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PRACA POGLĄDOWA
REVIEW

Current approaches to managing inflammatory bowel disease in the elderly: A literature review

Współczesne metody leczenia nieswoistych zapaleń jelit u pacjentów w podeszłym wieku – przegląd literatury

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ABSTRACT

Older adults (i.e., aged 65 years and older) suffering from inflammatory bowel disease (IBD) are a growing group of patients. This may be attributed to the aging of the population and the rising incidence of elderly-onset (i.e., at the age of 65 years or older) IBD. Treatment of this patient population is particularly challenging due to age-related physiological changes and the high prevalence of comorbidities. The purpose of this review is to examine these additional difficulties and verify which types of drugs are best suited for therapy in elderly patients with IBD. Relevant articles were identified through a targeted search of the databases PubMed, Embase, and Scopus to evaluate the efficacy and safety profile of various therapeutic agents used in the treatment of IBD: 5-aminosalicylates (5-ASAs), corticosteroids, thiopurines, tumor necrosis factor alpha (TNF-α) inhibitors, risankizumab, ustekinumab, vedolizumab, and Janus activated kinase (JAK) inhibitors. Considering their safety and efficacy profiles, 5-ASAs, vedolizumab, and ustekinumab emerged as the most favorable options. Steroids remain essential in managing moderate to severe flare-ups. Furthermore, risankizumab shows promise as a therapeutic agent; however, additional research is necessary to thoroughly evaluate its utility. In contrast, thiopurines, TNF-α inhibitors, and JAK inhibitors exhibited less favorable outcomes in both safety and efficacy. The treatment of elderly patients with IBD must consider the physiological changes associated with aging and the high prevalence of comorbidities, which often complicate therapeutic decision-making. Appropriate selection of therapy may enhance treatment efficacy and improve patients' quality of life.

KEYWORDS

inflammatory bowel disease, Crohn's disease, ulcerative colitis, elderly, drug therapies

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STRESZCZENIE

Odsetek pacjentów w podeszłym wieku (≥ 65 lat) chorujących na nieswoiste zapalenie jelit (*inflammatory bowel disease* – IBD) systematycznie rośnie. Wynika to zarówno ze starzenia się populacji, jak i rosnącej zachorowalności na IBD w wieku podeszłym (tj. w wieku ≥ 65 lat). Leczenie tej grupy chorych jest szczególnie wymagające z powodu zmian fizjologicznych związanych z wiekiem oraz częstych chorób współistniejących. Celem przeglądu jest ocena dodatkowych wyzwań terapeutycznych u osób starszych z IBD oraz analiza skuteczności i bezpieczeństwa stosowanych obecnie leków. Przeprowadzono przegląd literatury z wykorzystaniem baz danych PubMed, Embase i Scopus w celu oceny skuteczności i profilu bezpieczeństwa różnych leków stosowanych w IBD: 5-aminosalicylanów (5-ASAs), kortykosteroidów, tiopuryn, inhibitorów czynnika martwicy nowotworów alfa (*tumor necrosis factor alpha* – TNF-α), ryzankizumabu, ustekinumabu, wedolizumabu oraz inhibitorów kinazy Janus (*Janus activated kinase* – JAK). Najbardziej korzystny profil skuteczności i bezpieczeństwa wykazały 5-ASAs, wedolizumab oraz ustekinumab. Kortykosteroidy pozostają kluczowe w leczeniu umiarkowanych i ciężkich zaostrzeń. Ryzankizumab jest obiecującym lekiem, jednak konieczne są dalsze badania nad jego przydatnością. Tiopuryny, inhibitory TNF-α oraz inhibitory JAK wykazały mniej korzystne wyniki pod względem bezpieczeństwa i skuteczności. Leczenie starszych pacjentów z IBD musi uwzględniać zmiany fizjologiczne związane z procesem starzenia się oraz wysoką częstość występowania chorób współistniejących, które często utrudniają podejmowanie decyzji terapeutycznych. Odpowiedni dobór terapii może zwiększyć skuteczność leczenia i poprawić jakość życia chorych.

SŁOWA KLUCZOWE

nieswoiste zapalenie jelit, choroba Leśniowskiego i Crohna, wrzodziejące zapalenie jelita grubego, osoby starsze, farmakoterapia

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of conditions characterized by digestive disorders and inflammation within the digestive system. It is primarily comprised of the chronic diseases ulcerative colitis (UC) and Crohn's disease (CD), with the less common IBD unclassified (IBDU) [1]. The etiology of IBD is multifactorial, involving a dynamic interplay between genetic predisposition [2], gut microbiome composition [3], and environmental factors.

