

Editors: **Michael Woodward**, Head, Aged and Residential Care Services, **Stephen Campbell**, Consultant Geriatrician, **Rohan Elliott**, Clinical Pharmacist, **Graeme Vernon**, Drug Information Pharmacist, **Francine Tanner**, Clinical Pharmacist, Austin Health; **Robyn Saunders**, Consultant Pharmacist, Victoria.

Inflammatory Bowel Disease in Older People

Florian Grimpen, Paul Pavli

ABSTRACT

Inflammatory bowel disease (IBD) can affect patients of all ages. The majority of patients are diagnosed in the second or third decade of life, but a minority develop the disease at an advanced age. Diagnosis can be delayed due to the misconception that IBD mainly affects young people, and the broader spectrum of differential diagnoses in the elderly. Management and treatment options are similar to those in younger patients but adverse reactions and drug interactions may be of greater significance in the elderly. Precluding treatment with anti-tumour necrosis factor drugs on grounds of previous infection with tuberculosis or viral hepatitis, comorbidities or previous malignancy – factors often found with advanced age – can make treatment challenging. The increased risk of bowel cancer in IBD warrants regular screening, especially in the elderly as their absolute risk of cancer is higher.

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INTRODUCTION

The inflammatory bowel diseases (IBD) – ulcerative colitis and Crohn's disease are idiopathic conditions that differ in their pathogenesis as well as their clinical presentation. Crohn's disease can affect any part of the gastrointestinal tract from the mouth to the anus, although in most cases it affects the terminal ileum and/or the colon. Crohn's disease can cause fistulising disease and has a high risk of recurring after surgery. Depending on the localisation and extent, its clinical picture can be variable and patients may present with abdominal pain, tiredness, symptoms of bowel obstruction, or diarrhoea. Ulcerative colitis generally affects the rectum and colon to a varying extent, rarely causes fistulae and can be cured by surgery. Its presentation is less variable than Crohn's disease and typically patients present with pain and bloody diarrhoea.

Both diseases predominantly affect younger people, but 10 to 15% of new cases are diagnosed in patients over the age of 60 years.¹ The age of onset demonstrates a bimodal pattern, especially in Crohn's colitis, with the first peak in the third decade and the second peak in the eighth decade, although this pattern has not been replicated in all studies.² The incidence of IBD has risen over the past decades and the prevalence in older people is expected to rise as the population ages. In 2005 it was estimated that around 61 000 Australians were affected by IBD and 24% were over the age of 60 years. The financial cost was nearly AUS\$500 million dollars and the net disease burden was AUS\$2.2 billion dollars <www.acca.net.au>.

The clinical picture and management of IBD in older people is similar to younger patients, but a number of considerations

are needed regarding differential diagnosis, possible drug interactions, and adverse effects from treatment.

CLINICAL MANIFESTATIONS

The clinical features of new-onset ulcerative colitis in the elderly tend to be milder than in younger patients, as described in an analysis of data from 844 patients in a Japanese study. In this study, the proportion of mild colitis significantly increased along with advancing age of onset (36% in patients < 29 years; 47% in patients 30–59 years; 50% in patients > 60 years); conversely the proportion of severe colitis and the extent of the disease decreased with advancing age.³ A study that analysed data from a large inpatient database in the US, found that IBD patients over the age of 65 years had significantly higher mortality rates when hospitalised, less fistulising or stricturing disease, and a lower rate of bowel obstruction and surgery. Older patients presented more often with rectal bleeding and had higher rates of anaemia, electrolyte disturbance, and malnutrition, when compared with patients younger than 65 years.⁴

DIFFERENTIAL DIAGNOSIS

The diagnosis of IBD is not made as readily in older patients as it is in younger patients. The reasons for this include the preconception that IBD affects predominantly young people, as well as the broader range of differential diagnoses in the elderly. These include symptomatic diverticular disease, non-steroidal anti-inflammatory drug-induced small and large bowel ulceration, colorectal cancer, intestinal ischaemia, radiation-induced colitis, obstructive symptoms from adhesions, small bowel bacterial overgrowth and infection.

