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The elderly IBD patient in the modern era: changing paradigms in risk stratification and therapeutic management

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***Abstract*:** The incidence and prevalence of inflammatory bowel disease (IBD) is rising in the elderly population. Compared with patients with onset during their younger years, patients with elderly onset IBD have a distinct clinical presentation, disease phenotype, and natural history. Genetics contribute less to pathogenesis of disease, whereas biological changes associated with aging including immunosenescence, dysbiosis, and frailty have a greater impact on disease outcomes. With the advent of an increasingly wider array of biologic and small-molecule therapeutic options, data regarding efficacy and safety of these agents in elderly IBD patients specifically are paramount, given the unique characteristics of this population.

Keywords: COVID-19, Crohn's disease, elderly, frailty, inflammatory bowel disease, phenotype, treatment, ulcerative colitis

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Introduction

Inflammatory bowel diseases (IBDs), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory disorders of the gastrointestinal tract which result from an inappropriate immune response to environmental factors and an altered gut microbiome in genetically predisposed individuals.[1] IBD affects 6.8 million people worldwide and has a bimodal distribution, with a peak age onset of IBD at 30–40 years, and a second peak at 60–70 years.[2–5]

Approximately 15% of IBD cases are diagnosed after the age of 65 and up to 30% of the IBD population is currently above age 60, which indicates that the elderly IBD population is sizable.[6,7] Furthermore, the prevalence of IBD in the elderly is increasing, with 214 per 100,000 CD and 315 per 100,000 UC patients greater than age 60 in the US.[8] Notably, 25% of IBD healthcare costs are accounted for by 15% of IBD patients diagnosed after age 60, which reflects a disproportionate use of resources in this group.[9,10] Given the rising burden of illness in IBD in the elderly, it is becoming increasingly important to accurately characterize the unique traits of this population.

In the medical literature, definition of older age in the IBD population varies from age 55 to 70. However, in a recent topical review of IBD in the elderly, the European Crohn's and Colitis Organization established 60 years as the most widely accepted definition of elderly onset IBD.[11] In recent years, large population-based epidemiologic studies have sought to better characterize the phenotypic differences of this particular subgroup of IBD patients. The focus of this review is to provide an update on disease characterization, risk assessment and therapeutic management of elderly IBD patients.

Section I: updates in disease characterization and risk stratification of the elderly IBD patient

Overview

There is increasing recognition of IBD diagnosed at an elderly age, or elderly onset IBD, as a

Figure 1. Factors unique to elderly onset IBD when characterizing disease and risk.
CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

distinct phenotype from IBD in elderly patients with disease onset during adulthood.[7] This section will highlight the distinction between these two groups in regard to differences in disease presentation, natural history, and unique biologic traits, all of which impact the assessment and risk stratification of the elderly IBD patient (see Figure 1).

Distinct disease phenotype and natural history

Elderly onset IBD has a distinct phenotype and disease presentation compared with elderly patients with adult-onset disease, which is discussed below and summarized in Table 1. Overall, based on European and Asian population-based cohorts, UC is more common than CD in elderly onset IBD, with the proportion of patients with UC ranging from 53% to 79% compared with 21% to 47% with CD.[10,12–14]

Elderly onset UC is characterized by differences in disease extent and behavior. In the French-based EPIMAD (Registre Epidemiologique des Maladies de l'Appareil Digestif) registry, 45% of elderly onset UC patients had left-sided UC compared with 29% with proctitis, and 26% with extensive colitis.[15] In a population-based study from Sweden, UC was more commonly left sided in elderly onset (age >60) than the adult population (28% *versus* 15%), and less commonly, proctitis (14% *versus* 23%) or extensive disease (28% *versus* 34%). Similar findings have been reported in other large cohorts from Italy and western Hungary.[13,16,17]

Conversely, as the incidence of IBD has risen in non-western regions such as East Asia, differing phenotypic patterns have begun to emerge. In a population-based study from South Korea, 62% of elderly onset UC patients had proctitis, with left-sided and extensive colitis only accounting for 22% each.[18] Similarly, in a population-based study from Hong Kong, 37% of elderly onset UC patients had proctitis, followed by 32% with left sided, and 31% with pan-colitis.[14]

