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Inflammatory Bowel Disease in the Older Patient

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Inflammatory bowel disease (IBD) in the elderly is becoming increasingly prevalent as the general population ages. Patients diagnosed with IBD at an older age exhibit a different phenotype with less genetic predisposition, more colonic involvement, less penetrating disease, and higher rates of serious infection and in-hospital mortality. Misdiagnosis and delay to diagnosis are common, possibly due to the belief that IBD is a disease of the young or diagnostic confusion with illnesses that mimic the clinical presentation of IBD such as ischemic or infectious colitis. The effects of IBD and IBD treatments may compound other medical comorbidities. All providers of the older IBD patient, including the gastroenterologist and primary care provider, must pay careful attention to the effects of polypharmacy and adverse effects of medications used to treat IBD and other medical comorbidities.

INTRODUCTION

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic conditions characterized by inflammation of the gastrointestinal tract. The peak incidence of IBD occurs in the second to fourth decades of life.[1] Although IBD is often thought of as a disease of the young, the incidence of IBD in older patients has been reported to be 10-15%. As the global population ages and the overall incidence of inflammatory bowel disease increases, the number of older patients who are diagnosed with IBD and the number of aging patients diagnosed with IBD when they were younger will increase considerably.[2] With current estimates that 10-30% of patients with IBD are over the age of 60,[3] the anticipated growth of older patients with IBD introduce distinct challenges and considerations in the care of this patient population.

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Epidemiology and Pathophysiology

Older patients with IBD, also termed "elderly" or "geriatric," typically defined as ≥60 years of age, comprise a heterogeneous group due to a wide range of medical co-morbidities and functional status. Older-onset ulcerative colitis is more common than older-onset Crohn's disease, and older men have higher incidence rates of IBD than older women.[4]

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Genetics and family history appear to have less influence on the development of older-onset IBD when compared to younger populations suggesting other factors at play.[5] As the immune system ages, age-related T-cell impairment and decline in T-cell production can lead to a relative immunodeficiency. This immunodeficiency predisposes older patients to gastrointestinal infections, but immune dysregulation with advancing age also leads to the increased production of pro-inflammatory cytokines, which are implicated in the development of inflammatory diseases.[6] In addition to immune dysregulation, current theories of IBD pathogenesis suggest that alterations in the intestinal microbiome may trigger the development of IBD.[7] The composition of the intestinal microbiota also evolves with aging, with less overall diversity characterized by decrease in anaerobes, such as bifidobacteria, and increase in enterobacteria. These changes in the microbiota are hypothesized to be caused by changes in diet, mobility, intestinal motility, increased use of antibiotics associated with aging.[8] Frailty is also associated with decreased microbiota diversity compared to non-frail older individuals.[9]

Clinical Presentation

Clinicians experience more difficulty diagnosing IBD in older patients, leading to misdiagnosis and delayed diagnosis. 60% of older patients with CD are initially misdiagnosed, compared to 15% of younger patients.[10] The clinical presentation of IBD in older patients may be confused with infectious (such as Clostridium difficile), ischemic, radiation, non-steroidal anti-inflammatory drug-induced, or diverticular-associated enterocolitis.[11] Older-onset IBD patients present with more subtle disease compared to younger adults. They more frequently present with isolated colonic inflammation (61.9% vs. 36.7% in younger adults) and less frequently present with small bowel involvement or upper gastrointestinal disease (38.1% vs. 63.3% in adults). [12] In CD, older patients are more likely to present with rectal bleeding without profound diarrhea, abdominal pain, fever, or weight loss.[4] Additionally, older-onset CD patients more often have isolated colonic disease without penetrating disease, a phenotype similar to UC.[3] In UC, older patients are more likely to present with left-sided colitis rather than ulcerative proctitis or pancolitis, and often have milder symptoms of abdominal pain and rectal bleeding than younger patients.[12] Extraintestinal manifestations of IBD (e.g., arthritis, erythema nodosum, pyoderma gangrenosum, apthous stomatitis, uveitis) are less common in patients diagnosed with IBD at an older age.[13] Progression of disease, such as extension of ulcerative proctitis to left-sided colitis, or the development of penetrating disease, is less common in older-onset IBD.[4]

Outcomes and Complications of IBD

Despite having milder disease and less progression, older patients with IBD are less likely to utilize IBD-specific outpatient care[14] and more likely to be hospitalized for IBD.[15] A study of IBD patients in a Swedish National Registry found that older patients with IBD are less likely to have IBD-specific outpatient healthcare and more likely to have IBD-related hospitalizations and intestinal surgeries.[16] It has been hypothesized that increased hospitalizations and surgeries in older IBD patients may be related to reluctance to use corticosteroid-sparing immunomodulator and biologic medications in older patients due to other comorbid conditions and risk of complications.[17] Older age is an independent risk factor for hospital mortality in IBD-related hospitalizations.[18] Lastly, older patients who undergo surgery for IBD have longer post-operative length of hospital stay[19] and may have increased post-operative mortality.[20]

