet may help reduce symptoms including (a) eating small amounts of food throughout the day, (b) drinking plenty of water (drink small amounts throughout the day), and (c) avoiding high-fiber foods (bran, beans, nuts, seeds, and popcorn) (Burger et al., 2011; Rutgeerts et al., 2009; Sands et al., 2010).

Many people with ulcerative colitis have vitamin and mineral deficiencies (because of loss of appetite, reduced absorption by the colon, and chronic diarrhea). Some medications may also lower important nutrients in the body. Folic acid (800 mcg per day) is found to be helpful. Many people who have ulcerative colitis have low levels of folic acid in their blood. If you have had or are planning to have surgery that will create an ostomy, you may feel self-conscious or embarrassed. After a period of adjustment, most people are able to resume all of their usual activities. In fact, you may feel better than before surgery because you may no longer have painful symptoms. Support groups are available for people with ostomies.

Avoid gassy foods such as beans, cabbage, cauliflower, and broccoli: raw fruit juices and fruits - especially citrus fruits - spicy food, popcorn, alcohol, caffeine, and foods and drinks that contain caffeine, such as chocolate and soda. Very crunchy foods such as raw apples and carrots may also be problematic.

Low fat foods are helpful. With ulcerative colitis of the small intestine, digesting and absorbing fat is sometimes difficult, so it passes through the intestine, worsening diarrhea. Butter, margarine, peanut butter, nuts, mayonnaise, avocados, cream, ice cream, fried foods, chocolate, and red meat can be especially problematic.

Eat five or six small meals rather than two or three larger ones are preferable. You may feel worried, embarrassed, or even sad or depressed about having a bowel accident. Other stressful events in your life, such as moving, or losing a job or a loved one can cause digestive problems (Sands et al., 2010).

Lactose intolerance is noted in many ulcerative colitis patients. Those with suspicious symptoms should get a lactose breath hydrogen test. If lactose is restricted, calcium may need to be supplemented to avoid bone loss. Patients with abdominal cramping or diarrhea should avoid fresh fruit, caffeine, carbonated drinks, high fructose corn syrup and sorbitol containing foods.

**Therapeutic approaches**

**Approved drugs:** The main pharmacological approach for UC treatment includes budesonide, sulfasalazine, mesalazine, and corticosteroids such as prednisone (Table 1).

Unlike Crohn's disease, ulcerative colitis has a lesser prevalence in smokers than non-smokers. Patients who choose to use smoking as a treatment should keep a record regarding smoking cessation and the onset or relapse of ulcerative colitis to verify associations (Calkins, 1989; Lakatos et al., 2007). Studies using a transdermal nicotine patch have shown clinical and histological improvement (Guslandi, 1999).

**Nicotine:** In one double-blind, placebo controlled, study conducted in the United Kingdom 48.6% of patients who used the nicotine patch, in conjunction with their standard treatment, showed complete resolution of symptoms. Another randomized, double-blind, placebo-controlled, single-centre clinical trial conducted in the United States showed that 39% of participants showed significant improvement vs. 3% of placebo. Use of a transdermal nicotine patch without the addition of other standard treatments such as mesalazine has relapse occurrence rates similar to standard treatment without the use of nicotine.

**Iron supplementation:** The gradual loss of blood from the gastrointestinal tract, as well as chronic inflammation, often leads to anemia, and professional guidelines suggest routinely monitoring for this.
Adequate disease control usually improves anemia of chronic disease, but iron deficiency may require treatment with oral iron supplements. Occasionally, parenteral iron is required (Mowat et al., 2011).

**Bacterial recolonization:** Probiotics may have benefit in UC. One study which looked at a probiotic known as VSL#3 has shown promise for people with ulcerative colitis (Bibiloni et al., 2005). Fecal bacteriotherapy involves the infusion of human probiotics through fecal enemas (Borody et al., 2004). It suggests that the cause of ulcerative colitis may be a previous infection by a still unknown pathogen. This initial infection resolves itself naturally, but somehow causes an imbalance in the colonic bacterial flora, leading to a cycle of inflammation which can be broken by "recolonizing" the colon with bacteria from a healthy bowel. There have been several reported cases of patients who have remained in remission for up to 13 years (Borody et al., 2003). In the United States it can be difficult to find doctors who perform this procedure so some patients have performed the procedure at home using a protocol outlined in a published study (Silverman et al., 2010).

**Surgical therapy:** Surgery in ulcerative colitis should be reserved for those patients with refractory disease, complications associated with the medical therapy, or complications of colitis. Colectomy may be used in pediatric patients for amelioration of growth retardation in prepubescent children affected by ulcerative colitis. Current surgical alternatives include total proctocolectomy with Brooke ileostomy, the intra-abdominal Koch pouch, and restorative proctocolectomy with ileal pouch-anal anastomosis.

![Fig. 3. Surgical options for the treatment of ulcerative colitis. A. proctocolectomy; B. Brooke ileostomy; C. Koch pouch ileostomy; D. restorative proctocolectomy.](image-url)
**Fish oil** Eicosapentaenoic acid (EPA), derived from fish oil. This is an Eicosanoid that inhibits leukotriene activity. It is effective as an adjunct therapy. Usual dose is 15-18 capsules a day. Slow release phosphatidylcholine has some evidence of benefit in ulcerative colitis (Stremmel et al., 2005).

**Antioxidants** The free radical induction theory suggests that the initial cause of ulcerative colitis may be a metabolic defect that allows a build up of chemicals related to hydrogen peroxide beneath the membrane that protects the cells of the intestinal wall from the bacteria inside the intestine, resulting in destruction of the membrane. During remission the membrane is re-established, but may be subject to new damage, resulting in a flare up of the disease (Farmer et al., 1993). To the extent this may be true, it would be appropriate to take antioxidants, dietary supplements that may support the body’s defences against oxidants like hydrogen peroxide. Some antioxidants include vitamins A, C and E, coenzyme Q10, and metals selenium and manganese.

