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Inflammatory bowel disease: Sorting out the treatment options

ABSTRACT

An increasing array of treatments such as immunosuppressive drugs and tumor necrosis factor inhibitors can offer patients with ulcerative colitis and Crohn disease improved relief from symptoms with fewer adverse effects. Several additional drugs have shown promise, including nicotine, antimicrobials, and heparin.

KEY POINTS

First-line therapy for ulcerative colitis includes oral and rectal aminosalicylates for mild to moderate disease and steroids for moderate to severe disease. Steroids also are a preferred option for nonfistulizing Crohn disease.

Both azathioprine and 6-mercaptopurine have been shown to be safe and effective in ulcerative colitis and Crohn disease and enable adult and pediatric patients to avoid long-term use of corticosteroids.

Infliximab is an effective treatment for inflammatory and fistulizing Crohn disease.

PATIENTS WITH INFLAMMATORY bowel disease now have a variety of new treatment options. New uses are being found for old drugs, and new drugs are becoming available, including potent immunosuppressive drugs that control the unchecked inflammation of the gastrointestinal tract.

As internists and gastroenterologists, we need to be familiar with these new drugs as they become more widely used and as patients ask about new treatments they learn about via the Internet, television, and lay organizations. In this article, we offer an overview of current drugs and their indications for the treatment of ulcerative colitis and Crohn disease.

AMINOSALICYLATES

The aminosalicylates are among the oldest and most commonly used drugs for ulcerative colitis and Crohn disease.[1]

Sulfasalazine

Sulfasalazine, introduced in the 1940s for use in both inflammatory bowel disease and rheumatoid arthritis, is a compound of sulfapyridine and 5-aminosalicylic acid (5-ASA, mesalamine) linked by a diazo bond.

Action. Taken orally, the drug is delivered intact into the right colon and subsequently is degraded by colonic bacteria into 5-ASA (the active, anti-inflammatory moiety) and sulfapyridine, which helps transport 5-ASA to target areas.

Adverse effects. Although effective in treating ulcerative colitis and Crohn disease of the large colon, sulfasalazine is difficult to tolerate due to adverse effects in up to 50% of patients, principally due to the sulfapyridine moiety. The most common adverse effects are

TABLE 1

Aminosalicylates for the treatment of inflammatory bowel disease

MEDICATION	UNIT DOSE	DOSAGE	COLON ACTIVITY	SMALL BOWEL ACTIVITY
Sulfasalazine	500 mg	2–4 g/day	+++	–
Mesalamine (5-ASA)				
Asacol*	400 mg	1.6–4.8 g/day	+++	+
Balsalazide (Colazal)	750 mg	6.75 g/day	+++	–
Olsalazine (Dipentum)	250 mg	1–3 g/day	+++	–
Pentasa†	250 mg	2–4 g/day	++	++
Rowasa enema	4 g	4 g/day	+++	–
Rowasa suppository	1 g	2 g/day	+++	–

*Delayed-release tablet
†Controlled-release capsule

nausea, vomiting, anorexia, dyspepsia, malaise, and headaches, and these are especially troublesome at doses higher than 3 g per day. Rare, idiosyncratic reactions include fever, rash, hepatitis, pancreatitis, pneumonitis, and agranulocytosis. Patients with sulfa allergies should avoid sulfasalazine. Folate supplementation is recommended because sulfasalazine inhibits folate absorption.

All forms of 5-ASA are usually used only in colonic disease

Newer aminosalicylates

Newer aminosalicylates deliver 5-ASA to the distal bowel without the sulfapyridine, resulting in fewer adverse effects than sulfasalazine (TABLE 1, TABLE 2). These formulations are more expensive than sulfasalazine and, consequently, are generally prescribed if a trial of sulfasalazine fails.

Oral forms are indicated for treatment of mildly to moderately active ulcerative colitis, while the rectal forms are indicated for the treatment of active mild to moderate distal ulcerative colitis.

