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Inflammatory Bowel Disease in the Elderly: Hazards of Generalizing the Evidence

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The prevalence of inflammatory bowel disease (IBD) in the elderly population is on the rise. Several challenges exist in managing the geriatric population with these chronic disorders. The physiology of aging affects not only disease expression, but also the treatment and surveillance strategies. Despite such considerations, which are unique to elderly IBD patients, the existing evidence for their treatment is extrapolated from studies that often suffer from a suboptimal representation of this patient subgroup. In this review, we discuss the existing evidence for IBD in the elderly and the potential hazards of its unchecked extrapolation to, arguably, a more fragile and susceptible population.

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) collectively referred to as inflammatory bowel disease (IBD), continue to pose significant challenges to the healthcare system. The latest estimates show that IBD affects approximately 1.2 million Americans.[1] Despite such extensive burden, our understanding of the pathogenesis of IBD remains incomplete; and although significant strides have been made in the field of therapies aimed at keeping the disease under control, no definite cure has yet been identified. With the advent of new therapies, the epidemiology of IBD appears to be changing; and with improved patient longevity, gastroenterologists are expected to encounter more and more elderly patients with IBD in their clinical practice. Yet, there remains a remarkable paucity of literature focusing primarily on the geriatric IBD patient population.

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Changing Epidemiology: A Function of Overall Survival, or Missing Links in Pathogenesis?

Classically, IBD has been thought to carry a bimodal distribution of incidence with a peak in the 2nd-4th decade of life, followed by a smaller second peak in the 6th- 7th decade. As the etiology of IBD is considered multifactorial involving interactions

between environmental influences, adaptive and innate immunity, and genetics; the exact reason of such bimodal distribution is unclear.[2] Current epidemiologic studies demonstrate that approximately 10-15% of the newly diagnosed IBD patients are above 60 years of age.[3]

One such study analyzing over a decade of data in the Department of Veterans Affairs suggested that the incidence of IBD has stabilized in the USA, but there appears to be an increase in the prevalence.[4] Considering IBD is a chronic disease without a significant direct mortality risk, this can be thought of a direct result of increased survival.

Such change in epidemiology of IBD has several direct and important implications that affect short and long-term management of the disease. In the age of evidence-based medicine, the older, and arguably more fragile patient population has the least amount of evidence on management of IBD.

IBD in the Elderly: Hazards of Generalizing the Evidence

Despite the rising prevalence of IBD in the geriatric population, evidence- based data specifically addressing the management of older IBD patients is scarce. The reasons for such scarcity are manifold, starting with the definition of the term "elderly". In the literature, the age cut-off for defining the elderly population has been variable, ranging most commonly from 50 to 65 years of age. Without a standardized cut-off, the generalizability of evidence remains limited.

Similarly, the current opinions on the management of such patients are derived from subgroup analyses of clinical trials involving the general population. Geriatric patients are often excluded or poorly represented in such trials. A valid statistical analysis cannot be performed of the outcomes in non-predefined subgroups. Additionally, at extremes of the age distribution curve the statistical power is expected to be quite low given the low number of the patients analyzed.

Apart from statistical considerations, applying the results of clinical trials to the geriatric population would fail to take into consideration age-related physiologic changes such as alterations in pharmacokinetics of the medications, physiology of aging, presence of comorbidities and importantly, quality of life. This article aims at exploring practical considerations and caveats in application of current management principles of IBD to the geriatric population.

IBD in the Elderly: Review of Evidence and Caveats

Despite the limitations outlined above, given the lack of data addressing exclusively the geriatric population clinical decisions are often made extrapolating the current available evidence to the elderly population. The following section reviews the available evidence and problems unique to the elderly.

a) Disease Characteristics

The disease phenotype of IBD in elderly is distinct from that in the young. Several factors may account for such difference: immune senescence, less contribution of genetic influences and possibly, altered environmental factors such as the gut microbiota. Compared to the younger patients (17-59 years old), the elderly-onset patients with CD tend to have ileocolonic or colorectal involvement, less frequent involvement of the upper gastrointestinal tract, and a less aggressive disease course with relatively lower rate of progression to stricturing or penetrating disease.[5,6] Similarly, compared to the younger patients the elderly onset UC patients tend to have more limited (proctitis or left sided) colonic disease and also seem to have a less aggressive disease course.[5,6] Such key differences in epidemiology, disease phenotype and disease progression highlight the heterogeneity of the disease among the different age groups.

b) Medical Therapy: Drug Metabolism, Eficacy and Safety Considerations

Important pharmacokinetic changes in the elderly population result from the physiology of aging. These physiologic alterations include changes in body composition such as reduced lean body mass and subsequent reduction in total body water, reduced first-pass metabolism and a reduction in renal mass and glomerular filtration rate (GFR).[6] Also, the elderly patients are frequently on a variety of other medications increasing the risk of drug-drug interactions in the setting of altered pharmacodynamics.

