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MEDICAL MANAGEMENT OF INFLAMMATORY BOWEL DISEASE IN THE ELDERLY

Introduction

The optimal management of inflammatory bowel disease (IBD) can be challenging at the best of times; however, this notion becomes more salient when treating the niche population of elderly IBD. The prevalence of IBD in elderly Canadians has almost doubled in a span of 5 years, increasing from 1/160 in 2018 to 1/88 in 2023.[1] While the majority of IBD patients are diagnosed between 20-40 years of age, 10-15% are diagnosed at >60 years of age.[2] Elderly-onset ulcerative colitis (UC) patients more commonly have left-sided colitis with less disease extension whereas elderly-onset Crohn's disease (CD) patients typically exhibit an inflammatory colonic phenotype. Although elderly-onset IBD patients typically demonstrate a less aggressive natural history overall, they have a similar risk of surgery compared to their adult-onset IBD counterparts with the majority being treated with non-advanced therapies.[3] A lack of physician knowledge and comfort level in treating elderly IBD likely contribute to patients being maintained inappropriately on long-term steroids and/or 5-aminosalicylates.

The existing literature on elderly IBD often fails to differentiate between aging pediatric or adult-onset IBD patients and elderly-onset IBD patients; therefore, this article will discuss the management of both groups together. Nevertheless, it is important to note that these two groups likely have different underlying pathophysiological mechanisms driving their respective diseases which can have implications for therapeutic decisions.[4] Unfortunately, the majority of evidence to help guide decision-making in elderly IBD is derived from retrospective analyses of real-world data or health administrative datasets, as well as post-hoc analyses of randomized controlled trials (RCTs). Drug efficacy aside, nuanced care of the elderly IBD patient involves an appreciation of frailty and comorbidity to help contextualize the risks of immunosuppressive therapy. Not only is the safety of therapies contingent upon the intrinsic immunosuppressive properties of the drug, but in addition, drug efficacy needs to be considered with respect to the effectiveness in controlling disease activity and achieving corticosteroid-free remission.

Frailty

Although the European Crohn's and Colitis Organisation refers to a cut-off of 60 years of age to define elderly-onset IBD, using chronological age alone is insufficient to appropriately assess a patient's suitability for IBD therapy. Frailty is a multifaceted concept that includes aspects of psychosocial well-being, social supports, cognition, comorbidities, nutrition, and functional status reflecting the physiologic resiliency of an individual to withstand stressors such as immunosuppression or surgery. A recent systematic review summarized that the majority of literature in IBD patients revolves around modified frailty indices that have not been validated in the IBD population.[5] This systematic review explored non-surgical IBD outcomes wherein frailty predicted hospitalizations, readmissions, length of stay, and mortality. Effective IBD treatment has been demonstrated to improve frailty, underscoring the importance of not undertreating elderly IBD patients in the right clinical context.[6] Future studies will help to elucidate frailty risk stratification tools for IBD therapy in the elderly; however, physicians can incorporate hand-grip strength measurements and the Clinical Frailty Scale[7] directly in the clinic to better understand the biologic age of their elderly IBD patients.

Safety

Infection

Although advanced age and comorbidities increase the risk of infection in patients on biologic or small molecule therapy, the type of advanced therapy also appears to play a role. The literature contains limited safety data in the elderly and the data that does exist stems primarily from the use of anti-TNF therapy in observational real-world cohorts. In the Mayo Clinic's reporting of 100 consecutive IBD patients with opportunistic infection, those on infliximab had an 11.1 OR (P = 0.07) of developing an infection with the greatest risk seen in patients >50 years of age.[8] In an Italian multicentre cohort study, 11% of patients >65 years of age on infliximab or adalimumab developed severe infections, compared to 0.5% of patients >65 years of age not on a biologic and 2.6% of patients <65 years of age on biologic therapy[9]. In contrast, in a post-hoc analysis of four RCTs, although UC patients ≥60 years of age had an increased baseline risk of serious adverse events, no increase in risk was attributed to anti-TNF therapy.[10] While real-world effectiveness data demonstrates confounding bias, RCT data is victim to a lack of generalizability given that clinical trial patients tend to be more robust than the patients we see in clinic. Although data on other advanced therapies in the elderly is sparse, vedolizumab, ustekinumab, risankizumab, and ozanimod generally have more favourable side effect profiles with respect to infectious risk than tofacitinib and upadacitinib.[11] Last, although combination therapy is often not used in the elderly due to safety concerns, a post hoc analysis of the REACT trial reported no increased adverse outcomes in CD patients ≥60 years of age who were exposed to early combined immunosuppression.[12]

