Medical treatment

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Improved understanding of the complex cell signalling path ways that underlie aberrant immune responses in both UC and CD has radically changed treatment algorithms. The focus is now on both clinical and endoscopic remission end points with the aim of controlling symptoms and preventing disease progression. The particular c hoice of anti-inflammatory agent or immunosuppressive drug, the sequence and combination of use must take into account individual disease phenotypes, coexisting conditions, patient preferences, response to treat ment, side e ff ects and treatment availability . There has been a paradigm shift in treatment algorithms from escalation ther apy in response to treatment failure to a top-down approach predicated on achie ving clinical and endoscopic remission with subsequent de-escalation of treatment to maintain remission. Conventional first-line treatment has been 5-aminosalicylic acid (5-ASA) derivativ es given topically (per rectum) or system ically . These act as inhibitors of the cyclo-oxygenase enzyme system and are formula ted to protect the aspirin-related drug from degradation before reac hing the colon. Used as a single agent, 5-ASA is useful in treating ulcerative proctitis and as maintenance therapy following induction of remission. Corticosteroids have been the mainstay of treatment used either topically or systemically . They have a widespread anti inflammatory action and are frequently used in combination with 5-ASA derivatives to deliver prompt r elief of symptoms. The immunosuppressive drugs azathioprine and ciclosporin can be used to maintain remission and as steroid-sparing agents should maintenance therapy be r equired. Azathioprine is a purine analogue that is metabolised to 6-mercaptopurine (6-MP) and works by inhibiting cell-mediated immune responses. 6-MP may be given dir ectly for the same e ff ects. Approximately 10% of people have deficient thiopurine methyltransferase (TPMT) and 1 in 300 people have no enzyme activity , causing ine ffi cient metabolism of 6-MP . The resulting high pharmacological concentrations may cause adverse e ff ects such as myelosuppression. Testing of TPMT activity should be undertaken before commencing treatment. Short-course intravenous ciclosporin treatment is associated with remission in 80% of patients; however, many patients relapse after completion of treatment. The monoclonal antibodies infliximab and adalimumab both act as antagonists to tumour necrosis factor alpha (TNF α), which has a central role in inflammatory cascades. Infliximab, a murine chimeric monoclonal antibody , was the first av ailable monoclonal antibody for the treatment of CD. It is administered as an intravenous infusion most frequently to induce remission in moderate to severe disease and may be used as maintenance treatment once remission has been achieved. Adalimumab, an entirely human monoclonal anti - body , is an alternative to infliximab that also targets TNF α . It can be self-administered by patients, which is advantageous in long-term maintenance. T rough levels and antibodies to anti - TNF α monoclonal antibodies should be monitored to ensure optimal dosing and e ffi cacy of treatment. Recently , ustekinumab, a monoclonal antibody against interleukin-12/23; vedolizumab and etrolizumab, anti-integrin monoclonal antibodies; tofacitinib, a JAK (Jan us kinase) inhibitor; and ozanimod, an S1P (sphingosine-1-phosphate) - receptor modulator have receiv ed regulatory approval for treatment of IBD. The complexity and best sequencing of treatment options requires multidisciplinary

specialist input and is beyond the remit of this chapter (see Further reading). Medical treatment

Steroids Corticosteroids are widely used to treat acute flares of CD. They induce remission in 70–80% of cases of moderate to severe disease. They should be used in short courses and tapered once a response has been achieved. They reduce inflammation and are therefore ine ff ective in established fibro stenotic disease. Steroid enemas may be used in the rectum, John Leonard Kantor , 1890–1947, gastroenterologist, Presbyterian Hospital, New Y ork, NY , USA, described his string sign in 1934. - where the benefits include reduced systemic bioavailability , although long-term use may still cause adrenal suppression. Oral steroid formulations such as budesonide have been devised, where the steroid moiety is removed in the portal). circulation, thus reducing systemic side e ff ects. Steroids should - not be used as maintenance therapy and are usually replaced with immunomodulatory agents to minimise the risk of side e ff ects associated with long-term steroid use. - Aminosalicylates Colonic symptoms can be treated by 5-ASA agents in a similar - manner to those in UC. These agents have limited e ffi cacy in - small bowel CD. Antibiotics). A Metronidazole and ciprofloxacin may be used, particularly for periods of a few weeks at a time, especially in perianal disease. Long-term use of metronidazole should be avoided as there is a risk of peripheral neuropathy . Ciprofloxacin also has significant side e ff ects when used in the long term, including tendinitis and tendon rupture. Antibiotics may be used to treat an inflammatory mass or an abscess. In general, however, a confirmed abscess should be treated by percutaneous drainage and/or surgery as antibiotics alone will not treat a Crohn’s mass e ff ectively . Immunomodulatory agents Azathioprine is used for its additive and steroid-sparing e ff ects and currently represents standard maintenance therapy . It is a purine analogue, which is metabolised to 6-MP , and works by inhibiting cell-mediated immune responses (see Medical - treatment of ulcerative colitis).

Figure 75.14 Magnetic resonance enteroclysis demonstrating small bowel in /f_l ammation (courtesy of Dr D Kasir, Hope Hospital, Salford, UK).

Short-course intravenous ciclosporin treatment is associated with remission in 80%; however, there is relapse after comple tion of treatment in many cases. Methotrexate is a drug that has a wide e ff ect on DNA synthesis and immune signalling and can also be used in CD, although it is used less frequently in the biological era. Monoclonal antibody (biologic) therapy Infliximab, a murine chimeric anti-TNF α monoclonal antibody , and adalimumab, an entirely human anti-TNF monoclonal antibody , are widely used to induce remission in moderately severe and severe CD. Third-generation monoclo nal antibody therapies vedolizumab and etrolizumab prevent leukocyte migration preferentially in the gastrointestinal tract and may therefore have fewer side e ff ects. More recently ustekinumab has entered widespr ead use as a CD therapy . It targets interleukin-12/23 to dampen the autoimmune system. Monoclonal antibody therapy is currently widely used for induction and maintenance of remission. Early and aggressive use in patients at high risk for early recrudescent disease after surger y (for example, penetrating phenotype, early mucosal inflammation or aphthous ulceration at follow-up colonos copy) may reduce (or at least postpone) the need for subse quent surgery . Perforation and abscess formation are usually regarded as contraindications to the use of biological therapy , although biologicals may be safely used after percutaneous drainage. While biologicals may reduce inflammation and may occasionally achieve healing of fistula openings in anal disease, the fistula tracks may remain patent and cessation of therapy is associated with a high risk of reactivation. Care must be taken before starting biological therapy to ensure that there is no active sepsis and that a diagnosis of intestinal tuberculosis has been excluded (see Chapter 65).

Revision #1
Created 2025-12-31 15:27:39 UTC by Omar Ayman
Updated 2025-12-31 15:27:39 UTC by Omar Ayman