MANAGEMENT

5-Aminosalicylates

Ulcerative colitis generally affects only the colon, and treatment options are more varied than for Crohn's disease. First-line therapy for mild to moderate ulcerative colitis is the use of 5-aminosalicylates and its pro-drugs. The pro-drugs, sulfasalazine, olsalazine, and balsalazide are only available in oral form. Mesalazine can be used orally and also rectally as a foam or enema. A combination of oral and topical applications is more effective for the treatment of distal colitis than either form alone.⁵ The differences in absorption and efficacy among the oral drugs are small, and the Pharmaceutical Benefits Scheme mandates that sulfasalazine should be trialled before any of the newer drugs.⁶ Adverse effects such as nausea and headache may be more common with sulfasalazine than with the newer drugs and are partly due to the sulfapyridine component that is released after cleavage of the pro-drug by colonic bacteria. Therefore, sulfasalazine is started at a low dose and increased gradually over 10 to 14 days. Other adverse effects include fever, and rash, and the rare complication of agranulocytosis. Sulfasalazine may impair the absorption of folate and should be used with caution in advanced renal or hepatic impairment. Drug interactions with sulfasalazine may be more relevant in older

Florian Grimpen, MBBS, Registrar, **Paul Pavli**, PhD, MBBS(Hons), FRACP, Gastroenterology and Hepatology Unit, The Canberra Hospital, Woden, Australian Capital Territory

Address for correspondence: Florian Grimpen, Gastroenterology and Hepatology Unit, The Canberra Hospital, Woden ACT 2606, Australia
E-mail: florian.grimpen@act.gov.au

patients, e.g. digoxin absorption may decrease, effect of warfarin and oral hypoglycaemics may increase.

Mesalazine is well tolerated and its adverse effects profile is similar to sulfasalazine but they occur less frequently. Mesalazine will be available in a once-daily formulation which may improve compliance.⁷

There is no consensus about the induction dose of 5-aminosalicylates in active ulcerative colitis. There may be a dose-response relationship for sulfasalazine but this is less clear for mesalazine – starting doses may be low unless the clinical situation dictates urgency.⁸ Patients who respond to induction with 5-aminosalicylates should be maintained on them at the same dose in the long-term. There are data suggesting that 5-aminosalicylates reduce the risk of colorectal cancer in ulcerative colitis.⁹ Although there is no good evidence that 5-aminosalicylates are clinically useful in Crohn's disease, many patients worldwide are treated with them, partly because the 5-aminosalicylates have a favourable adverse effect profile and partly because of a perceived benefit. 5-Aminosalicylates may be trialled in mild Crohn's disease, but severe Crohn's disease necessitates the use of more effective therapy.

Corticosteroids

Corticosteroids are used if remission of mild to moderate ulcerative colitis cannot be induced with 5-aminosalicylate alone, or if the clinical picture mandates prompt treatment, e.g. bowel frequency greater than four to six a day, significant bleeding, systemic symptoms (night sweats, fevers, weight loss) or abnormal laboratory test results indicating anaemia or iron deficiency. Corticosteroids are the first-line treatment in a moderate to severe flare of Crohn's disease. Corticosteroids can be given as oral prednisolone or in severe disease as intravenous methylprednisolone. Corticosteroids are effective in inducing remission but are unsuitable and ineffective for maintaining remission. Their numerous adverse effects include hyperglycaemia, osteoporosis, opportunistic infections, proximal myopathy, glaucoma and cataracts, and the detrimental effects on cardiovascular health as documented in observational studies.^{10,11} A major problem associated with the use of high-dose corticosteroids is the changes in mental state – mood swings, agitation, insomnia and rarely psychosis.

Therefore, the duration of corticosteroid therapy should be kept as short as possible – there is evidence that low-dose corticosteroids are also associated with an increased risk of osteoporosis.¹² A bone mineral density scan should be considered at the start of therapy, and if the T-score is less than -1.0 to -1.5, or if the patient has sustained a fragility fracture, and antiresorptive therapy with bisphosphonates should be started in the absence of contraindications. The majority of bone loss occurs within the first few weeks of corticosteroid treatment and preventive therapy should not be delayed. Vitamin D and calcium deficiencies need correcting, but supplementation is of uncertain benefit, unless given with bisphosphonates.¹³

Corticosteroids are believed to have an adverse effect on lipoprotein levels, but there is some evidence to the contrary, especially in patients over 60 years of age.¹⁴ High doses of corticosteroids are a risk factor for opportunistic infections. Rectal applications of prednisolone or hydrocortisone are used in left-sided colitis and proctitis, but are less effective than topical 5-aminosalicylates. Oral controlled ileal release budesonide may be used if corticosteroids are needed in patients with Crohn's disease affecting the ileum and/or the caecum or ascending colon. Budesonide has a high first-pass liver metabolism and systemic adverse effects are less than with conventional corticosteroids. Budesonide is expensive and not available on the Pharmaceutical Benefits Scheme for IBD.