Thrombosis/CV risk

Janus kinase (JAK) inhibitors such as tofacitinib and upadacitinib should be used with caution in the elderly IBD population after carefully weighing the risks and benefits of therapy. The ORAL Surveillance safety data revealed increased rates of major adverse cardiovascular events, malignancies (excluding non-melanoma skin cancers), serious infections, venous thromboembolisms (VTEs) and mortality in rheumatoid arthritis (RA) patients aged ≥50 years with ≥1 additional cardiovascular disease risk factor who were treated with tofacitinib compared to anti-TNF therapy.[13] Of note, this data was derived from a RA cohort and reassuringly 7.8 years of safety data from the tofacitinib UC clinical trial programs have failed to reveal similar risks.[14] For the sphingosine-1-phosphate receptor modulators, pre-existing cardiovascular conditions within 6 months prior to initiating therapy, such as myocardial infarction, stroke, decompensated heart failure, and Type II second or third degree AV block, need to be considered and would be contraindications to initiating ozanimod or etrasimod. Of note, while anti-TNF therapy is contraindicated in patients with New York Heart Association Class III or IV congestive heart failure, there may be a protective benefit where anti-TNF reduces the risk of VTEs and arterial events in IBD patients.[15]

Malignancy

Due to the risk of lymphoma with azathioprine that approaches 1:350 per year once patients are older than 50 years of age,[16] it is advisable to use methotrexate over azathioprine if an immunomodulator is clinically indicated in patients with a previous history of immunogenicity and/or refractory disease. The decision surrounding withdrawal of azathioprine therapy in an elderly IBD patient in remission is slightly more contentious with a 5-year cumulative relapse rate of 46% previously reported.[17] The risks of disease flares need to be weighed against the risks of infection and malignancy (non-melanoma skin cancer, lymphoma).

Drug Interactions

Polypharmacy is prevalent in older patients with IBD,[18] therefore it is incumbent upon the prescribing physician to be aware of potential drug interactions. For elderly IBD patients on azathioprine, it is important to be mindful that interactions with allopurinol, a commonly prescribed medication for gout, can dramatically increase the risk of bone marrow suppression.[19] Furthermore, when azathioprine and warfarin[20] are used together, the anticoagulation effect of warfarin is impaired. While ozanimod is primarily metabolized by the CYP2C8 pathway,[21] JAK inhibitors are metabolized via the CYP3A4 pathway.[22] One needs to be aware of concomitant prescriptions for major CYP2C8/CYP3A4 inducers such as rifampin, phenytoin and carbamazepine that can decrease the bioavailability of the small molecule therapies.

Efficacy

Efficacy data of advanced therapies in elderly IBD patients is sparse and is primarily centered around the use of anti-TNF therapy due to its long duration on the market. While some retrospective studies have suggested that elderly IBD patients are more likely to develop a secondary loss of response to anti-TNF therapies[23] and are less likely to achieve short-term clinical response,[24] a post-hoc analysis of RCTs in UC patients revealed no difference in inducing or maintaining remission between older and younger patients.[10] The real-world data could be confounded by the fact that elderly IBD patients are less likely to be initiated on advanced therapy and therefore may have more refractory disease upon initiation. In addition, clinicians are more likely to discontinue therapy due to adverse events in the elderly IBD population. Interestingly, a multicentre retrospective Japanese study revealed that anti-TNF therapy may be less effective in bio-naïve elderly-onset IBD patients[25] and

while immunosenescence may lead one to surmise that immunogenicity plays less of a role with age, a post-hoc analysis from the REACT trial contradicts this hypothesis.[26] When comparing the effectiveness of anti-TNF therapy to vedolizumab therapy in the elderly, mixed results have been reported.[27,28]