In elderly onset UC, the extent of disease is relatively stable, and disease extension is rare in elderly onset patients, occurring in only 9–22% of patients in both western European and East Asian cohorts.[10,13,14] In regards to presenting symptoms, elderly patients with UC generally have less rectal bleeding, abdominal pain, or systemic signs of fever and weight loss, and more often have varying patterns of defecation or even constipation.[10,17,19]

Elderly onset CD is characterized by a predominance of pure colonic disease, whereas ileocolonic disease predominates in younger patients in western populations. In the aforementioned EPIMAD registry, 65% of elderly patients had colonic disease, in contrast to 25% and 10% with ileocolonic or ileal disease, respectively.[10] In contrast, in the Hong Kong cohort, 39% of elderly onset CD patients had ileocolonic disease, followed by 31% with ileal and 30% with colonic disease.[14] In all studied populations, disease behavior tends to be predominantly inflammatory, with 64–78% of elderly onset CD patients presenting with non-stricturing, non-penetrating (Montreal classification B1) disease.[10,14] Compared with adult-onset patients, elderly patients have lower rates of penetrating (Montreal classification B3) (12% *versus* 19%) and perianal (17 *versus* 23%) disease.[12] Data on rates of stricturing disease are mixed, with some studies reporting an increased rate of stricturing (Montreal classification B2) disease in both western (24% *versus* 13%) and Asian populations (31% *versus* 21%), while others report a decreased rate (33% *versus* 61%).[10,12,14,20] Similar to UC, change in disease distribution is rare in CD, with a stable location over time reported in 92% of patients.[10,15] Disease behavior also remains stable,

Table 1. Differences in disease phenotype and presentation in elderly *versus* adult-onset IBD patients.

	Elderly onset IBD	Adult-onset IBD
Ulcerative colitis		
Presentation	Less rectal bleeding, abdominal pain More constipation	More rectal bleeding, abdominal pain, systemic signs
Extent	More left-sided in western populations More proctitis in East Asian populations	More extensive or pan-colitis
Progression	Less disease extension	More disease extension
Crohn's disease		
Presentation	More rectal bleeding	More abdominal pain and non-bloody diarrhea
Extent	More colonic disease in western populations More ileocolonic disease in East Asian populations	More ileal disease
Behavior	Less fistulizing or perianal disease ± more stricturing disease	More fistulizing or perianal disease ± more stricturing disease
Progression	Less disease extension or progression	More disease extension or progression
Both UC and CD		
Extra-intestinal manifestations	Less common overall More arthritis	More common overall

CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

with only 9% of patients progressing from B1 to B2 or B3 disease.[10] Lastly, elderly CD patients have more rectal bleeding, and less diarrhea and abdominal pain than younger patients.[10]

Extra-intestinal manifestations (EIMs) are slightly less common in elderly onset IBD. The EPIMAD registry reported an EIM prevalence of 3% in the elderly population compared with 5% in the adult population ($p < 0.05$), while the GETECCU study reported a numerical difference of 12% *versus* 14%.[10,12,15] Arthritis is the only EIM that is more common in adult-onset patients (8% *versus* 6%, $p < 0.001$).[12,16]

Unique biology of the elderly: genetics, immunophysiology and microbiome

IBD is driven by an inappropriate immune reaction to environmental factors in genetically susceptible individuals.[21] In patients with elderly onset IBD, however, genetics appear to have a less important role. A family history of IBD is reported in only 7% of elderly onset CD and 3% of elderly onset UC patients, compared with 14% and 7% of patients with adult-onset CD and UC, respectively.[10] While several genetic mutations have been identified establishing the relationship between susceptibility genes and an earlier age of onset in pediatric-onset IBD, such as NOD2, POUF5F1, TNFSF15, and HLA DRB *501, no genetic mutations have yet been identified that are correlated with an older age of onset in elderly IBD.[22]

In contrast to decreased genetic susceptibility, there is increased understanding that aging is associated with declines in physiologic function over time and may increase the risk of IBD. These pathophysiologic alterations include cellular senescence, progenitor cell dysfunction and chronic inflammation.[23] Aging-related immunosenescence is the result of a decrease in hematopoiesis which leads to impaired innate and adaptive immune systems. The subsequent impairment in T- and B-cell responses promotes an aberrant immune response to environmental antigens, and can promote the development of IBD.[24] Aging is also associated with a chronic state of increased low-grade inflammation due to an increase of pro-inflammatory cytokines.[23,25,26]