Immunosuppressives

If 5-aminosalicylates are insufficient to maintain remission, azathioprine or its metabolite, mercaptopurine can be given at doses of 2 to 2.5 mg/kg and 1 to 1.5 mg/kg, respectively. Thiopurines are less effective at inducing remission as their onset of effect can be delayed by three to six months. Thiopurines are well tolerated and significantly reduce the number of disease exacerbations and the cumulative dose of corticosteroids.¹⁵⁻¹⁷ These benefits have to be weighed against serious adverse effects such as bone marrow suppression, pancreatitis, drug-induced hepatitis, photosensitivity, and flu-like syndrome causing nausea, vomiting, malaise, myalgia and fevers. However, less than 10 to 15% of patients stop treatment due to adverse effects. The possibility of drug interactions should also be considered, e.g. allopurinol will increase blood levels of the thiopurines and increase the risk of toxicity.

Bone marrow suppression is dose dependent and leads to leucopenia in 27% of patients.¹⁸ It may be appropriate to continue at a lower dose unless leucopenia is severe. The risk of serious liver function disturbance is small but may be higher in older patients.¹⁹ Regular blood tests (full blood count, liver function tests) are mandatory and should be done every two weeks for the first three months and every three months thereafter. Testing for inherited abnormalities of thiopurine methyltransferase, an enzyme involved in the metabolism of azathioprine and mercaptopurine, does not reliably predict all patients who develop bone marrow suppression. Eighty-nine per cent of the general population have normal levels of enzyme activity (homozygous wild-type thiopurine methyltransferase), 10.7% have intermediate (heterozygous with one allele for low activity) and 0.3% have low or no enzyme activity (homozygous for low activity).²⁰

Not all cases of heterozygosity will develop clinically significant bone marrow suppression, but cautious dosing of thiopurines can be instituted in these individuals if the genotype is known *a priori*. The identification of the small percentage of people with very low or absent enzyme activity will lead to the avoidance of thiopurines as these could lead to life-threatening bone marrow suppression. Normal thiopurine methyltransferase activity permits using higher doses from the onset of treatment and may reduce the time to clinical response.²¹ Another strategy to optimise thiopurine dosing is the measurement of thioguanine, the main active metabolite of azathioprine. This allows faster adjustment of the dose, according to blood levels of thioguanine measured every four weeks after starting the drug, rather than having to wait three to six months to be able to assess the clinical response. This strategy also expedites clinical response and may be used in combination with thiopurine methyltransferase testing, although it seems to be less cost-effective than thiopurine methyltransferase testing alone.²¹ A faster response translates into a shorter course of corticosteroids, and this may be important especially in older patients. However, neither test is in common clinical usage at present.

A recent meta-analysis concluded that malignancies were no more common in patients with IBD treated with immunosuppressives than those not on immunosuppressives.²² Whether or not treatment with thiopurines increases the risk of lymphoma has long been debated, and a recent meta-analysis concluded that the risk of developing lymphoma increased four-fold in IBD patients on immunosuppressives.²³ However, the absolute risk is small and early introduction of immunosuppressive therapy is beneficial due to the decreased need for corticosteroids and better disease control.

Methotrexate, an alternative immunosuppressive for the treatment of Crohn's disease, is often used if there is intolerance to azathioprine. The usual dose is 25 mg per week for 16 weeks,

given intramuscularly or subcutaneously. There may also be a role for methotrexate as maintenance therapy, with one study showing decreased rates of recurrence with methotrexate 15 mg intramuscularly once weekly.²⁴ One trial compared intravenous methotrexate to oral azathioprine for induction of remission in Crohn's disease. Three months of intravenous methotrexate followed by three months of oral dosing, was compared to six months of azathioprine. The primary outcome was induction of remission at three and at six months. There was no significant difference between the two groups, suggesting that intravenous methotrexate may be an alternative but no matter which route of administration, methotrexate like azathioprine, has a slow onset of action.²⁵ There is less evidence for its role in the treatment of ulcerative colitis.

