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REVIEW ARTICLE

Medical and surgical therapy of inflammatory bowel disease in the elderly — Prospects and complications

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Abstract

Population ageing is a global phenomenon. People aged 65 years and older comprise approximately 16% of the population of Europe. The medical management of elderly patients with inflammatory bowel disease (IBD) is challenging with respect to diagnosis, pharmaceutical and surgical treatment, and complications. IBD has a late onset in 10%–15% of patients, with the first flare occurring at 60 to 70 years of age; others suffer from the disease for several decades. Even though the natural course of the disease in geriatric populations and the diagnostic options may not differ much from those in younger patients, distinct problems exist in the choice of medical therapy. Recommended clinical practise has been rapidly evolving towards an intensified initial treatment in IBD. However, in patients older than 65 years, a gentler approach should be used, and a combination of immunosuppressive agents should be avoided because of increased risk of infectious and neoplastic complications. Furthermore, elderly patients with severe IBD show prolonged, complicated post-operative clinical courses with worse hospital outcomes, so early surgical intervention for elderly patients is recommended. This article provides an overview of elderly IBD patient care, including medical and surgical therapeutic considerations and emphasises the necessity of close collaborations between gastroenterologists and surgeons.

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Contents

1. Introduction

There is increasing awareness that clinical aspects of many gastroenterological diseases, as well as any corresponding therapeutic approaches, significantly change with ageing. Patients with inflammatory bowel disease (IBD) that has presented later in life and patients who have suffered from IBD for multiple decades both require notably different clinical and pharmaceutical management than younger patients. Elderly IBD patients with co-morbidities are a rapidly growing population at risk of drug interactions and of fragmentation of patient care between different medical disciplines. Unfortunately, there is no consensus about the definition of 'elderly'. In several publications, the term was arbitrarily assigned to patient groups between 40 and 75 years of age.[1–3] More recently, an age over 60 years has been considered elderly, but differentiation of the 'fit elderly' from the 'frail elderly', as proposed in a review by Katz and Feldstein,[4] may help to properly select patients for more aggressive therapy.

In our tertiary referral centre, 15.1% of 1202 patients treated for IBD have been 60 years or older (Fig. 1). The true incidence of IBD in the elderly is difficult to assess because of population differences, case definitions, and potential misdiagnoses in patients with ischaemic colitis or non-steroidal anti-inflammatory drug induced colitis. Population-based studies indicate that approximately 10%–15% of patients are older than 60 years at diagnosis of IBD, with an equal distribution between Crohn's disease (CD)[5] and ulcerative

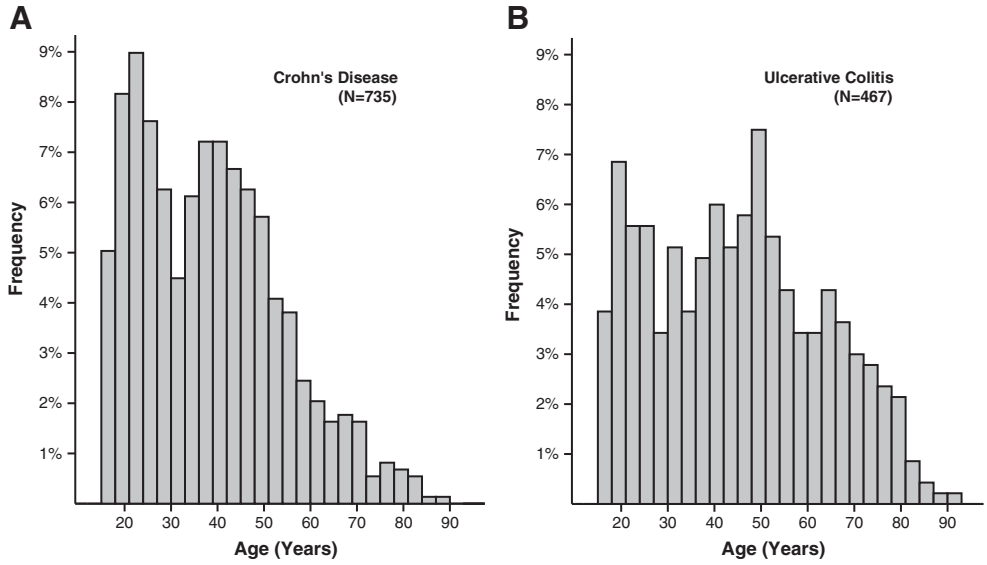

Figure 1 Age distribution of patients treated for IBD in a tertiary care centre. Age at last visit of 1202 patients treated for (A) Crohn's disease and (B) ulcerative colitis in our centre, demonstrating that 15% of the patients are ≥60 years old.

colitis (UC).[6] Recent annual incidence rates of IBD in patients ≥60 years are 6–12 per 100,000 person-years for CD and 4–17 per 100,000 person-years for UC, according to North American population-based studies.[7,8] The classical view on IBD proposed a bimodal age distribution, with an initial peak between 20 and 30 years and a second peak between 50 and 80 years. Epidemiological studies from Germany indicate, however, that the incidence of UC peaks between the ages of 16 and 25, with slowly declining incidence rates in the years thereafter.[9] Population-based studies from northern France[10] and[5] Sweden support these findings.

