

# AMERICAN GASTROENTEROLOGICAL ASSOCIATION INSTITUTE

## American Gastroenterological Association Institute Medical Position Statement on Corticosteroids, Immunomodulators, and Infliximab in Inflammatory Bowel Disease

See CME Quiz on page 932.

The following recommendations were developed to assist physicians in the appropriate use of medications to treat patients with inflammatory bowel disease (IBD). These recommendations represent the results of many years of research and many collaborative efforts. The medications reviewed include corticosteroids, azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate, mycophenolate mofetil, cyclosporine, and infliximab.

### Corticosteroids

Corticosteroids are potent, rapidly acting oral, topical, or parenteral agents used for acute treatment of patients with moderate to severe relapses of IBD. Budesonide (Entocort; AstraZeneca Pharmaceuticals, Wayne, PA) is a poorly absorbed corticosteroid with limited bioavailability due to extensive first-pass metabolism (degraded by the liver and red blood cells) that can produce therapeutic benefit with reduced systemic toxicity in patients with ileocecal Crohn's disease (CD). Topical agents in the form of suppositories or foam have been used to treat patients with proctitis, whereas enemas are effective for application in patients with disease up to the splenic flexure.

#### Recommendations for Corticosteroid Use

##### Mild to moderate IBD.

- Ileal-release preparations of budesonide (Entocort) are indicated for the treatment of patients with ileal and right-sided colonic CD. Ileal-release preparations of budesonide are not effective in patients with ulcerative colitis (UC). (Grade A)
- The use of conventional corticosteroids such as prednisone is generally reserved for patients with moderate to severe disease who failed to respond to first-line therapies for IBD such as mesalamine (UC) or budesonide (CD). (Grade B)
- Topical therapy with either hydrocortisone (Grade

A) or budesonide (Grade B) is effective for distal colonic inflammation.

##### Moderate to severe IBD.

- Corticosteroids such as prednisone are effective in both patients with CD and patients with UC. (Grade A)
- Corticosteroids are not effective for the treatment of patients with perianal fistulas (Grade C).

##### Severe and fulminant IBD.

- Hospitalization for parenteral corticosteroids is indicated for patients failing to respond to oral corticosteroids or for patients with severe disease with UC (Grade A) or CD (Grade B).

##### Maintenance therapy.

- Conventional corticosteroids are not efficacious in maintenance treatment of patients with CD (Grade A) or patients with UC (Grade B).
- Budesonide therapy is effective in the maintenance of short-term (3 months) but not long-term (1 year) remission compared with placebo in patients with mild to moderate ileocecal CD. (Grade A)

##### Dosing and tapering for IBD.

- Dosages in the range of 40–60 mg/day or 1 mg · kg<sup>-1</sup> · day<sup>-1</sup> of prednisone or equivalent are effective for induction of remission. (Grade A)
- Induction of response averages 7–14 days. A gradual taper by 5 mg/wk of prednisone (or equivalent corticosteroid) to a dose of 20 mg and then 2.5–5 mg/wk below 20 mg is recommended. (Grade B)
- Budesonide may be tapered gradually from the initial induction dose of 9 mg to doses of 6 mg and subsequently 3 mg. Budesonide does suppress the adrenocortical axis; clinicians should evaluate for

adrenal insufficiency as warranted by clinical symptoms. (Grade C)

- An inability to taper corticosteroids is an indication for antimetabolite and/or infliximab therapy (see following text). (Grade A)
- For patients failing to respond to 7–14 days of high-dose oral prednisone or equivalent corticosteroid therapy, parenteral corticosteroids are indicated. (Grade C)
- Dosages for parenteral corticosteroids typically are in the range of methylprednisolone 40–60 mg/day or hydrocortisone 200–300 mg/day. (Grade A)

#### Monitoring for complications.

- Periodic bone mineral density assessment is recommended for patients on long-term corticosteroid therapy (>3 months). (Grade A)
- Annual ophthalmologic examinations are recommended for patients on long-term corticosteroid therapy. (Grade C)
- Patients with corticosteroid use within the past year are at greater risk for adrenal insufficiency, especially following surgery, and may need stress-dose corticosteroids perioperatively. (Grade C)
- Patients who are using corticosteroids should be monitored for glucose intolerance and other metabolic abnormalities. (Grade B)
- Patients being treated with corticosteroids are at increased risk for infectious complications. (Grade B)