Pentasa (controlled-release capsule) consists of 5-ASA packaged in ethylcellulose microgranules that gradually release 5-ASA from the jejunum to the colon. It is approved only for ulcerative colitis but is often used for Crohn disease of the small bowel.

Asacol (delayed-release tablet), the most commonly used aminosalicylate, is 5-ASA enveloped in a coating that dissolves at a pH of 7 in the distal ileum and colon.

Rowasa, the enema and suppository forms of 5-ASA, is used for distal disease.

Olsalazine (Dipentum) is indicated for the maintenance of remission of ulcerative colitis in patients who cannot tolerate sulfasalazine. It consists of two 5-ASA molecules linked by a diazo bond and is activated only by bacterial cleavage. It is available in capsule form.

Balsalazide (Colazal) is indicated for the treatment of mildly to moderately active ulcerative colitis. It consists of 5-ASA molecules linked by a diazo bond to an inert, unabsorbed carrier molecule that is broken down by colonic bacteria.

Adverse effects. Mesalamine is well tolerated but can cause mild and transient headache and abdominal discomfort. Olsalazine causes secretory diarrhea in up to 10% of patients. Balsalazide can cause headache, abdominal pain, diarrhea, and nausea, but these are not usually severe enough to cause discontinuation of therapy. Rare side effects of 5-ASA drugs include pneumonitis, pericarditis, interstitial nephritis, and thrombocytopenia.

Recommendations for use

Whenever possible, sulfasalazine should be tried first due to its low cost.

Ulcerative colitis. Aminosalicylates are used in patients with mild to moderate disease activity or to maintain remission. For active disease, 5-ASA given both orally and topically is superior to either one alone in controlling

symptoms. Topical 5-ASA is superior to topical corticosteroids for distal disease.[2–6] 5-ASA suppositories (Rowasa 1 g) can be substituted in patients who cannot effectively retain enemas. For maintenance of remission in ulcerative colitis, all 5-ASA agents are similarly effective.

Crohn disease. All forms of 5-ASA have limited effectiveness in the small bowel and are usually used only in colonic disease. Pentasa has to be delivered at high doses, 4 g or 16 pills per day, to be effective in treating active disease of the small bowel.[7] These agents can be effective in maintaining remission in patients with ileitis or with surgically induced remission.[8]

STEROIDS

Steroids have been known since the early 1950s to be effective for both ulcerative colitis and Crohn disease.

Action

The mechanism of action of steroids is believed to be the blockade of phospholipase A_2 in the arachidonic acid cascade, causing an alteration in the delicate balance between the cytoprotective prostaglandins and proinflammatory leukotrienes.

Adverse effects

Prolonged use of steroids can cause osteoporosis, moon face, buffalo hump, impaired wound healing, hyperglycemia, and osteonecrosis of the femoral head.

Recommendations for use

Steroids are considered first-line therapy for patients with moderate to severe ulcerative colitis or nonfistulizing Crohn disease. The usual prednisone dosage is 40 mg per day with a taper over 2 to 4 months. For severe active disease, intravenous steroid regimens that provide the best response are hydrocortisone 100 mg every 8 hours or methylprednisolone 40 mg daily. Response to intravenous steroids is superior to that of equivalent oral doses.

Steroid analogues

Oral steroid analogues are locally active corticosteroids, designed to target areas of inflammation in the gastrointestinal tract before being inactivated by the liver during their first pass, thus avoiding some of the typical adverse effects of steroid use. Of the three steroid analogues tested in inflammato-

TABLE 2

Adverse effects of drugs commonly used for inflammatory bowel disease

Asacol
Headache, rash, nausea, diarrhea, abdominal pain, dry mouth, dysmenorrhea, anaphylaxis, hematologic effects, interstitial nephritis, hepatitis, myocarditis, peripheral neuropathy, Stevens-Johnson syndrome

Azathioprine or 6-mercaptopurine
Pancreatitis, leukopenia, bone marrow suppression, nausea, vomiting, diarrhea, rash, myalgia, alopecia