Unfortunately, few data are available that directly compare treatment efficacy in younger and older patients. So far, it is not known whether IBD treatment strategies, such as induction of remission, may be directly transferable to the care of elderly patients. Moreover, the safety and effectiveness of drugs used to treat IBD patients has not been extensively studied in this patient group. To meet the challenge of caring for a growing group of elderly patients, this comprehensive review will provide knowledge specific to IBD-related treatment-associated complications and limitations in the elderly population.

2. Infections in the elderly IBD patients — steroids potentiate the risk

The elderly have both an increased risk and increased severity of infection. Possible reasons include differences in epidemiology, increased concomitant morbidity, and immunosenescence, which is a state of age-related immune dysfunction.[11] Studies on healthy elderly humans have identified phenotypic and functional changes in the T cell component of adaptive immunity as an age-related alteration[12] leading to infections. Many elderly with infections present with non-specific clinical symptoms and non-specific functional decline, which complicates diagnosis and may lead to a life-threatening delay in diagnosis and therapy.[11,13]

Several studies confirm that age itself is an independent risk factor for infectious complications in IBD patients. Toruner et al.[14] demonstrated that the relative risk of acquiring an opportunistic infection was the greatest in IBD patients older than 50 years of age (Odds Ratio [OR] 3.0; 95% Confidence Interval [CI] 1.2–7.2). In another matched case–control study from the Mayo Clinic, age greater than 60 years was an independent risk factor for adverse events from biological therapy (HR 1.7; 95% CI 1.1–2.8),[15] with infections as the leading serious adverse events in the older cohort group (Fig. 2). A large retrospective analysis of IBD patients treated with infliximab (N=2475) or adalimumab (N=604) revealed that patients older than 65 years had a higher rate of severe infections (11% vs. 0.5%) and an increased mortality (10% vs. 2%) compared to patients who were treated with other drugs.[16] Three out of four deaths due to infectious complications under therapy with infliximab occur in patients older than 65 years.[17]

2.1. Immunosuppressive therapy and opportunistic infections

Immunosuppressive therapy is the leading risk factor for infectious complications in IBD patients. Immunosuppressive agents commonly used to treat IBD patients include corticosteroids, azathioprine (AZA) or 6-mercaptopurine (6-MP),

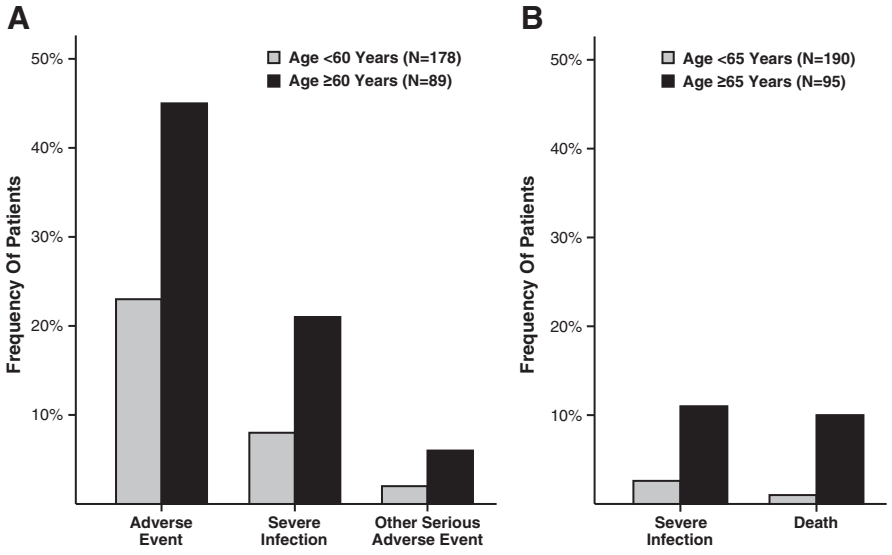

Figure 2 Frequency of adverse events in patients treated with biologicals for IBD with respect to age. The frequency of severe infections in patients treated with biologicals for IBD increases with age. (A) Frequency of adverse events, severe infections, and other serious adverse events (cancer, hepatotoxicity and liver failure, bleeding peptic ulcer, arthralgia, severe headache) in patients treated with infliximab or adalimumab for IBD with respect to age, according to a matched case–control study by Bhushan et al.[15] (B) Frequency of severe infections and death in patients treated with infliximab or adalimumab for IBD with respect to age, according to Cottone et al.[16]

methotrexate, calcineurin inhibitors (cyclosporin, tacrolimus), and biologicals such as anti TNF-α agents. Although their mode of action differs, they all compromise the patient's immune response to infectious agents. Thus, a wide spectrum of pathogens, including viral, bacterial, fungal, and protozoan organisms, has been reported in IBD patients receiving immunosuppressive therapy.[18] The relative risk for opportunistic infections is 3-fold increased (OR 2.9; 95% CI 1.5–5.3) when corticosteroids, AZA/6-MP, or infliximab is used alone. Pooled data from controlled clinical trials demonstrate that even corticosteroid mono-therapy with more than 10 mg prednisolone daily, a cumulative dose of 700 mg, or a duration of treatment of more than two weeks substantially increases the risk of infectious complications.[19] The risk, however, increases substantially when two or more drugs are used concomitantly (OR 14.5; 95% CI 4.9–43).[14] This observation was confirmed by two other studies, including the analysis of the TREAT registry, in which the risk of infectious complications was especially increased if infliximab was combined with corticosteroids.[20,21]

