

Lecture

Inflammatory Bowel Disease: Therapy for Active Disease

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SUMMARY

The optimal therapy for active inflammatory bowel disease (IBD) is individualized according to the severity and the location of the disease and furthermore, the particular needs of each patient.

For ulcerative colitis (UC), topical therapy can be useful in distal disease and the higher the dose of 5-ASA the better the response. In Crohn's disease (CD), budesonide is a promising treatment for mild to moderate ileitis and right-sided colitis. The anti-tumor necrosis factor- α (TNF- α) antibody infliximab is an effective therapy for moderate to severe inflammatory and fistulizing Crohn's disease. Recent studies have shown that infliximab is also effective in the treatment of moderate to severe UC. For both UC and CD, corticosteroids still remain the mainstay of treatment in active disease.

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ULCERATIVE COLITIS

Disease activity in ulcerative colitis

Ulcerative colitis (UC) activity is assessed by various indices that are useful mostly in clinical studies but also in clinical practice. The first activity index for UC was developed by Truelove and Witts and classifies UC activity as mild, moderate or severe based on clinical, physical and laboratory parameters.¹ One of the most validated indices is the Mayo scoring system that takes into account stool frequency, rectal bleeding, findings on endoscopy and the physician's global assessment.²

In general, endoscopic healing in UC correlates with histologic quiescence and clinical remission.

Aminosalicylates

Mesalamine is more effective than placebo to induce remission in mild to moderately active UC and appears to be a trend toward a dose-dependent relationship.³ Mesalamine is better tolerated than sulfasalazine.

No controlled trial has evaluated the use of 5-ASA for severely active UC.

Topical mesalamine is beneficial for inducing remission of mild to moderately active distal UC, either as an adjunctive therapy to oral agents or as monotherapy. Mesalamine enemas are comparable to oral sulfasalazine and superior to steroid enemas in the treatment of active left sided colitis.⁴ A combination of oral and rectal mesalamine may be more effective than oral therapy alone.

In patients with proctitis, mesalamine suppositories may be used to induce remission.

Corticosteroids

Corticosteroids are effective for the treatment of moderately to severely active UC. They are not beneficial for maintenance of remission in UC. Standard dose is 40-60 mg/day of prednisone, while in more severe disease the parenteral form is preferable. There is no additional benefit from increasing the dose more than 60 mg/day. About 34% of the patients with active UC require steroid therapy and of these receiving steroids about 55% will go to complete remission and 30% to partial remission.⁵ One year outcomes for UC were prolonged response in 49%, corticoid dependence in 22% and operation in 29%.

Studies have not shown the benefit of oral budesonide for the treatment of UC.⁶

Azathioprine and 6-mercaptopurine

Azathioprine (AZA) is the prodrug of 6-mercaptopurine (6-MP)

There is no role for the use of immunomodulators AZA and 6-MP as a monotherapy in acute UC, since a mean response time of 2 to 3 months is required for efficacy. One important utility of AZA and 6-MP is their steroid sparing effect and maintenance of disease remission.⁷

Cyclosporine

For patients with severe UC who fail to respond to intravenous corticosteroids, intravenous cyclosporine (CSA) is an alternative. The usual dose is 4 mg/Kg/d in continuous infusion.

Levels of CSA should be monitored and maintained in between certain limits. Side effects can be serious in up to 12% of the patients and include renal insufficiency, hypertension, infection, paresthesias and seizures especially with low magnesium and cholesterol levels less than 120 mg/Dl. CSA should not be used when colitis is fulminant or complicated by perforation, sepsis or toxic dilatation.⁸

Anti-Tumor Necrosis Factor therapy

Data from two recent double blinded clinical trials (ACT-1 and ACT-2) have indicated that infliximab treatment does reduce disease activity in patients with moderate to severe UC that have failed conventional treatment with steroids.^{9,10} The dosing regimen given was similar to that recommended for Crohn's disease (CD) patients. Clinical and endoscopic improvement has been reported in approximately 60-70% compared with about 40% in the placebo treated group of patients. A follow

up on long term outcomes of patients enrolled in these two large studies and the answer to the question of whether the use of infliximab modifies the natural history of UC and its complications, is awaited with great interest.