### AZA/6-MP

AZA and 6-MP are chemically related immunomodulators. AZA is nonenzymatically converted to 6-MP. Their onset of full activity is slow and may take 3 months. 6-MP and AZA are members of the thiopurine class of medications and are commonly used to treat patients with CD and UC who are corticosteroid dependent in an attempt to withdraw corticosteroids and maintain patients in remission off corticosteroids. AZA and 6-MP have also been shown in some studies to reduce clinical and endoscopic postoperative recurrence of CD.

#### Recommendations for AZA/6-MP Use

- When initiating therapy with either 6-MP or AZA, measurement of complete blood count with differential is advocated at least every other week as long as doses of medications are being adjusted. Thereafter, the measurement of complete blood count

with differential should be performed as clinically appropriate at least once every 3 months. Periodic measurement of liver-associated chemistries is also advocated. (Grade C)

- Current Food and Drug Administration (FDA) recommendations suggest that individuals should have thiopurine methyltransferase (TPMT) genotype or phenotype assessed before initiation of therapy with AZA or 6-MP in an effort to detect individuals who have low enzyme activity (or who are homozygous deficient in TPMT) in an effort to avert AZA or 6-MP therapy and thus avoid potential adverse events. Individuals who have intermediate or normal TPMT activity (wild type or heterozygotes) need measurement of frequent complete blood counts (as above) in addition to TPMT assessment because these individuals may still develop myelosuppression subsequent to use of AZA or 6-MP. (Grade B)
- Long-term treatment with corticosteroids is undesirable. Patients with chronic active corticosteroid-dependent disease (either CD or UC) should be treated with AZA 2.0–3.0 mg · kg<sup>-1</sup> · day<sup>-1</sup> or 6-MP 1.0–1.5 mg · kg<sup>-1</sup> · day<sup>-1</sup> in an effort to lower or preferably eliminate corticosteroid use. Infliximab is another option in this situation, as is combination infliximab/antimetabolite therapy. (Grade A)
- Individual patients with either CD or UC who experience a severe flare of disease requiring corticosteroid treatment or require re-treatment during the year with another course of corticosteroids should be considered for initiation of therapy with AZA 2.0–3.0 mg · kg<sup>-1</sup> · day<sup>-1</sup> or 6-MP 1.0–1.5 mg · kg<sup>-1</sup> · day<sup>-1</sup> in an effort to avoid future corticosteroid use (Grade C). Infliximab is another option in this situation, as is combination infliximab/antimetabolite therapy.
- 6-MP (and likely AZA) is modestly effective for decreasing postoperative recurrence in CD both endoscopically and clinically. Use of this agent should be considered for patients at high risk for postoperative recurrences or in whom postoperative recurrence would have deleterious effects. (Grade B)
- Some studies have shown AZA 2.0–3.0 mg · kg<sup>-1</sup> · day<sup>-1</sup> or 6-MP 1.0–1.5 mg · kg<sup>-1</sup> · day<sup>-1</sup> to have some efficacy in treating and healing perianal and enteric fistulae. (Grade C)
- Thiopurine metabolite monitoring in the treatment

of patients with 6-MP or AZA is useful when attempting to determine medical noncompliance and may be helpful for optimizing dose and monitoring for toxicity. (Grade C)

- AZA 2.0–3.0 mg · kg<sup>-1</sup> · day<sup>-1</sup> or 6-MP 1.0–1.5 mg · kg<sup>-1</sup> · day<sup>-1</sup> is effective for maintenance of remission in patients with CD regardless of disease distribution. (Grade A)
- AZA 2.0–3.0 mg · kg<sup>-1</sup> · day<sup>-1</sup> or 6-MP 1.0–1.5 mg · kg<sup>-1</sup> · day<sup>-1</sup> is effective for reducing corticosteroid dose in patients with UC regardless of disease distribution (Grade A). These drugs may also be effective in maintaining remission in patients with UC, but data are conflicting and this has not been confirmed by large well-controlled studies.
- Patients with gastrointestinal intolerance (except for fever, pancreatitis, or hypersensitivity reactions) to AZA may be cautiously tried on 6-MP before being considered for other therapy or surgery (Grade C). Similarly, patients with gastrointestinal intolerance (except for fever, pancreatitis, or hypersensitivity reactions) to 6-MP may be cautiously tried on AZA before being considered for other therapy or surgery (Grade C).