Several studies, case reports, and case series indicate that specific drugs seem to be associated with specific infections. Corticosteroids block neutrophil extravasation and monocyte/macrophage activation and may therefore increase the risk of infections at mucosal surfaces, such as candidiasis.[14] Thiopurines predispose patients to viral infections, including cytomegalovirus (CMV), herpes simplex virus (HSV), *Varicella zoster* virus (VZV), and Epstein–Barr virus.[22–24] Moreover, in a post-marketing surveillance over 10 years, herpetic infections were one of the leading infectious complications (23%) under infliximab therapy (data on file, Centocor, PSUR 18, October 2008).

Anti-TNF-α agents increase the risk of acquiring granulomatous infections, such as tuberculosis (TB), by 5- to 30-fold.[25] TB remains one of the most important infectious diseases worldwide. In Germany, the incidence of tuberculosis increases with age, and special caution is therefore warranted in the elderly.[26] Of importance is the fact that symptoms of fever, weight loss, and night sweats are mediated by TNF-α and may be therefore masqueraded by anti-TNF-α agents, leading to atypical presentations. Strategies to reduce the risk of TB due to TNF-α blockade emphasise the detection and treatment of latent TB infection (LTBI). The effectiveness of this strategy has been documented by the Spanish BIOBADASER registry, which showed a decline of TB infections by 78%.[27] However, in a study by Sichletidis et al., seven patients treated with TNF-α antagonists developed active TB despite correctly-performed chemoprophylaxis.[28] Therefore, it is important to note that even if chemoprophylaxis is performed correctly in patients with LTBI, they are still at risk of acquiring TB.

In addition to TB, several endemic and opportunistic infections in association with immunosuppressive therapy in IBD patients have been reported in case reports or small case series. Amongst others, local and systemic candidiasis, atypical bacterial infections, aspergillosis, coccidioidomycosis, legionellosis, cryptococcal infections, nocardiosis, toxoplasmosis, *Pneumocystis jiroveci* pneumonia, disseminated sporotrichosis, *listeriosis*, and *Histoplasma capsulatum* infections have been reported.[18] Another concern in IBD patients is the increasing incidence of *Clostridium difficile*-associated disease (CDAD).[29] Recently Schneeweiss and colleagues[30] showed that the risk of CDAD in IBD patients treated with corticosteroids was three times higher than with other immunosuppressive agents (RR 3.4; 95% CI, 1.9–6.1).

2.2. Prevention of infection

In light of the increased risk for infection and its associated mortality in immunosuppressed patients with IBD,[31] prevention rather than treatment of infection is fundamental in these patients. As outlined in a recent review by Viget et al., the preventive strategy should be based on risk identification, vaccination, and prophylactic treatment.[32] Before initiating therapy, patients have to be evaluated for LTBI (interferon gamma release assay, chest X-ray, contact with infectious patients, and travel history), hepatitis B virus (HBV), human immunodeficiency virus in a high-risk population, and history of VZV, HSV and CMV infection. Serum and urine screening studies for endemic mycoses are recommended. Furthermore, verifying vaccination status and regularly vaccinating for influenza (annually), HBV, and pneumococcal disease should be performed. Varicella vaccine should also be considered for sero-negative patients but only be administered before immunosuppression has been started, because varicella vaccine is a (attenuated) live vaccine. However, the response to vaccination, which requires intact cell-mediated immunity to drive the humoral immune response, is clearly diminished in the elderly population, especially in terms of an impaired response to influenza infection and/or immunisation to influenza,[13] and further attenuated by immunosuppressive therapy. After pneumococcal vaccination in one study, for instance, only 45% of the IBD patients on immunosuppressive combination therapy had an adequate antibody response, compared to 80% of patients not on immunosuppressive therapy.[33] Unfortunately, there are no data available concerning influenza vaccination in elderly IBD patients receiving immunosuppressive therapy. However, vaccination should be performed in the elderly because its benefits clearly outweigh the possible disadvantages. Data on chemoprophylaxis for *P. jiroveci* pneumonia in IBD patients are scarce. Extrapolating from other groups of immunocompromised patients, prophylaxis with sulfamethoxazole/trimethoprime is recommended for patients with a therapeutic regime that includes calcineurin inhibitors (cyclosporin A or tacrolimus) or a combination therapy of three immunosuppressant agents.