Older patients with IBD are also at increased risk for serious infection regardless of treatment type,[18] though use of immunosuppression, disease activity and use of narcotics also increase the risk of serious infection in older IBD patients. Due to immunosenescence, older patients with IBD are at increased risk for infection, including zoster infection.[21] Immunization (with inactive vaccines for patients on immunosuppresive therapies) for influenza and pneumonia are recommended for all older patients with IBD. Zoster vaccination is also recommended for all individuals 60 and older. A new, inactive vaccine for herpes zoster (Shingrix, GlaxoSmithKline), with >90% reduction in shingles incidence, is now commerically available and is likely safe in immunosuppressed patients with IBD.[22]

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Patients with IBD are at a two- to three-fold increased risk of developing a venous thromboembolism (VTE). This risk increases significantly with age; there is a 20% increased risk of a venous thromboembolism for each increased decade in age.[23] There are no specific guidelines for VTE prevention in older IBD patients, though smoking cessation, weight reduction in obese patients, and mobilization in the hospital, at home, and during long-distance travel should be encouraged.[24]

The most well-recognized risk factors for the development of colorectal cancer in inflammatory bowel disease are duration and extent of disease.[25] Based on these established risk factors, it is plausible that patients diagnosed with IBD at an older age would be at lower risk for IBD-associated colorectal cancer given shorter duration of disease and typically less extensive involvement. However, cohort studies from Hong Kong and the Netherlands have found that older-onset IBD is associated with a shorter time to the development of colon dysplasia and colorectal cancer.[26, 27] While this may represent sporadic disease, earlier colonoscopy for colon cancer surveillance than guidelines suggest (e.g., eight years after diagnosis) in elderly-onset IBD is advisable.

Management

The general approach to treatment in elderly-onset IBD is no different than in the younger IBD population. Treatment goals should focus on inducing and maintaining remission, preventing disease-related and treatment-related complications, and optimizing quality of life. The therapeutic choices may be more challenging in older IBD patients due to different disease phenotype, patient comorbidities, and concern for polypharmacy. Additionally, older patients with IBD are often excluded from clinical studies, particularly randomized control trials for IBD therapeutics. The paucity of efficacy and safety data specifically pertaining to older IBD patients, further complicates treatment decisions.

Mesalamine

5-aminosalicylic (5-ASA) agents are widely used for treatment of mild to moderate ulcerative colitis and may also be used for treatment of Crohn's colitis.[28] Over 80% of patients with IBD diagnosed after age 60 are treated with 5-ASA agents.[4] 5-ASA can be taken orally, with several formulations requiring dosing multiple times per day or with multiple pills for each dose.[29] Topical 5-ASA therapies include suppositories, which can treat inflammation in the distal 10 cm of the rectum, and enemas, which can theoretically treat inflammation distal to the splenic flexure. In the older IBD patient, several factors can influence adherence to medical therapy. Cost of medications, concern for side effects, difficulties with pill size and number, difficulty with enema and suppository administration, and complex dosing schedules all can affect adherence to medical therapy.[30]

Although 5-ASA agents are generally considered to have an excellent safety profile, side effects and adverse reactions can occur. The most common adverse reactions include nausea and vomiting, headache, and rash. Nephrotoxicity, which is typically due to interstitial nephritis, is rare but clinically important, with a mean occurrence of 0.26% per patient-year. The incidence of nephrotoxicity appears to be idiosyncratic, as it has not been found to be related to formulation, dosing, or duration of 5-ASA therapy.[31] As many older patients with IBD may have comorbid chronic kidney disease or risk factors for the development of renal insufficiency (e.g., diabetes mellitus, hypertension), renal function should be monitored closely before and during treatment.[32]

Corticosteroids

Corticosteroids are effective in establishing but not maintaining remission in moderate to severe IBD. Despite this, 30-40% of older IBD patients are on maintenance therapy with systemic corticosteroids.[33, 34] Long-term corticosteroid use is associated with many adverse effects, which are more frequent and severe in the geriatric population. Adverse effects include osteoporotic-related fractures, serious and opportunistic infections, altered mental status and delirium, precipitating or exacerbating diabetes mellitus and hypertension, and development of cataracts and glaucoma.[35,36] Budesonide, a newer corticosteroid with formulations targeting both the small intestine and the colon, possesses some safety advantage to conventional corticosteroids, such as prednisone. Budesonide has extensive first-pass metabolism in

the liver, leading to fewer systemic adverse effects and increased tolerability in patients. However, cost and lack of insurance coverage may limit use and corticosteroids may still be required for induction of remission in more severe disease activity.[17]