### **Methotrexate**

Methotrexate has been used in clinical medicine for nearly half a century. This agent induces clinical response more rapidly than 6-MP or AZA in patients with IBD. Over the course of the past decade, evidence has shown that methotrexate has an emerging role for the treatment of patients with CD.

#### **Recommendations for Methotrexate Use**

- Parenteral methotrexate is indicated for induction of remission in patients with active CD. (Grade B)
- Parenteral methotrexate is indicated for maintenance of remission in patients with inactive CD. (Grade B)
- The currently available evidence supports the use of methotrexate for induction of remission with corticosteroid withdrawal in patients with active CD who are corticosteroid dependent. (Grade B)
- Methotrexate maintenance therapy (15–25 mg intramuscularly weekly) is effective for patients whose active CD has responded to intramuscular methotrexate. (Grade A)
- Methotrexate 25 mg intramuscularly weekly for up

to 16 weeks followed by 15 mg intramuscularly weekly is effective in patients with chronic active CD. (Grade A)

- Methotrexate is absolutely contraindicated in pregnancy. (Grade B)
- The currently available evidence is insufficient to support the use of methotrexate for the induction or maintenance of remission in patients with active UC. (Grade B)
- Routine monitoring of laboratory parameters, including complete blood counts and liver-associated laboratory chemistries, is recommended in patients who are treated with methotrexate. (Grade C)
- Patients with persistently abnormal liver-associated chemistries should either discontinue therapy with methotrexate or undergo liver biopsy. (Grade C)

### **Mycophenolate Mofetil**

Mycophenolate mofetil inhibits lymphocyte proliferation by selectively blocking the synthesis of guanosine nucleotide in T cells. Its use in IBD was first proposed as an alternative immunosuppressive in patients intolerant to AZA or 6-MP. Early enthusiasm over the use of mycophenolate mofetil has been tempered by studies that showed lower efficacy rates and a higher incidence of patient intolerance.

This lack of convincing evidence of efficacy, coupled with concerning safety data, make it difficult to justify the use of mycophenolate mofetil in the treatment of patients with IBD at this time.

### **Cyclosporine**

Cyclosporine has a rapid onset of action (more rapid than AZA, 6-MP, or methotrexate) and when administered intravenously has been shown to be effective in the management of patients with severe UC. It often demonstrates clinical efficacy within 1 week when administered intravenously. Oral cyclosporine has a possible role in the induction of a clinical response in UC and short-term in the maintenance of an intravenous cyclosporine-induced response, allowing time for the slow-acting purine analogues to become effective. Its efficacy in patients with luminal CD has only been shown for higher doses, and the risks of therapy may not warrant its use. Intravenous cyclosporine is effective for the treatment of patients with fistulizing CD; however, toxicity has limited its applicability, and when administered orally, disease often reflare.

### Recommendations for Cyclosporine Use

- Intravenous cyclosporine is effective as a means of avoiding surgery in patients with severe corticosteroid-refractory UC. (Grade A)
- Intravenous cyclosporine at 2–4 mg · kg<sup>-1</sup> · day<sup>-1</sup> or colectomy should be considered if a patient with severe UC has failed to respond to medical therapy with 7–10 days of high-dose oral or parenteral corticosteroids. (Grade B)
- Concomitant administration of intravenous corticosteroids is recommended, but not required, to induce a clinical response in patients with severe UC receiving intravenous cyclosporine. (Grade B)
- A response or remission induced with intravenous cyclosporine in patients with IBD typically requires continuation of therapy with oral cyclosporine for a few months, along with a tapering dose of corticosteroids, initiation of AZA or 6-MP therapy, and prophylaxis against *Pneumocystis carinii* (Grade B). The purine analogue should be continued as maintenance therapy (Grade B).
- Oral cyclosporine is efficacious in patients with corticosteroid-refractory UC (Grade C) but requires AZA or 6-MP for maintenance of remission (Grade C).
- Neither intravenous (Grade C) nor oral (Grade A) low-dose cyclosporine has proven efficacy in patients with luminal CD. High-dose oral cyclosporine (7.6 mg/kg) has short-term efficacy (Grade B).
- Intravenous cyclosporine is effective for the treatment of patients with fistulizing CD (Grade B). AZA or 6-MP should then be used for maintenance of fistula closure (Grade C).