3. Immunosuppression and malignancies in older patients — myths and realities

3.1. The risk of lymphoma in elderly IBD patients

Because thiopurines are a well-established, effective maintenance therapy for moderate and severe CD[34] and for UC,[35] the use of azathioprine in CD has constantly increased since its first application in 1969 to a current cumulative 5-year probability of more than 50%.[36] However, thiopurine-related adverse events occur in 5% to 40% of patients,[37] which leads to therapy discontinuation in up to 26% of patients.[38]

Particular concerns exist about the carcinogenic potential of thiopurines because early studies revealed a 59-fold risk of non-Hodgkin's lymphoma (NHL) in renal transplant recipients receiving AZA.[39]

The activity and duration of the underlying disease, co-medication, age, and gender modulate the individual risk of lymphoma. Whereas patients with rheumatoid arthritis (RA) have a 2-fold increased risk of lymphoma compared to the general population,[40] most studies have failed to demonstrate such an increased risk of lymphoma in patients with IBD.[41–43] In a population-based prospective European study, the standardised incidence ratio (SIR) for lymphoproliferative disorders was 1.45 (95% CI 0.5 to 3.2) for IBD patients who had never received thiopurine or anti-TNF-α therapy.[44] According to a large Swedish population-based cohort study that followed more than 47,000 patients with IBD for up to 40 years, the risk of lymphoma in UC patients is similar to the general population (SIR=1.0; 95% CI 0.8 to 1.3), but only marginally elevated in CD (SIR=1.3; 95% CI 1.0 to 1.6).[45]

In the general population, the incidence of NHL is approximately 20 in 100,000 person-years, according to the U.S. Surveillance, Epidemiology, and End Results (SEER) cancer registry,[46] but substantially increases with age. More than 50% of patients diagnosed with NHL are older than 65 years. The use of thiopurines in IBD markedly increases the risk of lymphoma compared with the general population (SIR=4.2; 95% CI 2.1 to 7.5), as demonstrated by a meta-analysis of six cohort studies.[47] The recent prospective observational cohort study on 19,486 patients with IBD from the French CESAME group addressed this question and identified older age (HR 1.06, 95% CI 1.03 to 1.09 per 1-year increase) and longer duration of IBD (HR=1.04, 95% CI 1.00 to 1.08 per 1-year increase) as the main risk factors of developing a lymphoproliferative disorder. In a multivariate analysis, the hazard ratio for malignant lymphoma of patients who received thiopurines was 5.3 (95% CI 2.2 to 12.6).[44] This risk was further elevated for patients with a continuing combination therapy of thiopurines and anti-TNF-α therapy (SIR=6.5; 95% CI 3.5 to 11.2). Fig. 3 illustrates the reported effects of IBD, thiopurine therapy, and age on the incidence rate of malignant lymphoma.

Because life expectancy and potential benefits of treatment with AZA are greater in younger patients, the potential benefit of AZA therapy in older CD patients remains debatable. This question was assessed by Lewis and co-workers using a decision-analytic Markov model.[48] They showed that the gain of quality-adjusted life years (QALYs) decreased with age upon initiation of AZA therapy: an assumed 4-year therapy of AZA would yield an increase in 0.09 QALYs for a 15-year-old patient but only a $<$0.01 increase in QALYs for patients older than 55 years. According to this model, starting AZA at an age greater 65 years would not provide any benefit at all.

Whether a biological therapy further contributes to a significant risk of a lymphoproliferative disorder is controversial. The prospective, observational, multicentre TREAT registry failed to demonstrate an increased NHL risk for CD patients treated with infliximab compared to infliximab-naïve CD patients (RR=0.8; 95% CI=0.22–2.99).[49] According to a recent meta-analysis involving 21,178 patient-years of follow-up, patients treated with anti-TNF-α agents for CD have a 3-fold increased risk of NHL.[50] Thirteen cases of NHL were observed in patients treated with biologicals; five of them in patients older than 60 years. Almost all of the reported patients had current or prior exposure to thiopurines. When compared with CD patients taking immunomodulators alone, the rate of NHL for those exposed to anti-TNF-α agents was not statistically significant.

3.2. IBD in the elderly and cancer

Besides the risk of lymphoproliferative disorders, patients treated for CD have an overall increased risk of cancer, including of the small intestine (SIR=5.9), testes (SIR=2.4), kidneys (SIR=2.2), liver (SIR=2.1), skin (SIR=1.9), pancreas (SIR=1.8), colon (SIR=1.6), endocrine glands (SIR=1.6), and lung (SIR=1.5).[51] Compared to the general population, older

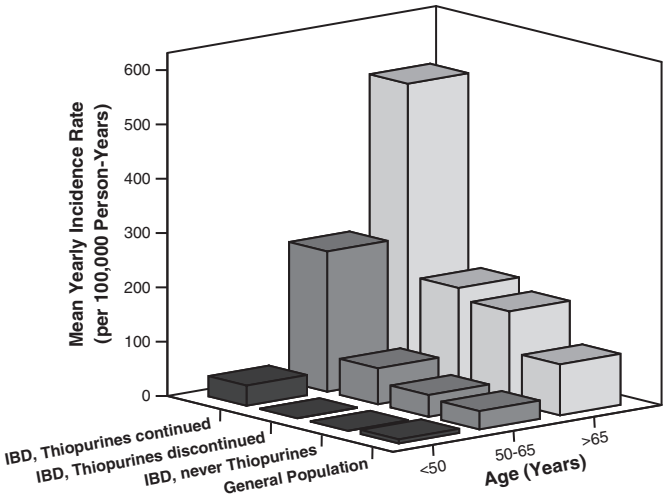

Figure 3 Incidence of lymphoma with respect to age, IBD, and immunosuppressive medication. The mean yearly incidence rates of lymphoproliferative disorders in patients with IBD increases with age and ongoing thiopurine therapy, according to data from the French Study Group CESAME.[44] For comparison, the age-dependent mean yearly incidence rates of malignant lymphoma from the US SEER cancer registry data[46] are displayed. IBD: inflammatory bowel disease.