**TABLE 1**

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug Name</th>
<th>pKa</th>
<th>Dosage</th>
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<tr>
<td>Aminosalicylates</td>
<td>Sulfasalazine (Azulfidine)</td>
<td>3.3</td>
<td>1.5-2 g/day</td>
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<td>Mesalamine (Asacol, Rowasa)</td>
<td>5.87</td>
<td>2.4 g/day</td>
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<tr>
<td>Corticosteroids</td>
<td>Balsalazide disodium (Colazal)</td>
<td>5.1-5.3</td>
<td>2250 mg/day</td>
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<td></td>
<td>Budesonide</td>
<td>&gt;7</td>
<td>9 mg</td>
</tr>
<tr>
<td>Immune system</td>
<td>Prednisone (prednisolone)</td>
<td>12.58</td>
<td>40 mg/day</td>
</tr>
<tr>
<td>suppressors</td>
<td>Azathioprine (Imuran)</td>
<td>8.2</td>
<td>2.5 mg/kg/day</td>
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<tr>
<td>Mercaptopurine</td>
<td>(Purinethol)</td>
<td>7.6</td>
<td>1.5 mg/kg/day</td>
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<td>Biologies</td>
<td>Cyclosporine</td>
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<td>2-4 mg/kg/day</td>
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<td></td>
<td>Infliximab (Remicade)</td>
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<td>5-10 mg/kg/day</td>
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<tr>
<td>Nitine patches</td>
<td>Adalimumab (Humira)</td>
<td>13.3</td>
<td>160 mg/day</td>
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<td></td>
<td>Antidiarrheal medications</td>
<td>7.1</td>
<td>20-40 mg/day</td>
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**Budesonide therapy of UC**

The FDA has approved budesonide using treatment of ulcerative colitis. Budesonide (Uceris) is an oral, extended release formulation of budesonide, a synthetic corticosteroid. It was formulated to delay the release of the active ingredient until the tablet reaches the indicated intestinal location where the controlled dissolution begins, where it decreases inflammation in the digestive tract. Budesonide retains the effectiveness of classical corticosteroids, but with reduced side effects due to its targeted controlled release in the colon with minimal systemic absorption. It is specifically indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis. It is supplied as a tablet for oral administration. The recommended dose is 9 mg taken orally once daily in the morning with or without food for up to 8 weeks. It should be swallowed whole and not chewed, crushed or broken.

Budesonide extended release tablets for oral administration contain budesonide, a synthetic corticosteroid, as the active ingredient (Fig. 4). Budesonide is designated chemically as (RS)-11β, 16α, 17, 21-tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16, 17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S).

Budesonide is an oral, extended release formulation of budesonide, a synthetic corticosteroid. The formulation contains budesonide is an extended release tablet core. The tablet core is enteric coated to protect dissolution in gastric juice which delays budesonide release until exposure to a pH > 7 in the small intestine. Upon disintegration of the coating, the core matrix provides extended release of budesonide in a time dependent manner.

**Fig. 4. Chemical structure of budesonide.**

Budesonide extended release tablets are indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis. The recommended dosage for the induction of remission in adult patients with active, mild to moderate ulcerative colitis is 9 mg taken orally once daily in the morning with or without food for up to 8 weeks. UCERIS should be swallowed whole and not chewed, crushed or broken. If concomitant administration with ketoconazole, or any other CYP3A4 inhibitor, is indicated, patients should be closely monitored for increased signs and/or symptoms of hypercorticism. Avoid grapefruit juice, which is known to inhibit CYP3A4, when taking budesonide. In these cases, discontinuation of budesonide or the CYP3A4 inhibitor should be considered. It is available as white, round, biconvex extended release tablets debossed. Each extended release tablet contains 9 mg budesonide. It is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of budesonide.

When glucocorticoids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Glucocorticoids can reduce the response of the hypothalamus-pituitary-adrenal axis to stress. Care is needed in patients who are transferred from glucocorticoid treatment with higher systemic effects to glucocorticoids with lower systemic effects, such as budesonide, since symptoms attributed to withdrawal of steroid therapy, including those of acute adrenal
suppression or benign intracranial hypertension may develop.

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressant doses of glucocorticoids. In patients who have not had these diseases, particular care should be taken to avoid exposure. Glucocorticoids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections. Replacement of systemic glucocorticoids with budesonide tablets may unmask allergies, which were previously controlled by the systemic drug. Reduced liver function affects the elimination of glucocorticoids, and increased systemic availability of oral budesonide has been demonstrated in patients with liver cirrhosis.

In budesonide therapy, caution should be taken in patients with hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticoids may have unwanted effects (Falt et al., 2007; Rachmilewitz, 1989). Systemic glucocorticoid use may result in the following:

- Hypercorticism and adrenal suppression
- Symptoms of steroid withdrawal in those patients transferring from systemic glucocorticoid therapy
- Immunosuppression
- Increased systemic glucocorticoid susceptibility
- Other glucocorticoid effects

Regarding teratogenic effect of budesonide, there are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Hypoadrenalism may occur in infants born of mothers receiving glucocorticoids during pregnancy. Such infants should be carefully observed.

Safety and effectiveness of budesonide in pediatric patients have not been established. Glucocorticoids, such as budesonide may cause a reduction of growth velocity in pediatric patients (Falt et al., 2007; Rachmilewitz, 1989).

Adverse events associated with the use of budesonide may include, but are not limited to, the following: headache, nausea, decreased blood cortisol, upper abdominal pain, fatigue, flatulence, abdominal distension, acne, urinary tract infection, arthralgia, constipation.

References