Crohn's Disease

Disease activity in Crohn's disease

Unlike UC where endoscopic remission correlates with clinical remission, in Crohn's disease (CD) this is not necessarily the case. As in UC there are also a variety of indices used for assessing disease activity. The most commonly used index is the Crohn's Disease Activity Index (CDAI), that takes into account a series of symptoms, laboratory criteria, complications and physician's, global assessment of patient's well being.¹¹ The Harvey Bradshaw Index is simpler and quicker than CDAI, whereas for fistulizing disease there is the Perianal Crohn's Disease Activity Index and the quicker Fistula Drainage Assessment.¹²

5-Aminosalicylic acid agents

Both sulfasalazine and mesalamine are more effective than placebo in treating mild or moderate CD, but sulfasalazine has limited usefulness due to side effects. As in UC higher doses bring better results, with about 4gr/d of mesalamine to induce clinical remission in 40-60% of the patients with mild to moderate CD.¹³

Although the role of 5-ASA agents in inducing remission is well established, its role in maintaining remission is less well documented.

Antibiotics

For mild to moderate CD, metronidazole and ciprofloxacin are used as first line treatment. They are also used for perianal fistulizing CD. Nevertheless, evidence that supports the efficacy of ciprofloxacin alone or in combination with metronidazole is sparse and vague.¹⁴

Corticosteroids

Corticosteroids are the standard conventional treatment of moderate to severe disease in patients who fail 5-ASA and antibiotic therapy. A 60% complete remission and a 26% of partial remission is reported with the first course of steroid.¹⁵ Furthermore, 50% of CD patients treated acutely with steroids become steroid resistant or steroid dependent, particularly the smokers and those with colonic disease.

While useful for inducing remission, long term use of steroids can have many side effects. There is no role for use of corticosteroids for maintenance of the remission.

Budesonide is a topical active corticosteroid with low systemic bioavailability. Budesonide is released mainly in the ileum and ascending colon and is effective in mild to moderate CD. In its most effective dose of 9mg/d it was found to be about 13% less effective than conventional steroids and was less likely to cause adverse effects.¹⁶ Budesonide has also been shown more effective than mesalamine in maintaining remission in patients with steroid dependent CD.

6- Mercaptopurine and Azathioprine

In patients who have achieved remission with steroids, azathioprine and 6-MP have been shown to be effective in maintaining remission.¹⁷ The optimal duration of treatment remains unclear.

Methotrexate

Low dose methotrexate is sometimes used as inductive therapy in patients with CD who have not responded to other treatments.¹⁸ Although methotrexate seems to work more rapidly than azathioprine and 6 MP, it also takes several months to begin working. Therefore these agents may be useful therapies for fistulizing disease and maintenance of the remission, but have little value in treating flare ups in CD.

Anti TNF alpha

Infliximab is a chimeric monoclonal antibody directed against the cytokine tumor necrosis factor- α (TNF – α), and induces apoptosis.

Infliximab is used to achieve clinical improvement and induce remission in patients with moderate to severe and fistulizing CD refractory to other treatments. For refractory inflammatory or fistulizing disease, infusions of 5 mg/Kg are given at 0, 2 and 6 weeks. A response rate of 65% for refractory active disease was shown, compared with 17% for placebo. Similarly, for perianal fistulizing disease, a response of 65% with infliximab was demonstrated over 26% with placebo.¹⁹ Reinfusion, typically every 8 weeks, is necessary to continue therapeutic benefit in many patients. Infliximab is fairly well tolerated in most of the patients, although serious side effects include acute infusion reactions, serum sickness-like disease, drug-induced lupus, infections, pneumonia, reactivation of latent tuberculosis and even death.

Adalimumab is a human monoclonal antibody administered subcutaneously and appears to be well tolerated in most CD patients, particularly those with reactions to infliximab.

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