patients diagnosed with CD at an age >64 years have increased risk for small intestine carcinoma (SIR=22.5), NHL (SIR=3.9), pancreatic cancer (SIR=3.3), cancer of the endocrine glands (SIR=2.9), kidney cancer (SIR=2.5), stomach cancer (SIR=2.0), and lung cancer (SIR=1.8),[51] but the same is not true for UC,[52] according to Swedish register data. These findings emphasise the importance of excluding a malignancy before beginning a therapy with immunosuppressants or biologicals in the elderly (see Table 1).

Colorectal cancer (CRC) occurs in 3.7% of UC patients (95% CI 3.2% to 4.2%, n=54,478) in surveillance programmes and tertiary care centres.[53] Population-based studies, however, indicate a rather low annual CRC incidence rate of 0.06% to 0.16% in UC patients.[54] The risk of colorectal carcinoma in CD and UC compared to the general population decreases with age of diagnosis, but the relative risk of colon cancer in patients diagnosed at an age >64 years is still increased in CD (SIR=2.4),[51] emphasising the necessity of endoscopic surveillance in IBD. However, this strategy has to be carefully adapted to 'frail elderly' and to patients older than 80 years considering individual co-morbidity and life expectancy.

In August 2009, the FDA began requiring stronger warnings about the possible occurrence of malignancies in patients receiving anti-TNF-α therapy.[55] In the controlled portions of clinical trials for all indications, the incidence rate of malignancies, excluding lymphoma and nonmelanoma skin cancer, in patients receiving infliximab was higher than in the control groups (520 vs. 110 per 100,000 patient-years),[56] but similar to that of the general population (RR=1.0; 95% CI 0.67 to 1.43).[57] Case series and cohort studies report overall malignancy rates between 0% and 6% in anti-TNF-α-treated patients, with a predominance of skin, breast, cancer, colorectal, prostate, and lung cancers,[58] but many trials do not provide an adjusted estimation of expected cases in the general population. Data from the TREAT registry on CD patients receiving infliximab comprising 10,796 patient-years demonstrated a malignancy rate similar to CD patients not receiving infliximab (RR=0.74; 95% CI 0.49 to 1.12), despite a higher disease activity and a higher co-medication rate of prednisone and immunosuppressants in the infliximab group.[49] Because the incidences of malignant and premalignant lesions increase with age, the ECCO evidence-based consensus on the diagnosis and management of CD is that biologicals are best avoided in patients with a history of malignancy,[59] and that a strict follow-up of premalignant lesions of the colon, bladder, and cervix is required in older patients that are under consideration of treatment with immunosuppressants and biologicals.

Table 1 Recommended examinations in older patients with IBD to rule out malignancy before starting immunosuppressants or biologics.

Procedure
Clinical examination for lymph nodes and palpable masses
Assessment of family history of cancer
Inspection for skin tumours and dermatologist consultation
Chest X-ray to rule out pulmonary and mediastinal masses
Abdominal sonography for solitary tumours
Colonoscopy for malignant and premalignant colorectal lesions
Gynaecologist consultation to rule out breast cancer and high grade cervical dysplasia (females)
Urologist consultation to rule out prostate cancer (males)

4. Surgical treatment — avoid complications, maintain function

4.1. Surgery for ulcerative colitis

The principles of surgical therapy in elderly patients do not differ from those of younger patients with UC. The dogma 'no pouch anal anastomosis in those over 50' established by some authors in the early 1990s can now be abandoned.[60] The gold standard for surgery is restorative coloproctectomy with ileal J-pouch anal anastomosis (IPAA). Depending on current medical treatment and the patient's general condition, IPAA can be performed in a two- or in a three-step technique, with total coloproctectomy, IPAA and protective ileostomy (which is closed at a second visit after 10–12 weeks), or it can be performed in an approach that includes total coloproctectomy, rectum blind closure, and terminal ileostomy, subsequent IPAA and protective ileostomy, and finally ileostomy closure 10–12 weeks later.