Cyclosporine
Seizures, leukopenia, thrombocytopenia, nephrotoxicity, susceptibility to infection, neoplasia, hypertension, hirsutism, tremor, gingival hyperplasia, paresthesias, nausea, vomiting, abdominal pain, diarrhea

Fish oils
Bad odor and taste

Infliximab
Susceptibility to infection, lupus-like syndrome, infusion reaction, lymphoma

Heparin
Hemorrhage, osteoporosis, thrombocytopenia

Methotrexate
Neurotoxicity, leukoencephalopathy, seizures, renal failure, leukopenia, pulmonary fibrosis, nausea, vomiting, photosensitivity, ecchymosis

Olsalazine
Secretory diarrhea, headache, rash, nausea, abdominal pain

Pentasa
Dysmenorrhea, anaphylaxis, hematologic effects, interstitial nephritis, hepatitis, myocarditis, peripheral neuropathy, Stevens-Johnson syndrome

Steroids
Adrenal insufficiency, osteoporosis, edema, appetite changes, mood changes, cushingoid features, avascular necrosis

Sulfasalazine
Headache, rash, nausea, diarrhea, abdominal pain, leukopenia, jaundice, fever, oligospermia, Stevens-Johnson syndrome, epidermal necrolysis, exfoliative dermatitis, agranulocytosis, hemolytic anemia

ry bowel disease, budesonide (Entocort EC) is the only one approved for use in the United States, and it is indicated specifically for mildly to moderately active Crohn disease involving the ileum or the ascending colon. Tixocortol and fluticasone are still undergoing testing.

Budesonide is designed to deliver steroid to the distal small bowel and proximal colon. Large randomized clinical trials[9–14] have shown that budesonide is more effective than placebo or 5-ASA in inducing remission by 8 weeks and nearly as effective as prednisolone in Crohn disease. Budesonide has fewer adverse effects than conventional steroids, but it is not free of adverse effects and is therefore not recommended for maintenance therapy. For left-sided ulcerative colitis, 2-g budesonide enemas (not available in the United States) are as effective as prednisolone enemas or 5-ASA therapy.[15,16]

AZATHIOPRINE AND 6-MERCAPTOPURINE

6-Mercaptopurine (Purinethol) and azathioprine (Imuran) are immunosuppressive agents that can be used instead of long-term corticosteroid therapy.

Budesonide has fewer ill effects than steroids, but it is not for maintenance therapy

Action

These drugs act by causing chromosomal breaks that blunt the proliferation of rapidly dividing cells such as lymphocytes. 6-Mercaptopurine is a purine analogue, and azathioprine is its S-imidazole precursor.

Adverse effects

Azathioprine was used as single-agent therapy in the large randomized clinical trial, the National Cooperative Crohn's Disease Study,[17] which compared azathioprine, prednisone, and sulfasalazine with placebo in treating active disease and in maintaining remission. The azathioprine arm was discontinued after only 17 weeks when three patients developed acute pancreatitis. Subsequently, fears of toxicity have led to azathioprine's fall from favor among gastroenterologists.

More recent studies have shown that these immunosuppressive drugs have a more favorable adverse effect profile than was originally believed. Fewer than 10% of patients stop therapy due to reversible bone marrow suppression, and fewer than 3% develop pancreatitis or allergy characterized by abdominal pain, fever, and rash.

Recommendations for use

Both azathioprine and 6-mercaptopurine have been shown to be safe and effective in ulcerative colitis and Crohn disease and enable adult and pediatric patients to avoid long-term use of corticosteroids.[18] 6-Mercaptopurine can be effective for closure of fistulas in Crohn disease.[19]

The duration of therapy most often required for effectiveness is at least 3 months, but delayed therapeutic responses have been demonstrated after 1 year of therapy. Because of the delayed response, the common practice of adjusting the dose according to the response may not be feasible. Some experts have suggested that the dose of immunosuppressive drug be increased until mild leukopenia (white blood cell count between 3,000 and $5{,}000 \times 10^9$/L) develops.[20] Patients treated to the point of leukopenia have a faster and more complete response.