Immunomodulators: Thiopurines and Methotrexate

Some patients who are unable to achieve disease remission with oral mesalamine may be treated with thiopurine agents (such as azathioprine or 6-mercaptopurine) or methotrexate for maintenance therapy in IBD. In older patients with IBD, use of thiopurines and methotrexate is quite uncommon, (6% and 1%, respectively in one retrospective study[33]), potentially due to concern for adverse effects associated with these agents.

Use of thiopurines can lead to leukopenia and elevated liver enzymes, though testing for thiopurine methyltransferase genetics and/or enzyme activity prior to initiation of thiopurine therapy can help to identify those at highest risk for leukopenia.[37] Acute pancreatitis is also associated with thiopurine use.[38] Thiopurine use has been associated with increase risk of lymphoma, with a median age of onset of 60.[39] Thiopurine use is also associated with an increased risk of non-melanoma skin cancer,[40] with risk increasing with age.

Common side effects of methotrexate use include nausea, fatigue, stomatitis and rash. Rarely, hepatotoxicity can occur; liver enzymes should be monitored routinely. Methotrexate appears to be safe in older patients. Renal function, rather than advancing age itself, predicts development of toxicity, and should be taken into consideration when initiating and monitoring methotrexate therapy.[41] Folic acid supplementation is recommended to prevent methotrexate-associated hepatic and gastrointestinal hepatotoxicity as well as associated folate deficiency.[42]

Biologic Therapies

Biologic agents, including tumor necrosis factor alpha (TNF-α), integrin and interleukin antagonists, are effective treatments for moderate to severe

Table 1. Common Drug Interactions with Drugs Used for Treatment of IBD

IBD Drug	Drug	Severity	Potential Interaction
Mesalamine	Non-steroidal anti-inflammatory drugs (NSAIDs)	Major	Increased risk of bleeding
Mesalamine	Warfarin	Moderate	Decreased warfarin efficacy
Mesalamine	Proton Pump Inhibitor	Moderate	Increased gastric pH may cause premature release of mesalamine and decreased drug delivery to colon
Corticosteroids	Fluoroquinolones	Major	Increased risk of tendon rupture
Corticosteroids	Loop Diuretics	Moderate	Increased risk of hypokalemia
Corticosteroids	Thiazide Diuretics	Moderate	Increased risk of hypokalemia
Thiopurines	Angiotensin converting enzyme (ACE) inhibitors	Major	Increased risk of myelosuppression
Thiopurines	Allopurinol	Major	Increased risk of thiopurine toxicity
Thiopurines	Warfarin	Moderate	Decreased warfarin efficacy
Methotrexate	NSAIDs	Major	Increased methotrexate toxicity
Methotrexate	Thiazide Diuretics	Major	Increased methotrexate toxicity
Methotrexate	Penicillin	Major	Increased methotrexate toxicity

Thiopurine toxicity: nausea, vomiting, leukopenia, anemia
Methotrexate toxicity: leukopenia, thrombocytopenia, anemia, nephrotoxicity, mucosal ulcerations

UC and CD. Although TNF-α agents have been in use for over a decade, use in the elderly IBD population is infrequent, possibly due to lack of safety data in this population or concern for side effects associated with these therapies.[17]

Anti-TNF agents may be less effective in older patients, as older IBD patients are more likely to be primary non-responders compared to younger IBD patients. Older IBD patients on anti-TNF therapy also have higher rates of IBD-associated hospitalizations, surgeries and serious infections compared to younger IBD patients.[43]

Anti-TNF use is associated with increased risk of serious infection that may be even higher in older patients with IBD and may lead to earlier discontinuation of anti-TNF compared to younger IBD patients.[44] The increased risk of infection is most pronounced in combination therapy when anti-TNF and thiopurine agents are given concurrently. Live vaccines should not be given to patients on anti-TNF therapy and inactive vaccines may be less effective in patients receiving anti-TNF therapy. The combination of inadequate immune response and non-adherence to vaccination increases the risk of infection in the vulnerable older IBD patient population. Anti-TNF therapy has also been associated with worsening congestive heart failure, and is contraindicated in New York Heart Association Class III and IV heart failure,[45] which is more likely to be a comorbid condition in older patients with IBD. There is also an increased risk of lymphoma with use of anti-TNF agents, particularly with combination therapy, and long-term combination therapy should be avoided in individuals 65 and older.[17,39] The risk of both non-melanoma and melanoma skin cancers are increased in patients taking anti-TNF, and they should undergo regular dermatologic skin examinations.[46]