Conclusion

Treatment decisions in the elderly are complex and need to take into consideration frailty, comorbidities, quality of life, mobility restrictions (barrier to travel for intravenous infusions and clinic appointments), physical limitations (difficulties self-administering rectal therapies or subcutaneous injections), suboptimal response to vaccination, and psychosocial supports. As older IBD patients are at increased risk of post-operative morbidity and mortality,[29,30] it is imperative that ageism does not creep into the decision-making process for escalating IBD therapy or offering timely surgery. Proposed algorithms for treating elderly UC and CD patients are depicted in **Figure 1** and **Figure 2** respectively. Although the American Gastroenterological Association has published clinical practice guidelines on the topic of elderly IBD,[31] a large knowledge gap remains for physicians, which hopefully will be informed by future clinical trials.

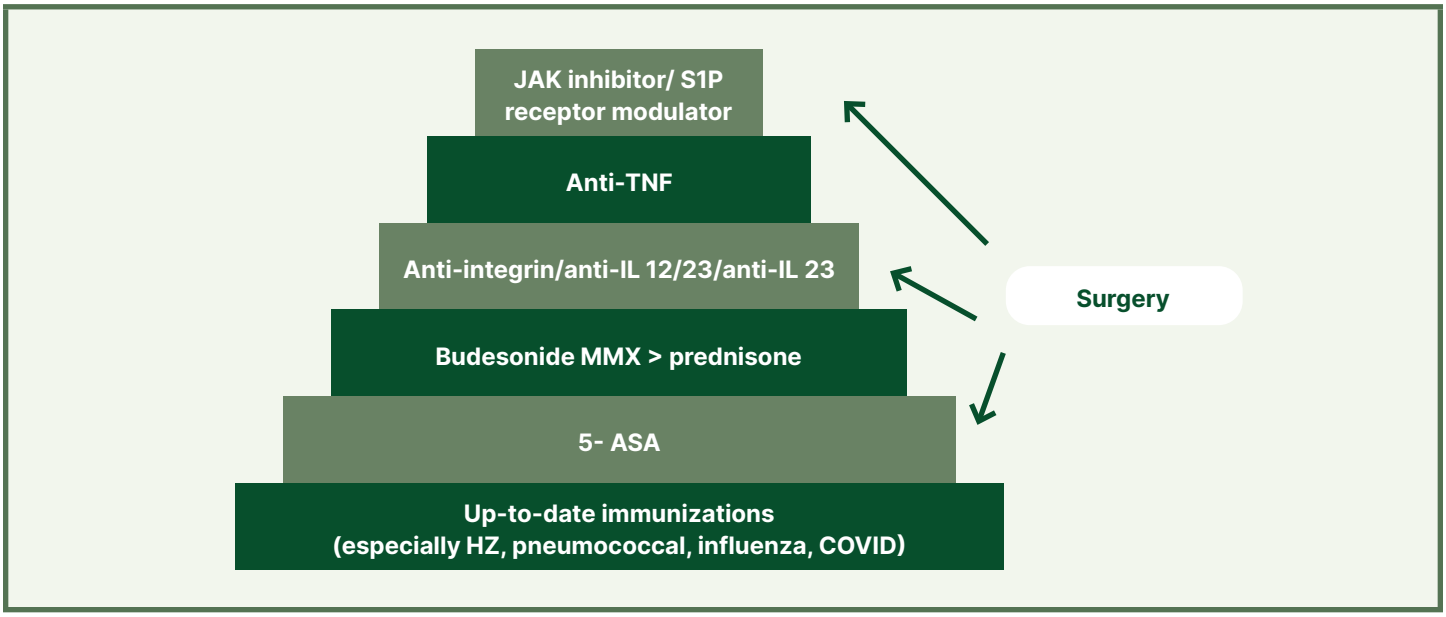

Figure 1. ELDERLY UC Proposed Treatment Algorithm; courtesy of Farhad Peerani, MD
JAK, Janus kinase; S1P, sphingosine 1-phosphate; TNF, tumour necrosis factor; IL, interleukin; MMX, multimatrix; ASA, aminosalicylate; HZ, herpes zoster