Anti-Tumour Necrosis Factor Drugs

The management of IBD has dramatically changed since the introduction of anti-tumour necrosis factor (TNF) drugs (infliximab, adalimumab, certoluzimab). Infliximab was the first monoclonal anti-TNF antibody and is part of the established treatment options in inflammatory diseases such as rheumatoid arthritis and ankylosing spondylitis. Infliximab has been used in IBD for nearly 15 years and can be used in ulcerative colitis as well as Crohn's disease.²⁶ Infliximab may induce remission in severe acute IBD in patients who are refractory to corticosteroids. If remission is induced, infliximab can be continued as eight-weekly infusions for maintenance treatment. Such scheduled maintenance treatment has benefits over episodic treatment as it increases the likelihood of remaining in remission, improves quality of life, decreases the need for surgery and reduces the risk of formation of neutralising antibodies to infliximab.

Infliximab is very effective and many patients will experience a dramatic improvement in symptoms and objective markers of inflammation. About 60% of patients with Crohn's disease will respond to a single infusion within two weeks and with eight-weekly infusions, the response can be maintained for one year in about 30% of this subgroup.²⁷ Infliximab can induce healing of fistulas in Crohn's disease and obviate the need for surgery.²⁸ Responders can reduce the amount of concomitant immunosuppressives and corticosteroids significantly, thereby reducing the risk of adverse effects. On the other hand, immunosuppressives have been shown to reduce the formation of antibodies to infliximab, which are a common cause of infusion reactions and secondary treatment failure. Patients with Crohn's disease who lose response to infliximab may benefit from an increase in dose or a decrease in interval between infusions.²⁹

Patients who either do not respond or initially respond to infliximab but subsequently lose response may be trialled on adalimumab, a fully humanised monoclonal antibody to TNF, which is less likely to become the target of an antibody response. Adalimumab is effective for induction as well as maintenance of Crohn's disease in anti-TNF naive patients, as well as induction of remission in patients who had initially responded to infliximab but subsequently lose response.³⁰⁻³² Whether adalimumab is effective in ulcerative colitis has not conclusively been determined, with some small studies suggesting modest benefits after secondary treatment failure with infliximab.^{33,34} Although anti-TNF drugs can dramatically improve the quality of life in patients with refractory IBD, the proportion of patients in remission after one year of treatment with either infliximab or adalimumab is in the order of 20 to 25%.

Certoluzimab, a humanised IgG-Fab fragment also directed against TNF, has shown to be effective for induction and maintenance of severe Crohn's disease. Overall, the data are limited and it is only available in Australia for clinical trials, although it has been approved for use in IBD overseas.

OPPORTUNISTIC INFECTIONS

In a recent paper examining risk factors for opportunistic infections in patients with IBD, age at diagnosis was an independent risk factor for opportunistic infections (OR 1.1 for every 5 years; 95% CI 1.1-1.2).³⁵ The relative risk was greatest in those older than 50 years of age (OR 3.0; 95% CI 1.2-7.2) relative to those 24 years or younger. Among the 100 patients with IBD and an opportunistic infection, the commonest infections were Herpes zoster (28 cases), *Candida albicans* (26 cases), Herpes simplex (18 cases), as well as Epstein-Barr virus, cytomegalovirus, histoplasma and other pathogens typically associated with immunosuppression. Not surprisingly, the use of IBD medications was associated with the risk of opportunistic infections, with corticosteroids (RR 3.3; 95% CI 1.8-6.1), azathioprine/mercaptopurine (RR 3.8; 95% CI 2-7) and infliximab (RR 4.4; 95% CI 1.1-17) all carrying a statistically significant risk. The use of two or three medications was associated with a relative risk of 14.5 (95% CI 4.9-43). Mesalazine use was not associated with opportunistic infections.

Anti-TNF drugs are associated with an increased risk of serious bacterial infections (absolute risk 3-5%). A review and meta-analysis of patients with rheumatoid arthritis treated with infliximab and adalimumab involving 3493 patients who had received an anti-TNF drug, and 1512 patients on placebo, revealed a pooled odds ratio of 2 (95% CI 1.3-3.1) for development of serious infection, and the number needed to harm with a serious infection within 3 to 12 months of treatment was 59 (95% CI 39-125).³⁶ Even with large pooled patient cohorts, the absolute number of serious infections is small, making risk calculations prone to error. The follow-up periods were short, with almost all recorded adverse events occurring within two years of starting treatment, and little is known about the long-term risk of developing adverse reactions. There were few older patients enrolled in these studies and most of the studies did not stratify the risk of infection by age.