5-Aminosalicylic acids

Oral 5- aminosalicylic acid (5-ASA) derivatives are used in the treatment of active disease as well as for maintaining remission in CD and UC, although their therapeutic utility appears to be more evident in UC.[7,8] The safety and efficacy of the various 5-ASA formulations

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appear to be uniform across all patient populations without any significant age-related variations.[9] Older data from rheumatoid arthritis patients treated with sulfasalazine suggest that the elderly patients have higher steady-state concentration of its metabolites;[10] however has not been observed with the newer 5-ASA (mesalamine) formulations. Pharmacokinetics of 5-ASA may not be very relevant from an efficacy standpoint as most of its therapeutic effect is topical in nature and pharmacokinetic variations may be driven more by genetic influences (such as enzymatic polymorphism) rather than age.[11] Nephrotoxicity, which is perhaps the most concerning adverse effect of these compounds, occurs at an incidence of less than 1 in 500.[11] A recent retrospective study showed that there was a significant dose- and treatment duration- dependent decline in creatinine clearance (CrCl) in IBD patients treated with 5-ASA. Although the patient age at treatment onset did not significantly affect the CrCl, a pre-treatment renal dysfunction correlated with a greater decline in CrCl.[12] To conclude, ASA drugs remain a reasonable option in the armamentarium of clinicians treating geriatric IBD patients but close monitoring of renal function, particularly during the initiation of therapy and yearly thereafter is warranted considering the physiological decline in renal function in this age group.

Antibiotics

Antibiotics are frequently used to treat infectious complications of IBD such as abscesses, fistulizing CD, and pouchitis in UC. Metronidazole and ciprofloxacin have been the most studied in IBD. Their role in modifying the primary disease process is controversial although alteration of gut microbiota has been recently suggested as a putative mechanism for their actions. Metronidazole is eliminated mainly via hepatic metabolism. Data regarding the influence of age on its pharmacokinetics, derived mainly from non-IBD patient population, suggest a decreased renal excretion of metronidazole and its metabolites in the elderly,[13] although age-dependent dose adjustment is not common.

Ciprofloxacin, on the other hand, is eliminated renally. While some studies have shown an increased serum concentration, slower renal clearance, and prolonged half-life of ciprofloxacin in the elderly, recommending a dose frequency of not less than every 12 hours;[14] whereas others did not find such difference its elimination half-life, and attributed the higher serum concentration to a lower volume of distribution.[15] Considering the physiologic decline in GFR, attention should be paid to the dosage even in the absence of overt renal insufficiency given that adverse effects of quinolones such as diarrhea can often be mistaken for a flare of the underlying IBD. Additionally, older age (>60 years) and concurrent steroid use are known risk factors for tendonopathy associated with quinolones.[16]

Clostridium difficile infection remains an important risk associated with antibiotic use. Other important risk factors include older age, fluoroquinolone exposure, and immunosuppression. These place the geriatric IBD patients at a significantly higher risk of acquiring C. difficile infection which, in addition to confounding the underlying disease activity assessment, is associated with a greater morbidity, mortality, healthcare costs as well as need for colectomy.[17]

Corticosteroids

Corticosteroids have long been used to induce remission in the treatment of IBD, which is either severe or unresponsive to 5-ASA therapy. The risks associated with prolonged steroid use in general population are well known. In the geriatric population steroids have been associated with increased relative risk for developing adverse effects such as hypertension, diabetes, altered mental status as compared to younger (< 50 years old) patients.[18] Additionally the age-specific incidence rate ratio (IRR) of osteoporotic fractures is 40% higher in all IBD patients as well as the elderly subgroup (>60 years of age) compared to the age- and sex- matched general population. The incidence of fractures in IBD patients increases with age.[19] Chronic use of steroids, combined with vitamin D deficiency, which is often coexistent in IBD,[20] further increases this risk. Age related loss of muscle mass and nutritional deficiencies may also exacerbate steroid-induced myopathy in the elderly. It has been suggested that persons above the age of 65 may have increased unbound (free) fraction of prednisolone;[21] although it is not clear whether a dose reduction is necessary in the elderly patients.