Increasing age is also associated with decreased microbial diversity and an increase in facultative and obligate anaerobes in the gut.[27] This is thought to be related to physiologic changes of aging that include prolonged transit time, decreased intestinal motility, fecal retention, along with an increased use of laxatives and antibiotics, and a decrease in fiber intake.[28] In the elderly, there is a decrease in the diversity and abundance of obligate anaerobes such as bifidobacteria, and an increase in facultative anaerobes such as enterobacteria, streptococci and staphylococci, which have been associated with IBD.[29,30]

Risk of surgery

Despite elderly onset IBD presenting with a less extensive or aggressive phenotype than adult-onset IBD, its disease course is not necessarily more benign. In Everhov *et al.*'s work,[16] 22% of elderly onset CD patients underwent surgery by 5 years, although the rate was lower in UC patients (6%). Similarly, the cumulative probability of surgery at 10 years was 32% in CD patients compared with 8% in UC in another population-based study.[10]

Data regarding the risk of surgery in elderly onset IBD compared with that of younger counterparts are conflicting. A large population-based study showed an increased risk of surgery [adjusted hazard ratio (HR) 1.34, 95% confidence interval (CI) 1.16–1.55] in patients with elderly onset UC (⩾65 years) compared with young adults (age 18–40),[31] and a recent systematic review and meta-analysis similarly reported an increased risk of surgery in patients with UC onset at age ⩾50 [odds ratio (OR) 1.36, 95% CI 1.18–1.57] when compared with onset of disease below age 50.[32] In contrast, a Dutch population-based study found no differences in risk for surgery for elderly onset UC (HR 0.88, 95% CI 0.53–1.46), and in the South-Korean-based cohort, elderly onset UC was not a significant predictor of colectomy (HR 0.88, 95% CI 0.20–3.8).[7,18]

In CD, rates of surgery are similar when comparing adult- *versus* elderly onset IBD patients. The risk of surgery in elderly CD patients was not increased in the aforementioned meta-analysis (OR 0.70, 95% CI 0.40–1.22) or Dutch study (HR 1.19, 95% CI 0.85–1.67).[7,32] A large multicenter study in the US found no differences in rates of surgery among different age groups, and a meta-analysis comprising 9 studies with 14,765 patients found similar rates of surgery between elderly and adult-onset CD.[33,34]

It is unclear if the varying risks of surgery in elderly IBD patients are related to differences in natural disease course or therapeutic management. Elderly patients with IBD are less likely than younger patients to receive immunosuppression, which may lead to more uncontrolled disease.[32,34] One earlier population-based study found that long-term thiopurine use of more than 12 months in elderly onset UC was associated with a 70% reduction in risk of colectomy.[35] Alternatively, earlier elective surgical intervention may be preferentially pursued to avoid the side effects of long-term medical therapy. This is supported by one retrospective analysis in which elective colectomy provided a survival benefit over medical therapy in UC patients older than 50, although the authors did not identify a specific reason for the improvement in mortality risk.[36]

Fit versus *frail: the new risk assessment*

Frailty is an emerging metric that is increasingly recognized as an important predictor of outcomes. It is defined as a state of increased vulnerability due to an erosion of homeostatic reserve that often follows an acute stressor. Frailty represents a state of accelerated functional decline, in contrast to the gradual decline of physiologic reserve seen with normal aging.[37] Multiple interrelated physiological systems including the brain, endocrine system, immune system, and skeletal muscle can have a marked decline in function, adaptive capacity, and resiliency.[37,38] The gut microbiome specifically in the frail elderly has been found to have a 26-fold decrease in lactobacilli and a 7-fold increase in enterobacteriaceae compared with healthy elderly without frailty.[39]

Frailty is an often neglected part of the routine assessment of IBD patients, which may be underdiagnosed in a considerable proportion of elderly IBD patients.[40] One cohort study of 135 IBD patients aged ⩾65 found that 23–44% had increased vulnerability and impairment on frailty testing.[41] Frailty is associated with increased morbidity, septic complications and cardiopulmonary complications in patients undergoing colectomies for UC.[42] In a recent study by Qian *et al.*[43] using a nationwide claims database of 47,402 patients with IBD, frailty was independently associated

with a 57% higher risk of mortality, 21% higher risk of all-cause re-admission and 22% higher risk of re-admission for severe IBD. Frailty is also associated with increased infections in elderly IBD patients on tumor-necrosis-factor antagonists [anti-TNF; adjusted OR (aOR) 2.05, 95% CI 1.07–3.93] and immunomodulators (aOR 1.81, 95% CI 1.22–2.70), as well as an overall increased mortality (aOR 2.90, 95% CI 2.29–3.68).[44,45]