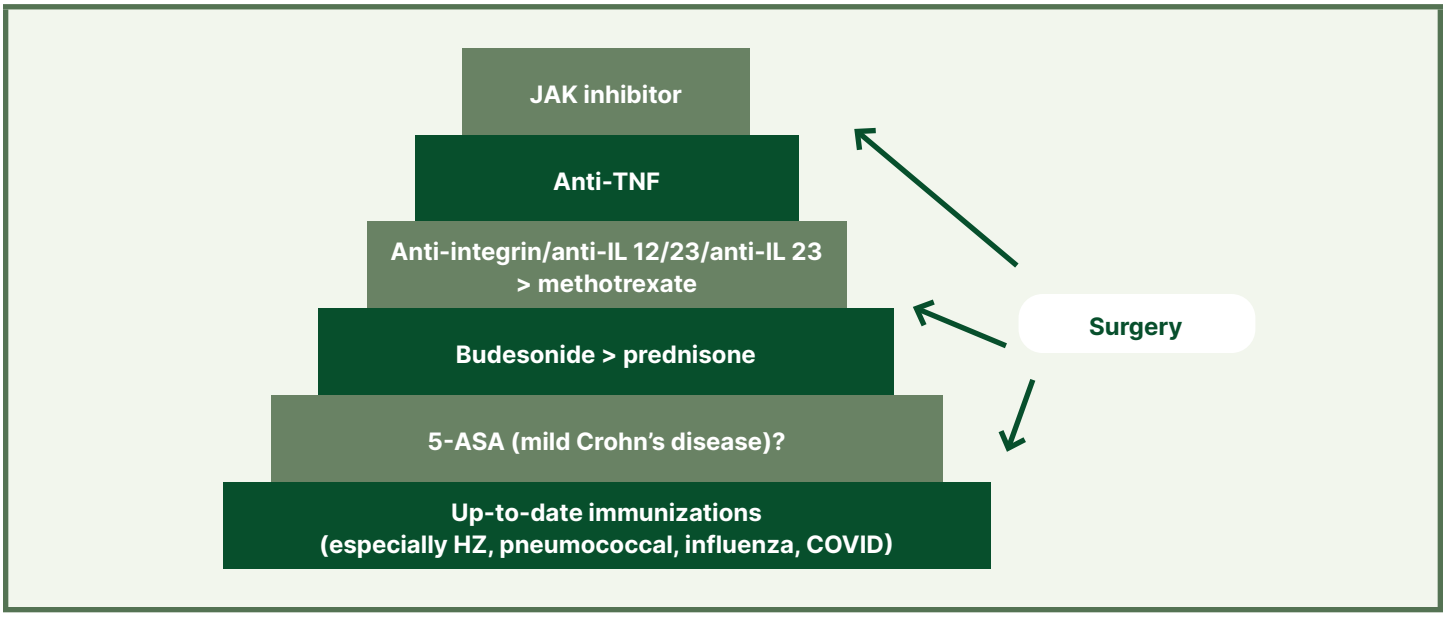

Figure 2. ELDERLY CD Proposed Treatment Algorithm; courtesy of Farhad Peerani, MD
JAK, Janus kinase; TNF, tumour necrosis factor; IL, interleukin; ASA, aminosalicylate; HZ, herpes zoster

Clinical Pearls

- When considering therapy for elderly IBD patients, do not fall victim to ageism but rather assess whether your patient is “fit” vs “frail”
- Avoid initiating azathioprine in IBD patients ≥ 50 years of age
- Anti-TNF therapies are the most extensively studied advanced therapies in elderly IBD patients with a signal for increased infection and perhaps decreased efficacy, especially in elderly-onset IBD patients
- Order a baseline echocardiogram in elderly IBD patients prior to commencing anti-TNF therapy
- Consider using a lower induction dose of JAK inhibitors in those patients with a history of cardiovascular risk factors or thrombosis who are not on concomitant antiplatelet or anticoagulant therapy
- A multidisciplinary healthcare team including family physicians, IBD nurses, gastroenterologists, colorectal surgeons, dieticians, pharmacists, psychiatrists, and geriatricians is ideal in providing optimal care

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