Currently, monitoring of the metabolites 6-thioguanine nucleoside (the active metabolite) and 6-methylmercaptopurine (the metabolite associated with hepatotoxicity in some patients) can help the clinician find the very narrow window between effectiveness and toxicity of these drugs.[21]

CYCLOSPORINE

Cyclosporine is a cyclic polypeptide derived from either of two fungi and commonly used in conjunction with organ transplantation.

Action

Cyclosporine reversibly inhibits interleukin-2 (IL-2) gene transcription, causing a decrease in activity of cytotoxic T cells.

Adverse effects

Cyclosporine has significant adverse effects, which include nephrotoxicity, hepatotoxicity, hypertrichosis, gingival hyperplasia, tremors, paresthesias, seizures, and lymphoproliferative disorders.

Recommendations for use

Ulcerative colitis. Intravenous cyclosporine is useful for the treatment of severely active ulcerative colitis. In the only randomized clinical trial of cyclosporine use in ulcerative colitis,[22] all patients had severely active ulcerative colitis that failed to respond to intravenous corticosteroids. Cyclosporine was given at 4 mg/kg/day intravenously for no more than 7 days. The overwhelming success of cyclosporine (82%) compared with placebo (0%) forced an early termination of the trial. Five (45%) of the original 11 patients randomized to cyclosporine had a sustained response and did not require colectomy.

Experience with cyclosporine in clinical practice has not been as good[23,24]: only approximately 50% of patients had a response and avoided colectomy in the short term, and 33% avoided colectomy in the long term. This is most likely due to the inconsistent bioavailability of the oral form of cyclosporine.

Cyclosporine enemas are not effective in left-sided ulcerative colitis.[25]

Crohn disease. For Crohn disease, intravenous cyclosporine temporarily decreased drainage of fistulas and induced a remission in inflammatory disease.[26,27] Unfortunately, most patients have a relapse when cyclosporine therapy is converted to the oral form. Oral cyclosporine has been largely ineffective in treating inflammatory-type Crohn disease.[28,29]

Prophylaxis against *Pneumocystis carinii* pneumonia is advised in all patients taking cyclosporine.[30,31]

METHOTREXATE

Methotrexate, which was introduced in 1947 for the treatment of patients with acute leukemia, has been used in the treatment of chronic inflammatory disorders such as rheumatoid arthritis, psoriasis, asthma, primary sclerosing cholangitis, and primary biliary cirrhosis.

Action

Methotrexate binds to tetrahydrofolate reductase and interferes with purine synthesis of rapidly proliferating cells.

Adverse effects

Minor adverse effects such as nausea and abdominal cramps are due to folic acid antagonism by methotrexate and can be prevented with coadministration of folic acid 1 mg/day, without interfering with the effectiveness of the methotrexate.

Other adverse effects include hepatic fibrosis (when the total dose exceeds 1.5 g, with a lower threshold for obese and alcoholic patients), liver function test abnormalities, alopecia, pneumonitis, hypersensitivity, and teratogenicity. Due to the risk of teratogenicity, methotrexate is contraindicated during pregnancy, and women and men of reproductive age who take methotrexate should use birth control.

Clinical trial results

A small 12-week open-label trial of methotrexate 25 mg/week intramuscularly in Crohn disease patients[32] showed a 79% response rate, defined as lowering disease activity and prednisone use.

A randomized clinical trial of 141 patients[33] comparing the same dose of methotrexate with placebo over 16 weeks demonstrated a 39.4% rate of induced remission in the methotrexate group vs 19.1% in the placebo group. Seventeen percent of methotrexate-treated patients withdrew due to adverse effects, most commonly liver function test abnormalities and nausea.

Another randomized clinical trial[34] in patients whose Crohn disease had responded to methotrexate showed that 15 mg/week of methotrexate was significantly better than placebo in maintaining remission.

Folic acid 1 mg/day prevents nausea and cramps due to methotrexate use

Recommendations for use

Currently, methotrexate is used as long-term therapy in patients who do not respond to or cannot tolerate azathioprine or 6-mercaptopurine.