Assessment of frailty is now recommended as part of the standard preoperative evaluation of geriatric patients.[46] Once identified, interventions such as prehabilitation and interdisciplinary geriatric co-management may improve surgical outcomes in high risk patients.[38] Structured multi-component exercise programs should be done for at least 4 weeks prior to surgery for optimal benefits.[47,48] In patients undergoing colorectal surgery, the use of prehabilitation is associated with improved walking distance and a significant improvement in physical fitness in 60% of patients, compared with 21% in patients who do not undergo prehabilitation.[49] Further studies are required to identify the optimal frailty assessment tools and intervention strategies in IBD patients when assessing risks of therapeutic agents and surgical interventions.

Emerging health crises: COVID-19 and the elderly IBD patient

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a novel virus which emerged in late 2019 in Wuhan, China, and quickly spread to become the deadly global pandemic known as coronavirus disease 2019 (COVID-19). The mortality of COVID-19 in older patients is remarkably high, with 80% of deaths in the US occurring in patients age 65 or older.[50] An early analysis of 72,314 cases in China revealed an overall case fatality rate of 2.3% for all adults, compared with 8% in patients aged 70–79 years and 14.5% in those older than age 80.[51]

Given the increased mortality associated with higher age and the immunocompromised status of IBD patients, there is concern about the susceptibility of elderly IBD patients to COVID-19. It is known that the mechanism of cell entry for SARS-CoV-2 is *via* angiotensin-converting enzyme-2 (ACE-2) receptors which are found throughout the body.[50,52] ACE-2 receptors are found in the absorptive enterocytes of the ileum and colon and 41% of patients with COVID-19 have been found to have fecal shedding of SARS-CoV-2 with a median duration of 22 days.[53,54] Furthermore, ACE-2 receptor expression is increased in IBD patients compared with controls, suggesting that patients with IBD might be particularly susceptible to COVID-19.[55]

However, evidence thus far suggests that IBD alone does not appear to be an independent risk factor for severe COVID-19 outcomes.[56] Furthermore, advanced age did not increase the risk of contracting COVID-19 in IBD patients, based on a nationwide Veterans Administration cohort study of 37,857 patients.[57] However, in IBD patients who do develop COVID-19, increasing age and increasing number of co-morbidities were associated with more severe outcomes (defined as intensive care unit admission, ventilator use, and death) in the international SECURE-IBD registry.[58]

Immunosuppressive therapies in IBD patients with COVID-19 are a source of concern, given their effect inhibiting intracellular signaling cascades needed to fight infections.[55] In studies thus far, corticosteroids are the only IBD-related immunosuppressants consistently associated with worsened outcomes.[56,58] In contrast, anti-TNFs do not appear to increase the risk of COVID-19. A recent meta-analysis of 249,095 patients showed that IBD patients on anti-TNFs have a lower average pooled incidence of COVID-19 (0.68 per 1000) than those not on therapy (1.93 per 1000), which suggests the possibility that anti-TNF use may protect against COVID-19.[59] Furthermore, data from the SECURE-IBD registry and US-based studies report that anti-TNF use is not associated with more severe outcomes, even when adjusting for increasing age in multivariate regression modeling.[58–60] The COVID-19 pandemic has highlighted the need for early assessment, collaborative research, and appropriate responses to increasingly prevalent zoonotic illnesses and global health crises, especially when caring for immunologically vulnerable populations such as elderly patients with IBD.[61]

Section II: updates in therapeutic management of the elderly IBD patient

Overview

The last 2 decades have seen a rapid expansion in the therapeutic armamentarium for IBD, with

approval of several new biologic and small-molecule therapies. Despite these advances, little is known about the effect of these drugs in the elderly IBD patient. One retrospective study of 356 patients found that elderly onset IBD patients had a higher risk of treatment-related complications compared with adult-onset elderly patients.[20] Important physiologic changes in the elderly may alter the pharmacokinetics and metabolism of drugs, including a reduced glomerular filtration rate, increased body fat, decrease in lean muscle mass, and a decrease in total body water.[26,62] An increased risk of polypharmacy and medication interactions among elderly patients with IBD may combine to impact the efficacy and side-effect profile of therapies for IBD.[63] Furthermore, data regarding efficacy and safety of biologic therapies on the elderly are limited, as large registry trials generally exclude the elderly (e.g. over 60 years). In this section, we will review the current data on efficacy and safety of therapies in elderly IBD patients, which are also summarized in Table 2.