Since the introduction of the double-stapled anastomotic techniques, the functional outcome has improved compared to the hand-sewn IPAA initially described in 1978 by Parks.[61] In the elderly, stapled IPAA should be preferred to preserve sphincter function and improve functional outcome. Indeed, the anal transitional zone (ATZ) plays an important role in maintaining continence by probing rectal contents and discriminating between gas, liquid and solid stool.[62] The preservation of a small rectal mucosa cuff, also called a columnar cuff (1.5–2.0 cm of length in the upper anal canal), and of the ATZ (4–5 mm above the dentate line) by the double-stapled technique yields better functional outcomes, with a low risk of malignancy (<1% after 10 years) in the remaining rectal mucosa cuff.[62–64] On the other hand, several publications have shown that mucosectomy does not provide a 100% protection from anal malignancy after ileal pouch anal surgery.[63–66] This aspect should be considered in the elderly UC patient. Because of lower life expectancy, the functional outcome might be more important than the potential long-term risk of malignancy. For the same reasons, ileorectal anastomosis, which is mostly abandoned in young UC patients, still has indications in the elderly. Another option in patients with impaired continence is coloproctectomy with permanent Brooke ileostomy.[67] This procedure, which can easily be performed by laparoscopy, is a valid option for old patients with co-morbidities or with impaired sphincter function. Especially in the elderly, a well-functioning ileostomy seems to be preferable over an IPAA with poor functional outcome and incontinence.

Functional outcome after ileal anal pouch surgery has been encouraging in the elderly, provided that the patient retains preoperatively good anal sphincter function.[60,68–70] The double-stapled technique has resulted in a much better functional outcome compared to hand-sewn anastomosis in patients over 50 or 55 years.[68–71] The incidence of anastomotic leaks, pouch-related septic complications,[4] and ileal anal pouch failure rates do not differ between younger and older patients undergoing surgery for UC.[60,69,72] In small case series,[73,74] three independent factors of poor surgical outcome

in older UC patients were defined: male gender, preoperative albumin level <28 g/L, and the need for urgent surgery.

Delaney et al.[60] examined day-time stool frequency, continence, bowel movements, seepage at night, and quality of life in patients who underwent IPAA for UC or for familiar polyposis: there was no major difference in day-time and night-time stool frequency in the different age groups. Continence was better during the first 5 years in younger patients, but this advantage was lost at the 10 year follow-up. More than 89% of patients older than 65 years at the time of surgery would undergo the same surgery again, and more than 93% would recommend it to others. Thus, patient satisfaction after IPAA is high in elder UC patients and seems more important than manometric data on sphincter pressure.

4.2. Surgery for complications of crohn's disease

The necessity for surgery seems to be lower in CD patients with a higher age at the onset of disease, according to a case–control study of 132 patients[75] and a retrospective cohort study of 552 patients.[75] Possible mechanisms include less small bowel involvement and ileocaecal disease localisation in the elderly and an age-associated decline of the innate, humoral, and cell-mediated immune responses. When surgery for CD complications is necessary, it is technically not different from that in younger patients: abscesses should be evacuated, and stenoses should be resected, or strictureplasty has to be performed with the dogma of bowel-sparing surgery. However, surgery for obstruction, fistula, and bleeding has been associated with an increased risk of postoperative complications in the elderly IBD patient compared to other indications.[76] Although the risk factors for postoperative complications increase with age, age itself seems to be an independent risk factor[77] leading to an increased rate of postoperative complications, increased length of hospital stay, and increased operating room time in elderly IBD patients.[76] In elderly CD patients, recurrence after bowel resection was reportedly less common than in younger patients (43 vs. 64%), but when it occurred, the time to recurrence was significantly shorter in the elderly patients (3.7 vs. 5.8 years).[78]

Several controversial publications exist on postoperative complications in IBD patients treated preoperatively with steroids,[79–81] immunosuppressants,[82,83] or biologicals.[84–88] Whether perioperative corticosteroid or immunosuppressive treatment in IBD patients increases the postoperative complication rate is still not clear, especially in elderly patients, but it appears that in CD patients more than in UC patients, high-dose corticosteroid therapy is worse than any immunosuppressive treatment. In general, the influence of cognitive function or other conditions relating to the ability to comply with treatment should be taken into account. That is essential before making the diagnosis of corticosteroid-refractory disease.

In summary, surgical principles in elderly CD or UC patients do not differ from those in younger ones. In UC, sphincter function has to be carefully evaluated preoperatively if ileal–anal pouch surgery is intended. Hand-sewn anastomosis should be avoided in the elderly in favour of the double-stapled technique. If continence is impaired, an ileostomy will be the better alternative. Ileal–rectal anastomosis still has a place in elderly UC patients.

5. Drug interactions and side effects in the elderly IBD patient

The prevalence of comorbidity from chronic disease increases with age, which complicates the management of IBD in older people. More than 50% of older people aged 65 years or more have at least three comorbidities and a substantial portion have five or more[89] that which often remain unrecognised and untreated.[90] Since drug interactions and polypharmacy are important complications that accompany comorbidity in IBD, cardiovascular events, especially heart failure and renal insufficiency are of special interest.