Budesonide and budesonide MMX, synthetic corticosteroids that have linear pharmacokinetics, differential absorption when administered orally versus rectally, and fewer acute adverse effects;[22] is an alternative to prednisone for elderly patients. However, it should be noted that most patients included in major trials evaluating the conventional corticosteroids as

well as the formulations of budesonide were in the 3rd to 4th decade of life.[23-26] Older age and chronic steroid use have been associated as the two key risk factors for potential drug interaction.[27] As noted by Parian and Ha, a majority of late-onset IBD patients- including those in remission or those with mild disease activity- often receive chronic maintenance therapy with steroids and steroid-sparing therapies remain underused in these patients. Therefore, caution should be exercised in older patients on long-term steroids (typically, >7.5 mg per day of prednisone for > 1 month).

Appropriate screening including bone mineral density, vitamin D levels, electrolytes and blood glucose must be periodically performed; feasibility of a steroid-sparing regimen should be considered early; medications should be reviewed for potential drug-drug interactions and clinical predisposition for infections should be assessed frequently in older patients on steroid therapy.

Immunomodulators

Immunomodulators such as methotrexate (MTX), azathioprine (AZA), and 6-mercaptopurine (6-MP) are most commonly used as steroid-sparing agents or in combination therapy with biologic agents. AZA and 6-MP, the thiopurine compounds are catabolized by the enzyme thiopurine S-methyltransferase (TPMT). Patients with TPMT gene mutations and enzyme deficiency are at higher risk for developing severe hematological toxicity such as bone marrow suppression. While screening patients for TPMT deficiency prior to starting thiopurine therapy is standard of care, age-related variations in TPMT activity have been documented.[28,29] Although these findings suggest a multifactorial regulation and not necessarily only age related linear association of TPMT activity, clinicians should be aware of a potentially exaggerated myelosuppression in the elderly patients, particularly considering the physiological changes in the bone marrow activity with aging.[30]

Concern exists regarding the risk of malignancy- particularly lymphomas, melanoma and non-melanoma skin cancers in association with immunomodulator therapy. Studies have shown an increased risk of lymphoma as high as fourfold with thiopurines.[31] Of note, a German study demonstrated 18% incidence of lymphoma in IBD patients over 50 years of age, as compared to 4% incidence in those less than 50 years old, when treated with thiopurines.[32] A meta-analysis of immunomodulator use with AZA/6MP/ MTX showed a bimodal risk distribution with relative risk of lymphoma being higher in patients below 35 years of age but the highest absolute lymphoma risk with a standardized incidence ratio of 4.78 (1:354 cases per patient-year) was seen in IBD patients older than 50 compared to the younger IBD population. However these observations were not reproduced when data from a previously excluded "outlier" study were included in the analysis.[33]

With regards to skin cancer, a large population-based study showed an association between immunomodulatory use for more than 5 years and non-melanoma skin cancer [Odds ratio (OR) 1.78],[34] whereas a similar study from Olmstead County, Minnesota reported an increased risk of melanoma in patients treated with immunomodulators.[35] A meta-analysis addressing the association between non-melanoma skin cancers and thiopurine use demonstrated a modest risk (pooled adjusted hazard ratio 2.28), but this association lost statistical significance after excluding studies with a relatively short-term (< 3 years) follow-up. The authors concluded that there is not enough evidence to suggest that the cancer risk outweighs the treatment benefit with thiopurines.[36] None of these studies identified age as an independent risk modifier.

Periodic monitoring of complete blood count, liver and kidney function and skin examinations should be a part of routine surveillance of all IBD patients on immunomodulator therapy but special precautions should be taken in the elderly as they are at higher risk of the drugs adverse effects than their younger counterparts.

Biologics

The fourth major class of drugs used to treat moderate to severe IBD is biologics, either antibodies against tumor necrosis factor (TNF)-α (infliximab, adalimumab, certolizumab, golimumab), or anti-integrins (natalizumab and vedolizumab). These agents have been shown to induce and maintain remission, improve quality of life, and reduce hospitalizations for IBD patients.[37,38]

An analysis of IBD patients >65 years of age treated with TNF-α inhibitors demonstrated an 11% incidence of severe infections and 10% total mortality in the elderly group- as compared to 2.6% and 1% incidence of severe infections and mortality, respectively, in the younger patients.[39] Another study confirmed these results with a 3 times high risk of severe adverse events

in the >65 year old IBD patients compared to those <65 on anti-TNF therapy.[40] These findings further prompt concerns about the applicability of results of clinical trials to the geriatric population.