Generally, anti-TNF drugs can only be used after latent tuberculosis and infection with hepatitis B or hepatitis C virus have been excluded. Reactivation of varicella infections has also been described and the risk of serious viral infections such as influenza may be increased, making vaccination important. The antibody response to influenza vaccination in patients treated with anti-TNF is modestly impaired, but the proportion of patients who achieve a protective titre is not significantly diminished by the use of anti-TNF therapies.³⁸ Pneumococcal vaccination seems to be less effective when on anti-TNF therapy - significantly fewer patients respond to the vaccine.³⁹ If possible, pneumococcal vaccine should be given before starting anti-TNF drugs, especially in the elderly, but the timing is problematic.

There is ongoing debate over the relative risk of developing malignancy as a consequence of anti-TNF treatment. An increased risk of developing lymphoma and a variety of solid tumours has been described, although conclusive data are sparse and are difficult to interpret due to the confounding use of other immunosuppressives and the relatively short duration of experience with anti-TNF drugs. The general consensus is that a history of malignancy is a contraindication to their use.

There are some data to suggest that anti-TNF drugs can cause and exacerbate congestive heart failure - a dose-dependent effect. Anti-TNF drugs are contraindicated in New York Heart Association III and IV heart failure, and in New York Heart Association II it should be used with great caution, after consultation with a cardiologist, and only where strictly indicated.

COLORECTAL CANCER

The risk of developing colorectal cancer in IBD rises with disease duration, and yearly or second-yearly colonoscopic screening is recommended after 8 to 10 years of pancolitis and after 12 years of left-sided colitis. The recommendations for Crohn's disease are less clear but should be similar if there is colitis. Colorectal cancer is responsible for up to 15% of deaths in patients with IBD, and there is speculation that the incidence of colorectal cancer in IBD patients will rise as prevalence in the elderly increases.⁴⁰ Screening in the elderly with IBD should be adhered to strictly. The risk is higher if patients have concomitant primary sclerosing cholangitis.

SURGERY

Unlike Crohn's disease, ulcerative colitis can be cured by surgery. A total proctocolectomy with formation of an end-ileostomy may be indicated in acute fulminant colitis, in the case of colonic neoplasia or high-grade dysplasia (perhaps even low-grade dysplasia), or if chronic symptoms are difficult to control and/or there are intolerable risks or adverse effects from treatment. While this type of surgery is safe and curative, it leaves the patient with an ileostomy and bag which may have a negative impact on their quality of life. In many patients it is possible to form an ileal J-pouch with an anal anastomosis, which preserves the continuity of the bowel passage and obviates the need for a stoma. In a minority of patients the new pouch may become affected with auto-inflammation, pouchitis, which can be an ongoing source of pain and bleeding, although in most cases it responds well to oral metronidazole or topical therapy with 5-aminosalicylates or corticosteroids.

In the absence of malignancy, surgery in Crohn's disease should be to remove parts of the bowel that are severely affected and symptomatic, such as fibrotic strictures in the small bowel, or other focal disease that is refractory to treatment. Surgery may be necessary for abscesses or fistulae. The majority of patients with Crohn's disease will undergo surgery at some stage and most of them will require further surgery at a later time. An Australian study demonstrated that the perioperative morbidity from laparotomy for Crohn's disease was higher in the elderly compared with younger patients, with cardiac and respiratory complications occurring much more commonly. However, the postoperative mortality and the risk of anastomotic leaks were similar across the age groups.⁴¹

DIET

There is no evidence to suggest that a certain type of diet alters the course of IBD. However, many patients report that certain foods worsen their symptoms, especially spicy or fatty foods, and high residue diets. It is not uncommon for patients with prolonged periods of symptomatic IBD to become malnourished. This may be due to a combination of higher energy expenditure through the chronic inflammatory process, decreased oral intake because of pain and nausea, and malabsorption through small bowel involvement in Crohn's disease. The early involvement of a dietician is invaluable.

THROMBOEMBOLISM

Hospitalised patients with exacerbation of IBD are at high risk of thromboembolic complications. Measures for thrombosis prophylaxis should be put in place, including regular low-dose unfractionated or fractionated heparin. There may be concern about giving heparin to patients with haematochezia (rectal bleeding), but the risk of deep vein thrombosis is greater than the risk of causing significant haemorrhage through anticoagulation.

CONCLUSION

The management of IBD is complex, and treatment can involve a number of pharmacotherapeutic options as well as surgery. Compared with IBD in young patients there are a number of special considerations in the management of IBD in older patients – broader spectrum of differential diagnoses, troublesome adverse drug effects, higher risk of drug interactions given the larger number of concomitant medications. Older people are also more likely to have comorbidity affecting the therapeutic options and the risks of surgery.

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