As mentioned above, anti-TNF-α therapies are highly effective at reducing disease activity in IBD. As a pro-inflammatory cytokine, TNF-α is implicated in all stages of atherosclerosis including endothelial dysfunction, plaque formation and rupture and promotion of a prothrombotic state. Therefore, it has been anticipated that TNF-α blockade may reduce the cardiovascular burden in patients with IBD. However, clinical studies with anti-TNF-antagonists have disclosed the potential of aggravating severe heart failure with excess mortality in patients with heart failure and worsening of lipid profile.[91] Therefore, the use of anti-TNF-a agents in heart failure (NYHA class III and IV), a co-morbidity which often seen in the elderly IPB population, is contraindicated.[92]

There is evidence to support the use of methotrexate (MTX) in patients with IBD as a second-line treatment. However, metabolism and renal or biliary excretion of MTX may be affected by age and should be considered when using this drug. Although efficacy and the qualitative adverse event profile of MTX is equivalent in the young and elderly, a higher frequency of gastrointestinal and haematological toxicity occurs in older patients.[93] The risk of MTX toxicity is increased in patients with poor renal function as a result of drug accumulation.

To assess renal function and MTX metabolite excretion, serum creatinine is most commonly used for diagnosis despite it having several limitations in the elderly. Before starting MTX therapy in older patients, determination of the glomerular filtration rate and of urinary albumin loss may help to detect patients at increased renal risk.

Concerning the side effects of immunosuppressive agents and liability of surgical procedures in the elderly, some experts favour continuing a low dose of prednisone or budesonide in the very elderly as maintenance therapy in inflammatory disorders.[22] It should be critically remarked, that the efficacy of systemic corticosteroids in the maintenance of disease remission in CD has not been clearly demonstrated. A European study demonstrated that continuous administration of low doses of 6-methylprednisolone was beneficial in patients who responded initially to treatment of active disease.[23] Nevertheless, long-term use is more controversial because the increased risk of adverse events in low doses.

Drug interactions are defined by an increased or decreased effectiveness of one medication as a result of adding another medication. The consumption of medicines rises disproportionately with age: one-third of all medications are taken by persons above 65 years of age.[94] Thus, geriatric patients are treated on average with five pharmaceuticals,[95,96] and 25% of them regularly take more than six different medications.

The frequency of drug interactions increases with age, the degree of morbidity, and the number of medicines prescribed.[94,97] There is a 13% risk of drug interactions with two medications, 38% with four medications and 82% with seven medications.[98] If an individual patient takes eight or more medications a day, the probability of the occurrence of drug interactions is close to 100%. Furthermore, the frequency of adverse drug reactions (ADR) rises exponentially with the number of medications taken.[99] Above the age of 70 years, 56% ADR is registered, and 22% of these are caused by interactions.[100] Patients older than 65 years suffer from interaction-related ADR 4.5 times more frequently than patients younger than 65 years.[95] The high frequency of medication interactions in the elderly can be largely explained by multi-morbidity and multi-medication. Relevant age-specific changes, which contribute to the occurrence of drug interactions, are caused by reduced liver and kidney function.

Interactions of medications may occur through the influence of the pharmacokinetics and pharmacodynamics, as well as through pharmaceutical interactions and incompatibilities. Interactions pertaining to biotransformation and excretion are of special significance. Many medications are metabolised through the cytochrome P-450 isoenzyme. The following interactions are theoretically conceivable: (i) two medications are substrates of the same isoenzyme (affinity); (ii) medications inhibit an isoenzyme (degradation inhibition); (iii) medications induce an isoenzyme activity (degradation enhancement); (iv) one medication is a substrate and one is an inhibitor.[98]

Standard medication for IBD patients includes 5-aminosalicylic acid (5-ASA), corticosteroids, and thiopurines. When polymedication is employed for elderly patients, it is important to examine the medication before the start of therapy for possible interactions because they may cause serious side effects in the patients. In the literature, numerous interactions of 5-aminosalicylic acid, steroids and azathioprine are described.[101] To elucidate this problem, several particularly important examples are discussed below.

5.1. 5-Aminosalicylic Acid

Patients receiving digoxin for congestive heart failure or atrial fibrillation should be closely monitored when on concomitant medication with 5-ASA. In one study, in 2 out of 10 patients, a 40% reduced digoxin level was determined 8 h after the last dose of 5-ASA (2 g qid), presumably due to a reduced absorption of digoxin by 5-ASA.[101] Further interactions of 5-ASA may occur with the tuberculostatic drug isoniazid (INH) and the second-line anti-TB drug ethionamide. 5-ASA can reduce or diminish the acetylation of isoniazid, especially in patients with rapid acetylator phenotypes, and result in higher blood levels of the drug and thus, to an increase in toxic reactions. Patients must be monitored for the occurrence of symptoms of isoniazid toxicity (nausea, vomiting, and dizziness).[102] The simultaneous application of 5-ASA and ethionamide may cause side effects such as jaundice, hepatitis, nausea, vomiting, diarrhoea, abdominal pain, and lack of appetite. Regular liver function tests are essential in patients who receive 5-ASA and ethionamide because hepatotoxic side effects are more likely to occur, especially in the presence of diabetes mellitus. For this reason, ethionamide should be discontinued when serious side effects occur.