Older age has been shown to be a statistically significant predictor of suboptimal early response to anti-TNF therapy.[40,41] Additionally, Desai et al. noted a 70% discontinuation rate at the end of 2 years of anti-TNF therapy in patients > 60 years of age, and concluded that older age was a significant risk factor for discontinuation of this treatment.[42]

Of the two anti-integrin molecules, vedolizumab was recently approved for the treatment of moderate to severe IBD. The mean age of patients in the two phase 3 randomized trials comparing vedolizumab to placebo for CD and UC was 35-40 years.[43,44] Similarly, randomized clinical trials involving natalizumab for the treatment of CD had the mean patient age of approximately 35-40 years.[45,46] Although no age-specific differences were seen in efficacy or safety analyses in these clinical trials, surveillance strategies in patients above the age of 65 on anti-integrin therapy remain undefined as the clinical data of anti-integrin therapy in the elderly population is quite sparse.

c) Surgical Therapy: Restorative Surgery versus Permanent Ileostomy

Advanced age is a significant risk factor and predictor of outcomes for patients undergoing surgery for IBD. Advanced patient age is associated with a longer operating room time, longer length of hospitalization and higher odds for postoperative complications.[47] Ileo-pouch anal anastomosis (IPAA), being a more complex procedure was traditionally reserved for "younger" patients with IBD. In a population-based study of veterans above 50 years of age with UC, Longo et al. noted that 64% of the patients underwent proctocolectomy and permanent ileostomy.[48] However, a recent systematic review evaluating medical and surgical complications in IBD patients observed encouraging outcomes after IPAA in the elderly population. Neither was there an increase in mortality in the IPAA group compared to total proctocolectomy group regardless of age, nor an association between age and IPAA failure rates seen. The functional outcomes were also comparable between the older and younger patients with no difference in daytime functional impairment. However, an increased incidence of post-IPAA nocturnal bowel incontinence was noted in the elderly group, as well as an association between age and nocturnal bowel movements.[49] From the patient perspective, however, 89-100% reported that they would undergo their surgery again, and 93-100% reported that they would recommend it to others.[50]

d) Colorectal Cancer Screening/Surveillance

While the IBD population is at a higher risk for developing colorectal cancer (CRC), the exact magnitude of this relationship is not clear. A meta-analysis from 2001 showed an increased risk for developing CRC in UC patients- 2% by 10 years, 8% by 20 and 18% by 30 years.[51] In contrast, more recent data have suggested a progressive reduction in the excess CRC risk in IBD patients and that the disease extent and duration are important risk factors for developing CRC.[52] In a case-control study, the histological inflammation score was the only significant determinant of CRC risk.[53] Taken together, the risk of CRC in IBD patients has reduced in magnitude but remains present as long as the patients are not in histological remission. Therefore, elderly patients- particularly the early-onset subgroup- will still carry a higher risk of progression to CRC, unless complete histological remission is achieved. This brings forward the issue of screening and surveillance strategies in the elderly subgroup. The current guidelines do not specify an upper age cutoff for endoscopic screening and surveillance in the IBD population. In general population, colonoscopy in the elderly has been shown to be associated with a lower rate of procedure completion,[54] a higher likelihood of suboptimal bowel preparation,[55] and an incremental risk of perforation with increasing age and comorbidities.[56]

Although the risk of neoplasia increases with age, overall life expectancy decreases. A study showed that the mean extension of life expectancy in the patients undergoing routine screening colonoscopy was 0.17 years in the healthy population between the age 75-79, and 0.13 years in those older than 80 years of age; as compared to 0.85 years in those between 50-54 years of age, respectively.[57] However, data addressing this issue specifically in the IBD are lacking, and decisions regarding surveillance need to be individualized.

CONCLUSION

The growth of the elderly IBD population in the upcoming decades will bring on a unique set of management challenges. Studies evaluating this population are disproportionally low as clinical trials often exclude this population. Thus, extrapolating the

efficacy and risk data from the younger population may not always accurately describe the effects that we need to take into account for the geriatric population. Specifically, changes in metabolism and potentially poorer response to medications, increased risk of infections, and lack of specific guidelines such as colorectal cancer surveillance for this population contributes to this challenge. At this time providers should take into account not just physiologic age but also comorbidities to individualize potential risks and create a treatment plan that provides optimal benefit for the elderly IBD population. ■

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