

TREATING INFLAMMATORY BOWEL DISEASE (IBD) BACKGROUNDER

Why treat IBD?

IBD describes a range of chronic diseases of the gastrointestinal system, encompassing Ulcerative Colitis (UC) and Crohn's Disease (CD). IBD is characterised by intermittent flares with debilitating symptoms (such as diarrhoea, abdominal pain and weight loss) that can result both in a significant worsening of the patient's quality of life as well as causing emotional distress and social isolation. In addition, patients can also suffer from a number of serious complications of the disease and may require life-long treatment and often surgery.

Although, there is no cure for IBD (except in UC where removal of the colon is curative), doctors can treat the symptoms of the disease very effectively, thereby improving the quality of life for patients. In addition, it seems as if long-term maintenance therapy with some specific drugs (such as aminosalicylates) not only diminishes the disease activity, but also has a long-term added benefit of reducing the otherwise increased risk of developing colorectal cancer.^{1,2}

What are the goals in the management of IBD?

The goal of medical treatment is to control or reduce the inflammation. This relieves the acute symptoms of the disease, while also allowing the bowel time to heal. Once the symptoms are under control (which is known as inducing remission), drugs can then be used to try to prevent the disease coming back again or 'flaring' (which is known as maintaining remission, or maintenance).

Thus, the main aims for the doctor in the management of IBD are four-fold to:

- control the symptoms of the 'flare-up' as quickly as possible
- correct any disturbances in the body's levels of water and nutrients
- prevent the development of serious complications
- reduce the risk of future 'flare-ups' by treating the patient with an effective maintenance therapy.

How is IBD treated?

IBD is a very complicated condition; involving many different symptoms, disease stages and types of bowel damage and, as such, the approach to treatment is not straightforward or standardised.

Treatment must be tailored to whether a patient has UC or CD, as well as to whether they require management of active symptoms or maintenance therapy to help keep them in remission.

First and foremost management of IBD involves drug therapy, and the range of treatments available to treat IBD is expanding all the time. However, doctors and their patients also need to address other factors, such as diet and stress, which are both known to affect the course of the disease. Finally, despite advances in medical therapies, when medication and lifestyle changes can no longer control their symptoms, many patients living with IBD will eventually need surgery – either to control their disease or to deal with its various complications by removing diseased sections of the bowel.

What treatments are available?

Several types of drugs are available to treat the symptoms of IBD; including aminosalicylates (5-ASA, mesalazine, mesalamine, sulphasalazine), corticosteroids, immunomodulators/immune suppressants, antibiotics and biological therapies. Indeed doctors are now being faced with an ever-increasing choice of therapies, some of which are very potent, and have to make treatment choices based, not only on how effective the drug is, but also on other important issues, such as whether the drug has harmful side effects, how easy it is for the patient to use and how much it costs.

For each type of treatment, another key factor in determining how well it will work is the degree to which the patient follows the recommended course of treatment. This is called adherence (or compliance) to treatment and is known to be a major problem in IBD (as well as in many other chronic diseases), particularly in those patients who are in the symptom-free state and feel well. In view of this, treatments that are more convenient to take tend to improve patient adherence, and so improve outcome.

Aminosalicylates

Aminosalicylates were the first class of drug shown to be beneficial in IBD and contain 5-aminosalicylate (5-ASA) which has anti-inflammatory properties. However, early 5-ASAs such as sulphasalazine contained a part of the drug that caused harmful side effects in patients, and so less toxic, sulpha-free drugs are now more commonly used.

There are many oral drugs that contain 5-ASA, and among these is mesalazine (available in Europe as Pentasa[®], CLAVERSAL, SALOFALK or ASACOL), which is the treatment of choice for mild-to-moderate UC, and, in many countries, also been found to be an effective therapy in active mild-to-moderate CD, as recommended by clinical guidelines.³ There are also several ways that 5-ASA can be delivered to the bowel: orally as tablets or sachets, or topically as liquid suspensions, foam enemas or suppositories.

However, not all 5-ASAs are the same, but rather they differ considerably in the way they are released throughout the bowel and how convenient they are for the patient.

One of the most commonly used 5-ASAs is Pentasa[®] (mesalazine), which is a prolonged release form of mesalazine, meaning that it releases active drug predictably and reliably throughout the entire length of the bowel, from the duodenum to the rectum, so that it can reach all the inflamed areas.⁴ In mild-to-moderate UC, Pentasa[®] has been shown to significantly improve symptoms and bring about rapid remission,^{4,5,6} as well as being able to keep patients in remission^{7,8} – findings that support the current position of mesalazines as the cornerstone of therapy for mild-to-moderate active UC and for maintaining remission.^{3,9,10}

By contrast, optimal treatment of CD is slightly less clear. However, the balance of evidence suggests that Pentasa[®] is an effective treatment for both active mild-to-moderate CD and for maintaining remission (especially after a surgical intestinal procedure), and should at least be tried before resorting to other therapies, which may have potent side effects,^{11,12,13,14} with the option of either continuing long-term or reverting to more potent therapies if treatment is not successful.¹¹ Furthermore, administering Pentasa[®] at the higher end of the dosage range results in a better outcome.^{15,16} PENTASA has been approved in a number of countries for the treatment of Crohn's Disease.²³

Other 5-ASAs include olsalazine (DIPENTUM) and balsalazide (COLAZIDE).