Aminosalicylates

According to current US society guidelines, aminosalicylates (5-ASAs) are recommended as maintenance therapy in mild-to-moderate UC, with biologic therapy preferred in moderate-to-severe disease.[64,65] In CD, 5-ASAs have not demonstrated effectiveness and are not generally recommended for long-term maintenance therapy, although CD patients with colitis may have some benefit from sulfasalazine.[66]

Despite these society recommendations, 70–90% of elderly patients with UC and 36–77% of those with CD are taking 5-ASAs based on population-based studies.[16,67,68] This indicates that a substantial proportion of elderly patients are treated with 5-ASA therapy, despite evidence demonstrating a lack of effectiveness in CD and risk of suboptimal treatment of moderate-to-severe UC. The persistence of 5-ASA therapy is likely driven in part by its low cost and relatively benign side-effect profile, as up to 92% of patients on 5-ASAs tolerate such therapy without adverse events necessitating drug discontinuation.[69,70]

Overall, 5-ASAs are generally safe, although common adverse events such as nausea and vomiting, headache, abdominal pain, and rash may occur.[30] 5-ASAs have been linked to interstitial nephritis in prior case series, but more recent studies suggest that renal injury in IBD patients is likely related to underlying inflammatory disease, not 5-ASA use.[71,72] The main risk of 5-ASAs may be non-adherence due to pill burden, since adherence rates are only 60–68% based on self-reporting and urinary drug-measurement studies.[73]

Corticosteroids

Corticosteroids play an important role in inducing remission, but their long-term use is limited by unfavorable side effects, which include congestive heart failure, hypertension, osteoporosis, glaucoma, diabetes, psychosis, and infection.[74] Despite these risks, elderly IBD patients are more likely to receive corticosteroids and less likely to receive immunomodulators or biologics than their younger counterparts.[16,75] In the EPIMAD registry, the cumulative probability of receiving corticosteroids over a 10-year period was 40% and 47% for UC and CD, respectively, compared with a 15% and 27% probability of receiving immunomodulators or biologics for UC or CD, respectively.[10]

The adverse risks of corticosteroids in the elderly can be substantial. In the prospective TREAT registry of 6290 patients with IBD, 0.9% patients died over a mean follow up of 5.2 years, and the predictors of mortality in multivariate logistic regression were corticosteroid use, narcotic use, and increasing age. Similarly, multivariate analysis of severe infections, which occurred in 1.7% patients, identified corticosteroid use and increasing age as significant predictors.[76] In a population-based study of 3552 elderly onset IBD patients in Quebec, CA, corticosteroids given within 45 days were associated with a 2.8-fold increased risk of serious infections compared with non-steroid users.[77] In addition to these serious outcomes, other significant adverse events associated with corticosteroids in elderly IBD patients include risk of fractures, venous thromboembolism, depression, anxiety, and sleep disturbance.[77,78] Given all of these risks, corticosteroids in the elderly should only be initiated with an appropriate 'exit strategy' that is, plan for transition to an alternate long-term maintenance therapy.

Immunomodulators

Current US society guidelines state that thiopurines (azathioprine or 6-mercaptopurine) can be used for maintenance of remission in UC or CD,[66,79] but there is a paucity of literature

Table 2. Overview of current therapeutic options: guideline recommendations, and effectiveness and safety in elderly IBD patients.