FISH OILS

Eicosapentaenoic acid (EPA, fish oil) is thought to suppress production of inflammatory agents, and its use has been suggested in the treatment of rheumatoid arthritis and psoriasis.

Action

Arachidonic acid metabolism produces leukotriene B_4, a potent proinflammatory cytokine. EPA in high doses interferes with arachidonic acid metabolism, leading to the production of the less-potent cytokine leukotriene B_5. High oral doses of fish oil also inhibit thromboxane A_2 production and thereby act as an anticoagulant.

Adverse effects

Unfortunately, the high doses of fish oils required in inflammatory bowel disease have a distasteful, odoriferous effect.

Clinical trial results

Crohn disease. In a study of Crohn disease patients who were in remission but were at high risk of relapse,[35] 28% of those who took 2.7 g of EPA daily had a relapse by 12 months vs 69% of placebo-treated patients. Diarrhea was the principal adverse effect requiring discontinuation of treatment. These results, though, could not be confirmed subsequently.[36]

Ulcerative colitis. In a study of the effects of fish oil supplementation in moderately active ulcerative colitis,[37] 18 patients taking prednisone and sulfasalazine took 18 capsules per day of fish oil (equal to 3.24 g/day of EPA and 2.16 g/day of docosahexaenoic acid) for 4 months, followed by a 1-month "washout" period, then 4 months of 18 placebo capsules. The investigators observed that fish oil supplementation allowed steroids to be tapered significantly.[37]

In another study,[38] more than 5 g of EPA per day delayed relapse for 3 months compared with placebo, but the rate of relapse was similar at 2 years, leading the authors to conclude that fish oil supplementation can "temporarily retard, but not prevent," relapse in patients with ulcerative colitis.[38]

Bad taste and odor limit use of fish oil

Recommendations for use

Even though there are some promising studies, the lack of long-term effectiveness and the bad taste make this a medicine not actively being used in clinical settings.

INFLIXIMAB

Infliximab (Remicade) is a chimeric mouse-human monoclonal antibody approved for the treatment of inflammatory Crohn disease (one 5-mg/kg infusion over 2 hours) and fistulous Crohn disease (three 5-mg/kg infusions over 6 weeks).

Action

Elevations of tumor necrosis factor-alpha in the stool of patients with Crohn disease are associated with an increase in disease activity. A single intravenous infusion of infliximab induces lysis of mononuclear cells, thereby causing a decrease in all of the inflammatory cytokines that they produce, including tumor necrosis factor-alpha.[39,40]

Adverse effects

Adverse effects of infliximab include upper-respiratory infections, abdominal pain, fatigue, myalgia, infusion reactions, nausea, and the development of both anti-ds-DNA antibodies and anti-chimeric antibodies. The development of lymphoma has been reported in patients receiving infliximab infusions,[41–43] but the incidence is very low, and more data are needed to better estimate the risk of lymphoma in these patients.[44]

Clinical trial results

In one clinical trial of patients with inflammatory Crohn disease,[45] infliximab induced a clinical response in 81% of patients taking the drug vs 17% in placebo-treated patients; it induced clinical remission in 33% vs 4% of placebo-treated patients. Adverse effects were minor, short-lived, and no different than in placebo-treated patients.

In a study of Crohn disease patients with enterocutaneous or perianal fistulas,[46] infliximab induced a response in 68% of patients vs 26% in the placebo group and induced complete fistula closure in 55% vs 13% in the placebo group; these fistulas remained closed for a median of 3 months.[46] Adverse effects in treated patients were no different than in the placebo group.

Maintenance therapy with infliximab given every 8 weeks for four additional doses was more effective than placebo,[47] but maintenance therapy with infliximab has not been approved.

Recommendations for use

Infliximab is an effective treatment for both inflammatory and fistulizing Crohn disease.

HEPARIN

Interest in heparin in the treatment of inflammatory bowel disease was fueled by interesting case reports of unexpected side effects of heparin used in patients with other conditions.