Corticosteroids

Corticosteroids (such as prednisone, methylprednisolone, hydrocortisone) also work to control inflammation, and they are particularly used in patients who fail 5-ASA treatment or for the rapid control of symptoms in acute 'flare-ups'. They can be given either in pill form or, in more severe disease, intravenous administration may be necessary. Rectally administered steroids (enemas, suppositories or foams) can be helpful for some patients. However, steroids are of no benefit in between 20 to 30 percent of UC and CD patients with acute symptoms. In addition, after using

steroids, 30 to 40 percent of patients develop what is termed 'steroid-dependent' disease, which means that they cannot stop taking steroids without experiencing severe 'flare-ups' in their IBD.

In studies against dummy treatment (placebo), steroids have not been shown to be beneficial for maintaining remission in either UC or CD and should not be used long-term due to their undesirable side effects (eg, osteoporosis (bone loss), cataracts, weight gain, diabetes, high blood pressure and psychiatric symptoms). Thus, doctors often choose safer medications (such as mesalazine) as initial therapy.

Budesonide (ENTOCORT EC, BUDENOFALK, RAFTON) is a new class of corticosteroid which acts topically in the gut and where the small amount which is absorbed is removed rapidly by the liver, reducing the unpleasant side effects often seen with other steroids. Due to the release mechanism of budesonide it can be used for the treatment of mild-to-moderate active CD in the lower parts of the small bowel and the first part of the large bowel. However, it is not effective long term, with 60–70% of patients relapsing within one year of treatment.¹⁹

Antibiotics

Antibiotics (such as metronidazole and ciprofloxacin) are also used to treat IBD, even though no specific infectious agent has been identified as the cause of these illnesses. However, it is thought that antibiotics may control IBD by reducing the number of bacteria in the bowel and suppressing the bowel's immune system directly.

Immunomodulators

Immunosuppressant drugs (such as azathioprine and 6-MP) decrease the activity of the patient's immune system, which is believed to play a key role in producing the inflammatory symptoms of IBD. They are used in patients who fail standard treatment (ie. with mesalazine) or who require continuous steroids, as they cause fewer long-term side effects than steroids. However, use of these drugs is limited by their slow onset of action (three to six months for the full effect) and more than one fifth of patients stop taking their medication early due to the adverse side effects.²⁰

Biological therapy

Biological agents, such as monoclonal antibodies directed towards some of the substances released during the inflammatory process (such as TNF-alpha antibodies), are effective for

bringing about remission in approximately 60% of patients, with this easing of symptoms being seen within the first month of treatment.²¹

The first biological therapy to be made available for use in CD is infliximab (REMICADE), which can be used for active CD patients who have not responded to standard therapy (such as with mesalazine). Recent investigations have shown that infliximab provides clinical benefit for some patients with UC who do not respond to steroid treatment and it has recently been approved by the Food and Drugs Administration in the US for UC.²²

Why is maintenance therapy needed in IBD?

Both CD and UC are ongoing diseases and, although symptoms may disappear with treatment, they tend to come back over time. Thus, patients are at risk of future attacks unless they continue to take their medication to keep them in remission.

During the acute, active phase of IBD doctors may prescribe stronger therapies to control the inflammation, despite their potential harmful effects, if they will help the patient get better. However, side effects from a treatment being used for maintenance therapy are far less acceptable, since patients most probably will have to take these medications over their entire lifetime. Because maintenance medications are needed over long periods of time, they must be both effective and safe. Mesalazine fulfils these requirements, as well as being convenient for the patient.

What guidelines are available on the treatment of IBD?

Because of the complexity of the condition, and the range of treatments available, clinical guidelines have been developed in many countries across Europe, such as the UK,³ to help physicians treat IBD optimally. In addition, guidance from the European Crohn's and Colitis Organisation (ECCO) on best practice in the treatment of CD has already been developed and will be published soon, and the UC guidelines are due to follow in 2006. Both these guidelines support the usage of mesalazine for both UC and CD.

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23. Ferring licenses the PENTASA trademark to Shire US, Inc. for the US market, where it is not approved by the FDA for treatment of Crohn's Disease.