	Current guidelines	Effectiveness	Risk profile
Aminosalicylate	Recommended for maintenance therapy of mild-to-moderate UC	No data regarding differential rates of effectiveness in elderly *versus* adult patients	Risk of polypharmacy, up to 40% rates of non-adherence
	Sulfasalazine can be used for mild-to-moderate CD colitis	High rates of real-world use	Generally well tolerated but can have mild side effects Prior reports on nephrotoxicity, although recent data suggests this is related to underlying IBD
Corticosteroid	Can be used for induction of remission in UC and CD	No data regarding differential rates of effectiveness in elderly *versus* adult patients	Increased mortality
	Recommended *against* use for maintenance in UC or CD	Increased rates of real-world use compared with younger patients	Increased infections Increase in other complications (osteoporosis, fractures, VTE, diabetes, psychologic disturbance)
Thiopurines*	Recommended for maintenance therapy in moderate-to-severe UC and CD	Associated with reduced colectomy rates in elderly UC patients	Increased serious and non-serious infections Increased malignancy (NMSC, leukemia, MDS, Hodgkin's and non-Hodgkin's lymphoma) Significant drug–drug interactions (warfarin, 5-ASA, furosemide and allopurinol)
TNFα antagonist	Recommended for induction and maintenance therapy in moderate-to-severe UC and CD**	Prolonged time to effect, can take 6–12 months for maximal improvement Decreased clinical remission with increasing age	Higher rates of discontinuation in the elderly Increased infections (both severe and overall) compared with younger patients Earlier studies showed threefold increase in lymphoma, but more recent studies suggest TNFα monotherapy (without IMM) may *not* increase malignancy risk
Vedolizumab	Recommended for induction and maintenance therapy in moderate-to-severe UC and CD	Similar rates of corticosteroid-free remission, clinical, and endoscopic response at 52 weeks, as younger patients Slower onset of action than TNFα at 3 months, but similar effectiveness at 6 and 12 months	Theoretically safer due to gut-selective nature, but conflicting real-world data Possible increase in non-severe infections compared with younger patients Infection and malignancy rates numerically lower compared with TNFα
Ustekinumab	Recommended for induction and maintenance therapy in moderate-to-severe UC and CD	Lack of RCT or real-world data in the elderly	No increase in adverse events compared with placebo in meta-analysis of all RCTs (IBD and non-IBD) No data yet re: age-specific risk
Tofacitinib	Recommended for induction and maintenance therapy in moderate-to-severe UC	Lack of RCT or real-world data in the elderly	Increased risk of VTE seen in RA population, often with risk factors (cardiovascular disease, DM, CAD, older age, past history of VTE)

*6-mercaptopurine and azathioprine.
**Infliximab, adalimumab, and golimumab approved for UC, infliximab, adalimumab, and certolizumab approved for CD.
5-ASA, aminosalicylates; CAD, coronary heart disease; CD, Crohn's disease; DM, diabetes mellitus; IBD, inflammatory bowel disease; IMM, immunomodulator; MDS, myelodysplastic syndromes; NMSC, non-melanoma skin cancer; RA, rheumatoid arthritis; RCT, randomized controlled trial; TNF, tumor necrosis factor; UC, ulcerative colitis; VTE, venous thromboembolism.

regarding efficacy of thiopurines specifically in the elderly population. One population-based study of 4107 elderly onset IBD patients in the UK found that thiopurine use for more than 12 months was associated with a 70% reduction in risk of colectomy in UC patients, but not in those with CD.[35] Of note, the time period of this study was 1990–2010, when overall use of biologics in the studied population was extremely low compared with thiopurine use (1–3% *versus* 12–16%, respectively).

Despite their potential therapeutic benefit, the real-world usage of thiopurines in the elderly IBD patient remains low. Data from the French population-based cohort EPIMAD reported a 3% probability of starting thiopurine within the first year of diagnosis. Over the course of their lifetimes, only 16% of patients received immunomodulator therapy.[10,80]

These low rates of usage are largely due to concerns about the substantial side-effect profile of thiopurines. Elderly IBD patients at baseline have an increased risk of lympho- and myeloproliferative disorders compared with the general population.[81] Large prospective observational studies performed by the CESAME group demonstrated that exposure to thiopurines is associated with an increased risk of several malignancies, including non-melanoma skin cancer (NMSC), myeloid leukemia, myelodysplastic syndromes and lymphoproliferative disorders (both Hodgkin's and non-Hodgkin's lymphoma).[82–85] The risk of pancreatic cancer is also elevated (SIR 7.29, 95% CI 1.82–29.16) in elderly IBD patients with thiopurine exposure.[81] In addition to malignancy, thiopurine use is associated with increased infections. In a French nationwide study, patients exposed to thiopurine monotherapy were at increased risk for serious and opportunistic infections compared with those who were not exposed. The absolute risk of infection was 2- to 3-fold greater in patients 65 or older.[86]