A patient with active ulcerative colitis who required heparin for deep venous thrombosis experienced a complete remission of his colitis after heparin administration.[48] Eight of 9 additional patients with active ulcerative colitis (and no deep vein thrombosis) refractory to corticosteroids who were treated with 10,000 units of heparin subcutaneously twice daily showed a complete remission; the other patient showed a partial response.

Heparin also has been shown to induce a rapid resolution of chronically active symptoms of diarrhea, hematochezia, arthralgia, and pyoderma gangrenosum in a patient with ulcerative colitis.[49]

Unfractionated heparin given to patients with either ulcerative colitis or Crohn disease had a beneficial effect in ulcerative colitis patients only.[50] Seven of 13 ulcerative colitis patients achieved complete remission within 4 weeks, but one patient had massive lower gastrointestinal bleeding.

In another series, 12 of 16 steroid-resistant ulcerative colitis patients given heparin had a marked improvement in symptoms within 1 week.[51]

Action and recommendations

Such findings suggest that the pathogenesis of ulcerative colitis may involve microthrombosis in the intestinal circulation, which is resolved by heparin. While these reports are encouraging, further studies are warranted to determine what utility heparin will have for steroid-refractory ulcerative colitis.

ANTIMICROBIALS

Investigators have long postulated that a transient infection may initiate a cascade of inflammatory events that may lead to ulcerative colitis in predisposed individuals.

Ciprofloxacin

The literature contains conflicting reports about the use of ciprofloxacin (Cipro) in inducing remission in such patients. For example, for an acute flare-up of disease, ciprofloxacin in addition to prednisolone and 5-ASA had no additional beneficial effect when compared with placebo.[52] But 6 months of maintenance therapy with ciprofloxacin in ulcerative colitis patients with a medically induced remission was associated with a relapse rate of only 21% at 6 months vs 44% in placebo-treated patients ($P < .02$).[53]

Metronidazole

Metronidazole (Flagyl) has been shown to be effective in active colonic Crohn disease. Some benefit can be derived from adding metronidazole in Crohn disease patients whose disease is only partially responsive to 5-ASA or to steroids. Metronidazole also has beneficial activity in treating perianal complications in Crohn disease patients.

Both metronidazole and ciprofloxacin have benefit in certain clinical situations, eg, in the treatment of acute pouchitis in ulcerative colitis patients following proctocolectomy and ileal pouch-anal anastomosis.

Adverse effects

Adverse effects of metronidazole include peripheral neuropathy, neutropenia, nausea, vomiting, and a metallic taste. Adverse effects of ciprofloxacin include nausea, diarrhea, vomiting, abdominal pain, and headache in up to 10% of patients.

Recommendations for use

Although these antibiotics are useful in the treatment of pouchitis, antibiotics currently have no role in the therapy of ulcerative colitis or inflammatory Crohn disease. Although ciprofloxacin is more expensive than metronidazole, it is frequently substituted if patients cannot tolerate metronidazole.

Evidence of heparin benefit in ulcerative colitis needs more study

NICOTINE

Intriguing case reports of improvements in ulcerative colitis disease activity with the intake of nicotine from cigarettes or nicotine gum led to equally intriguing epidemiologic studies. The consistent finding of these studies was that cigarette smoking protected against the development of ulcerative colitis.[54,55] At

diagnosis, fewer than 15% of adults with ulcerative colitis smoke vs approximately 35% of the general US adult population.

Action

The cellular mechanism for this effect is not known, but cigarette smoking is associated with global suppression of the immune system, as well as potentiation of the protective mucus barrier in the colon.

Clinical trial observations

Ulcerative colitis patients with moderately active disease often improve with nicotine intake. Nicotine gum, up to 10 squares or 20 mg/day, is effective and is best tolerated among former smokers.[56] The nicotine patch (up to 25 mg/day) is a delivery system that minimizes side effects and has also been found effective.[57,58] Nicotine patches are not effective for maintenance, and using them for more than 8 weeks risks addiction.[59]

Adverse effects

Adverse effects include parched throat, tachycardia, headache, and nausea.

Moderately active ulcerative colitis often improves with nicotine intake

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