5.2. Thiopurines

AZA and 6-MP are pro-drugs that undergo extensive metabolism: 6-MP is metabolised by the enzymes thiopurine S-methyltransferase (TPMT), hypoxanthine guanine phosphoribosyltransferase (HPGRT), and xanthine oxidase (XO). HPGRT catalyses the metabolic steps to produce the predominantly active metabolites of thiopurine production, the 6-thioguanine nucleotides (6-TGN), but TPMT competes with HPGRT for its substrate 6-MP to produce 6-methylmercaptopurine (6-MMP), which is considered responsible for distinct side-effects of thiopurine therapy.[103] XO inactivates 6-MP to 6-thiouric acid, so its inhibition by allopurinol leads to an increase in efficacy of this immunosuppressive agent.[104] If allopurinol cannot be discontinued in a patient, the dosage of AZA should be reduced to one-third or one-quarter of the usual dose. When both agents are administered, determination of TPMT enzyme activity prior to initiating thiopurine therapy and close-meshed control of full blood count and liver function tests is recommended.[103] In patients with congestive heart failure or hypertension, the combination therapy of an ACE inhibitor and azathioprine should be avoided because the employment of ACE inhibitors in patients receiving AZA may lead to leucopenia and anaemia.[105] If the drugs must be prescribed simultaneously, monitoring for anaemia and leucopenia is necessary.[101]

Both increasing age and IBD are strong risk factors for the development of first and recurrent venous thromboembolism.[106,107] Thus, therapy with coumarin derivates, such as phenprocoumon, is often necessary. Decreased INR has been reported in a few patients following additional dosage of azathioprine during therapy with phenprocoumon. Possible mechanisms for these interactions include enhanced phenprocoumon metabolism via enzyme induction, lowered resorption of phenprocoumon and increased prothrombin synthesis. Prothrombin time or INR, as well as the clinical state of patients, should therefore be strictly controlled, if AZA is started during oral anticoagulant therapy or discontinued.[108] The same applies to warfarin.[101]

5.3. Methotrexate

Although most co-medications do not significantly affect the pharmacokinetic profile of MTX, serious toxicity may occur when it is combined with other antifolates. Similar to MTX, the inhibitor of Dehydrofolate reductase, sulfonamides and trimethoprim inhibit pathways to generate tetrahydrofolic acid that is necessary for synthesis of purines and thymidine. As a

result, the concomitant use of trimethoprim–sulfamethoxazole has been described as a risk factor for developing cytopenia in patients treated with low-dose MTX for RA.[109] Furthermore, more than 30 case reports attribute the adverse event of MTX-related cytopenia to the concomitant use of nonsteroidal anti-inflammatory drugs according to a recent systematic literature search.[110] Several pharmacokinetic and observational studies suggest an increased risk of MTX interaction with ASA in high but not in low doses.[110] Since the combination of MTX and salicylates also increases the frequency of abnormal liver function tests in a retrospective study on more than 2500 patients with RA this combination should be avoided.[111]

5.4. Corticosteroids

Metronidazole and ciprofloxacin are the most widely used antibiotics in clinical practise for the treatment of complicated CD, although their efficacy has not been convincingly demonstrated in controlled clinical trials. The simultaneous administration of quinolones and glucocorticoids, especially in older patients, harbours an increased risk of tendon ruptures, as demonstrated in post-marketing studies. For this reason, quinolones should be discontinued if pain, inflammation, or tendon ruptures occur.

Immunosuppressant therapy in the elderly is associated with an increased risk of fungal infections, as we pointed out above. When antifungal therapy is started, it is important to consider that these agents are effective cytochrome P450 3A4 inhibitors. It is assumed that they increase the plasma concentrations of glucocorticoids such as budesonide and methylprednisolone.[112] As soon as side effects caused by steroids occur or intensify, the dose of corticosteroids in patients treated with antimycotic agents should be reduced. Regular control of the pituitary–adrenocortical axis is recommended.

Similar to thiopurines, the combination of corticosteroids and anticoagulants may be accompanied by an increase or decrease in the effectiveness of the anticoagulants, and more frequent control of coagulation parameters is recommended. For patients who undergo surgery, it is important to know that several case reports have demonstrated an effect of corticosteroids antagonistic to the effect of muscle relaxants.[113–115] On the other hand, extended simultaneous administration of both medications increases the risk or the severity of myopathy and may result in a prolonged muscle-relaxing effect.[116] If muscle relaxation is necessary, the effectiveness of the muscle relaxants should be checked and the dosage accordingly adapted. This particularly applies to patients receiving high-dose corticosteroid therapy. If the therapy is continued for a longer period of time, a reduced dose of muscle relaxants should be considered.

6. Conclusions

Immunosuppressive agents carry an increased risk of infection or malignant complications in elderly IBD patients, although the degree of this effect has not yet been fully quantified for each substance. Importantly, concomitant immunosuppressive therapy increases the risk of side effects substantially, and it seems that it is the use of corticosteroids that plays the largest role in the development of serious or opportunistic infections. Steroids, TNF-α antagonists, and other immunosuppressive medications may mask the symptoms of serious infections; therefore, patients on immunosuppressive medications should be monitored for early signs and symptoms of infection. It is important to note that treatment strategies for complications in elderly IBD patients consider co-morbidity and the use of other medications. Clinical suspicion of complications in elderly IBD patients should prompt careful anamnesis and clinical investigation, hospitalisation if necessary, and diagnostic procedures without delay.

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