Several drug–drug interactions are important to consider when using thiopurines in the elderly. Azathioprine inhibits the effects of warfarin necessitating dose uptitration.[87,88] Drugs that interfere with the metabolism of thiopurines and potentially lead to drug toxicities include sulfasalazine and its metabolite 5-ASA, furosemide, and allopurinol.[89,90]

TNF-antagonists

TNF-antagonists are recommended for moderate-to-severe UC and CD, yet data on effectiveness and safety on elderly patients in randomized control studies are limited. Therefore, the use of anti-TNF therapies in elderly IBD is guided by retrospective studies. A nested case-control from Leuven, Belgium, noted that clinical response rates were lower at 10 weeks in patients aged ≥ 60 (68% *versus* 89%, $p < 0.001$), but were not significantly different at 6 months (80% *versus* 83%, $p = 0.64$), which suggests a prolonged time to treatment effect.[91] A multicenter retrospective study by Adar *et al.*[92] reported clinical remission rates of 50% and 58% at 3 months and 12 months, respectively, in IBD patients initiated on anti-TNFs after the age of 60. Notably, in this study, the rate of clinical remission decreased with increasing age [OR 0.94 for each 1-year increase in age, (95% CI 0.89–0.99)].

While long-term remission rates appear to be similar in the elderly, rates of discontinuation are higher with 25% of patients older than 60 discontinuing anti-TNF therapy by 12 months compared with 7% of younger users.[93] In a multicenter study from Italy, anti-TNF persistence at 12 months was lower in both elderly CD and UC patients, and this remained true when analyzing each anti-TNF agent individually (i.e. infliximab, adalimumab, etc.).[94] One reason for lower treatment persistence is that infection occurs in a larger proportion of elderly patients requiring anti-TNF cessation than in younger patients.[93] Studies have reported overall infection rates from 11% to 22% in elderly IBD patients on anti-TNFs, with rates of severe infections as high as 15%.[91,93,95] Reported infection rates in elderly patients are consistently 2–4-fold higher than those in younger patients.[12,93]

The risk of malignancy is a concern for elderly IBD patients on chronic immunosuppression. Advancing age is a risk factor for lymphoproliferative diseases in IBD patients compounded by thiopurine use.[95,96] An initial meta-analysis on anti-TNF therapy found a threefold increase in the risk of lymphoma over the general population.[97] However, the majority of these patients had prior immunomodulator exposure, and more recent studies have not replicated these findings.[98–100] In the TREAT (Crohn's Therapy, Resource, Evaluation, and Assessment Tool)

Registry, the risk of lymphoma with anti-TNF monotherapy was similar to those who were anti-TNF naïve over a mean follow up of 5 years.[100] Longer-term studies are required to establish the risk of lymphoproliferative disorders in the elderly IBD population on anti-TNF monotherapy.

Vedolizumab

Vedolizumab, a monoclonal antibody directed against the integrin subunit α4β7, prevents migration of inflammatory cells into the intestinal lumen and is approved for treatment of both moderate-to-severe CD and UC.[101,102] Given its gut-selective nature, it is seen as a favorable option for elderly patients, and current evidence suggests that it is effective in this population. In *post hoc* analyses of the GEMINI 1 and 2 registry trials, vedolizumab was similarly effective across three different age groups (age ⩽35, 35–55, ⩾55), with 33% *versus* 27% *versus* 29% of CD patients and 33% *versus* 42% *versus* 39% of UC patients, respectively, achieving corticosteroid-free remission at 52 weeks.[103] A multicenter retrospective cohort study of 284 patients found that both clinical and endoscopic response rates at week 52 were similar between elderly (age 60 or older) and younger (age 40 or younger) patients, and in another real-world effectiveness study of patients with a mean age of 66 years, 60% of patients were in steroid-free remission at 52 weeks.[104,105] In the aforementioned Adar *et al.*[92] study, rates of remission were numerically higher for TNFα than vedolizumab at 3 months (38% *versus* 50%, $p = 0.07$), but were comparable at 6 months (45% *versus* 54%, $p = 0.23$) and 12 months (54% *versus* 58%, $p = 0.63$). These findings suggest a slower onset of action but an equivalent long-term effectiveness and durability of response of vedolizumab in elderly IBD patients.