The administration of anti-TNF agents, which are given as an infusion (infliximab) or as a self-administered injection (adalimumab, certolizumab-pegol, golimumab), may provide logistical challenges for the older patient with IBD, who may have difficulty with transportation to infusion centers, with venous access, with self-administration of injectable agents due to poor dexterity and decreased visual acuity, and with adherence to a complex dosing schedule.[47]

Vedolizumab is a gut-selective monoclonal antibody that inhibits α4β7 integrin to block lymphocyte trafficking to the intestinal endothelium that is used for moderate to severe UC and CD. Vedolizumab has an excellent safety profile, with no increased risk of serious infection and low rates of malignancy in the general IBD population.[48] The safety profile of vedolizumab in older patients with IBD, has not been extensively studied, though preliminary data suggests that vedolizumab is low risk for use in older patients with IBD,[49] and may be a preferred treatment choice for moderate to severe IBD due to its low lymphoma and infection risk.

Ustekinumab

Ustekinumab is a monoclonal antibody against IL-12 and IL-23, initially approved for the use in psoriasis, but now is approved for use in moderate to severe CD. Clinical trials of ustekinumab in Crohn's disease have also demonstrated an excellent safety profile with no increased risk of adverse events compared to placebo.[50] There is a paucity of data regarding safety of ustekinumab in the older IBD population, but studies of ustekinumab use in older psoriasis patients have demonstrated favorable safety profile,[51] and may also be a preferred treatment choice for older patients with Crohn's disease.

Similar to anti-TNF agents, older patients with IBD on vedolizumab or ustekinumab may have difficulty with adherence to intravenous (IV) infusions and self-administered subcutaneous injections with complex dosing schedules.

In general, immunosuppressive regimens should be minimized or avoided, if possible, in patients with multiple poorly controlled comorbidities, poor functional status, severe malnutrition, and cognitive decline. However, older IBD patients with minimal or well-controlled comorbidities with excellent cognitive, nutritional, and functional status are suitable candidates for immunosuppressive therapy if clinically indicated.

Drug-drug interactions

Older patients with IBD are prescribed an average of nine routine medications to manage their IBD and other comorbid conditions. Nearly one-third of medication regimens in older patients with IBD

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have major drug-drug interactions.[34] (Table 1.) Careful review for drug-drug interactions with IBD medications should be considered prior to introducing a new medication. As 5-ASA agents are the most common medications used in older patients with IBD, drug-drug interactions with mesalamine agents are common, including with non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors, histamine blocker, and warfarin use. Corticosteroids have many drug-drug interactions, including increased risk of tendon rupture when taken with fluoroquinolones, and increased risk of hypokalemia when taken with thiazide and loop diuretics. Allopurinol and angiotensin-converting-enzyme (ACE) inhibitors use may increase myelotoxicity when given with thiopurines and thiopurines may decrease the anticoagulation effect of warfarin. NSAIDs, aspirin, thiazide diuretics, and penicillin may inhibit renal excretion of methotrexate, leading to increased risk of methotrexate toxicity. Antibiotics given as treatment for and management of complications of IBD, such as metronidazole, have an increased risk of neuropathy when given with statins, and ciprofloxacin has the potential to increase the anticoagulation effects of warfarin.[52] Biologic therapies have not been associated with significant drug-drug interactions with other common medications.[53]

In order to minimize drug-drug interactions, all providers caring for older patients with IBD, including gastroenterologists and primary care providers, should review the patient's medication regimen carefully. Factors to consider include determining if there is an appropriate indication for the drug, that is effective for its intended condition, and that the dosage and directions are correct and practical given the patient's comorbidities and functional limitations. Other considerations include ensuring that there are no significant drug-drug interactions or drug-disease interactions, that the duration of therapy is acceptable, and that the cost of the patient's medical regimen compared to alternatives of equal usefulness is minimized.

CONCLUSIONS

Older patients with IBD require special attention due to comorbidity, polypharmacy, functional status, and increased risk of infection and malignancy compared to younger IBD patients. Medication interactions, prevention of infection, and management of comorbidities may require closer monitoring to determine therapeutic response and to ensure adequate safety of medical therapy for IBD. Although the side effects and risks of corticosteroids are well-known, many older IBD patients are maintained on long-term corticosteroid use, which should be avoided in favor of other corticosteroid-sparing agents. A treatment strategy for older patients with IBD should be focused on restoration of normal bowel function and improved quality of life, avoiding hospitalization and unnecessary surgery, and minimizing long-term risk of therapies. ■

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