### Infliximab

Infliximab is a chimeric monoclonal antibody to human tumor necrosis factor  $\alpha$  that was introduced into clinical practice in the United States in 1998. Infliximab is effective for the treatment of patients with inflammatory and fistulizing CD that has failed to respond to other therapies. Several recent studies have shown efficacy of infliximab in the treatment of patients with UC.

Indications for infliximab use include the following:

- Treatment of patients with CD who do not achieve adequate clinical response despite treatment with conventional therapy. Patients who respond to induction therapy should receive maintenance therapy.

- Treatment of fistulizing CD. Patients who respond to induction therapy should receive maintenance therapy.
- Treatment of patients with UC who do not achieve adequate clinical response despite treatment with conventional therapy. Patients who respond to induction therapy should receive maintenance therapy.

### Recommendations for Infliximab Use

The recommended initial dose of infliximab for all IBD indications is 5 mg/kg body wt, administered by intravenous infusion over 2 hours in an induction regimen of 3 doses at weeks 0, 2, and 6. This should be followed by maintenance therapy every 8 weeks in patients who respond. For patients with CD who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. The treatment should be administered under the supervision and control of a specialized health care deliverer, with emergency equipment for severe infusion reactions available. A follow-up observation period of approximately 1 hour is advocated. Current indications for infliximab include the following:

1. Treatment of moderately to severely active CD or UC in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent (AZA, 6-MP, or methotrexate). These patients are individuals who are resistant to medical therapy (complete and adequate therapy with a corticosteroid or an immunosuppressive agent) or who cannot receive such therapies due to intolerance to medications (corticosteroids or medical contraindications [therapy intolerant]).

For induction therapy, the administration of infliximab at time 0 and 2 and 6 weeks is recommended; in the case of nonresponse to 3 infusions, further treatment with infliximab is not recommended.

Withdrawal or tapering of concomitant corticosteroid therapy: if a patient is on infliximab and achieves remission, an attempt to withdraw or taper any concomitant corticosteroid therapy is sensible.

Patients who respond to induction therapy should receive maintenance therapy with infusions every 8 weeks.

2. Treatment of CD with fistulas in patients who have not responded despite complete and adequate therapy with conventional treatments (including antibiotics, surgical drainage with examination under anesthesia, and/or immunosuppressive therapy): the use of infliximab should be avoided in patients with known hypersensitivity to infliximab, active infections, demyelinating disorders, severe congestive heart failure, and current or recent malignancy. Appropriate screening for latent and active

tuberculosis should be performed on all patients before administration of infliximab.

Although there is evidence-based data to support the use of corticosteroids, immunomodulators, and infliximab in the treatment of patients with IBD, there are many aspects of therapy with these agents for which the data are lacking or inadequate. Additional prospective data are needed to resolve the areas of controversy. The gastroenterologist who uses these agents must have a clear understanding of the proven benefits and risks of these therapies to provide optimal care to the patient with IBD.

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The Medical Position Statements (MPS) developed under the aegis of the American Gastroenterological Association (AGA) and its Clinical Practice and Economics Committee (CPEC) were approved by the AGA Governing Board. The data used to formulate these recommendations are derived from the data available at the time of their creation and may be supplemented and updated as new information is assimilated. These recommendations are intended for adult patients, with the intent of suggesting preferred approaches to specific medical issues or problems. They are based upon the interpretation and assimilation of scientifically valid research, derived from a comprehensive review of published literature. Ideally, the intent is to provide evidence based upon prospective, randomized placebo-controlled trials; however, when this is not possible, the use of experts' consensus may occur. The recommendations are intended to apply to health care providers of all specialties. It is important to stress that these recommendations should not be construed as a standard of care. The AGA stresses that the final decision regarding the care of the patient should be made by the physician with a focus on all aspects of the patient's current medical situation.

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