The safety profile data for vedolizumab in the elderly are somewhat conflicting. In the GEMINI *post hoc* analyses, rates of malignancy and infection in the older patients (⩾55) were similar to their younger counterparts.[103] In contrast, Cohen *et al.* reported an increased risk of infections in the elderly compared with younger patients (12% *versus* 2%, $p = 0.002$). All were non-fatal infections, predominantly of the nasopharynx, urinary tract, skin and vulva or *Clostridioides difficile*.[104] In Adar *et al.*,[92] rates of significant infections were modestly lower between TNFα and vedolizumab (20% *versus* 17%), as were rates of *C. difficile* (21% *versus* 18%), but these differences were not statistically significant. Further data from long-term extension studies and real-world use are required to better elucidate the potential safety benefit of vedolizumab over other biologic agents.

Ustekinumab

Ustekinumab, a monoclonal antibody that targets the p40 subunit of interleukin (IL)-12/23, has demonstrated efficacy and safety in both UC and CD.[106,107] However, in the UNITI/IM-UNITI and UNIFI registry trials, outcomes were not stratified by age, and the study population was relatively young, with a mean age range of 37–42 years old in all treatment arms. No retrospective data exist yet for the elderly IBD population. In the psoriasis literature, two small retrospective studies (total 46 elderly patients) noted no serious infections over a follow up of 1–2 years, although dosing for psoriasis is significantly lower than that for IBD.[108,109] A recent meta-analysis of 30 ustekinumab randomized control trials (for IBD and non-IBD indications) noted no increase in serious or mild/moderate adverse events compared with placebo.[110] Although this data suggests that ustekinumab has an overall favorable safety profile, more studies are needed to determine its effectiveness and safety in elderly IBD patients.

Tofacitinib

Tofacitinib, an oral small molecule which targets the Janus kinase pathway, has shown efficacy in UC, but not CD.[111,112] The initial registry trials and subsequent *post hoc* analyses did not show an increase in venous thromboembolism (VTE) in the IBD population.[113] However, in the rheumatoid arthritis (RA) population, an increased risk of deep vein thrombosis, pulmonary embolism, and death has been identified with the 10 mg twice-daily dose in post-marketing studies.[114] Consequently, the US Food and Drug Administration drug labeling for tofacitinib now includes a boxed warning, recommending use of the lowest effective dose for the shortest duration possible.[114] This risk is generally higher in patients with baseline cardiovascular or VTE risk factors, including age ⩾50, hypertension, diabetes, current smoking status, and coronary artery disease. Given the theoretical increase in risk of VTE in the elderly IBD population who may share many

of the same co-morbidities as the RA population in post-marketing studies, it is advised that tofacitinib be used with caution in the elderly IBD population.

Emerging therapies

An in-depth discussion of emerging novel biologic and small-molecule therapies is beyond the scope of this review, but there are numerous promising therapies.[115] Based on the experience with the α4 integrin inhibitor natalizumab, and the more gut-selective α4β7 integrin inhibitor vedolizumab, emerging therapies may improve efficacy and safety. Etrolizumab blocks the β7 subunit of both α4β7 and αEβ7 integrins, blocking *both* lymphocyte recruitment and retention in the gut. Risankizumab and brazikumab selectively target IL-23 by binding the p19 subunit, in contrast to the inhibition of both Il-12 and -23 by ustekinumab. Filgotinib is an orally administered JAK inhibitor with a much higher selectivity for JAK1, compared with the 'pan-JAK' blockade of tofacitinib. Ozanimod targets a novel pathway of sphingosine-1 phosphate, a metabolite involved in pro-inflammatory cellular signaling.[115] However, future studies must consider the unique disease characteristics and risk factors of the elderly IBD population which may impact treatment outcomes and risks of adverse events.

Conclusion

Elderly onset IBD is increasing in prevalence and will account for a substantial proportion of all IBD patients in the future. The phenotypic and physiologic differences between elderly and adult-onset IBD have an important impact on therapeutic management and outcomes. Furthermore, an increasing understanding of altered biology, frailty, and surgical risk will better inform care of the elderly patient. Newer biologics have increasingly improved safety profiles, but further studies are needed to clarify these risks given the baseline increased risk of treatment-related complications in the elderly IBD population. Lastly, as both new global health challenges such as COVID-19 emerge, it is important to be aware of their unique impact on the elderly IBD population.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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