A 2019 meta-analysis by Piovani et al. [4] highlighted nine key environmental risk factors that significantly contribute to IBD development: smoking (CD), urban living (CD and IBD), appendectomy (CD), tonsillectomy (CD), antibiotic exposure (IBD), oral contraceptive use, soft drink consumption (CD), vitamin D deficiency (IBD), and the presence of non-*Helicobacter pylori* enterohepatic *Helicobacter* species (IBD). Scientists remain uncertain about the pathomechanism leading to these diseases. A significant issue is the disruption of the protective barrier of the intestinal epithelium, which serves as the primary defense. It is caused by dysregulation of the immune system. This disruption is accompanied by the activation of pro-inflammatory components of the specific immune response (interleukin 12 [IL-12], interleukin 23 [IL-23]), alongside a simultaneous suppression of the anti-inflammatory effects of intercellular signaling molecules [1].

The symptoms of IBD include weight loss, rectal bleeding, anal fistulae, fever, extraintestinal manifestations, abdominal pain, anemia, and diarrhea [5]. It is notable that the symptoms of IBD in elderly-onset cases are generally milder, although rectal bleeding occurs more frequently in the population suffering from CD [6]. In elderly-onset CD, the condition typically manifests primarily as colonic disease [6].

IBD occurs more frequently in highly developed countries [7]. The peak incidence is observed between the third and fourth decades of life, with another significant increase in the sixth to seventh decades [8]. The disease presents with higher frequency in females than males [9]. Elderly individuals with IBD can be categorized into those with early-onset IBD who have reached old age (long-standing IBD) and those with late-onset IBD. With an aging population and low IBD-related mortality, the prevalence of IBD in the elderly is increasing. Aging introduces additional challenges that complicate IBD diagnosis and treatment. In older individuals, distinguishing IBD from more prevalent conditions such as colitis associated with diverticulosis, ischemic colitis, and non-steroidal anti-inflammatory drug-induced colitis becomes particularly difficult [10]. Additionally, there is limited research available regarding the treatment of elderly individuals with IBD, as clinical trials primarily recruit younger participants [11].

Given the challenges in treating elderly IBD patients, we conducted a review to compare new biological therapies. Noting the fragmented nature of existing data, we aim to evaluate and systematize available treatment options. In our study, we compare the effects of treatment with 5-aminosalicylates (5-ASAs), corticosteroids, thiopurines, tumor necrosis factor alpha (TNF-α) inhibitors, risankizumab, ustekinumab (UST), vedolizumab (VDZ), and Janus activated kinase (JAK) inhibitors in older adults.

METHODOLOGY

This literature review includes elements prepared according to the 2020 PRISMA guidelines, although it does not fulfill them completely. The primary goal was to identify drugs with favorable efficacy and safety profiles for elderly patients suffering from IBD. We searched the databases PubMed, Embase, and Scopus for articles published between January 1, 2014 and June 1, 2024 that included elderly patients suffering from IBD and treated with one of the following drugs: 5-ASAs, corticosteroids, thiopurines, TNF-α inhibitors, risankizumab, UST, VDZ, or JAK inhibitors. The search focused on studies that compared results of drug therapy in elderly and younger patient cohorts with the rates of remission, disease severity, therapy persistence, and adverse events (AEs) in order to judge the outcome. We did not include studies that did not examine elderly patients or studies that were judged to provide inadequate or insufficient methodology and analysis. The search strings are available in Appendix A.

Three authors did the search independently and compiled the studies they found. Duplicates were removed. The authors independently read the titles and abstracts during the preliminary selection; selected articles were read in full by at least two authors independently before being finally included or excluded. Necessary data was then extracted from the selected texts and compiled in a narrative and tabular synthesis.

REVIEW OF LITERATURE

5-aminosalicylates

5-ASAs, including sulfasalazine and mesalazine, continue to be the predominant pharmaceutical agents prescribed to elderly patients with IBD [12]. This class of medication remains the prevailing approach for both inducing and sustaining remission in cases of mild-to--moderate UC [13]. The precise mechanisms of action of 5-ASAs are not fully clear, though it is believed that mesalazine diminishes the synthesis of prostaglandins and leukotrienes, reducing the inflammatory response linked to the cyclooxygenase and lipoxygenase pathways. Additionally, it is suggested that 5-ASAs primarily affect the mucosa of the intestine [14].

Although current guidelines do not recommend 5-ASAs for CD management [13], clinical practice often diverges. In a cohort study of 2,980 patients across 34 sites, 19.5% of those aged ≥65 years received 5-ASAs, with elderly patients being significantly more likely to be treated than younger groups [15]. Among older UC patients, 50.2% were prescribed these agents. Similar trends were confirmed in other cohort studies [13,16]. The frequent use of 5-ASAs in elderly patients likely stems from their perceived safety compared to immunomodulators and biologics, along with the ease of oral administration [15]. When considering the form of administration, research has demonstrated that a combination of oral and topical 5-ASA therapy is more effective in UC compared to oral therapy alone. However, anorectal dysfunction commonly experienced by elderly individuals poses a limitation to this approach [16].

5-ASAs are generally safe and well-tolerated over extended periods of use in the treatment of IBD. Common AEs are typically mild and may include diarrhea, abdominal pain, nausea, headache, myalgia, and skin lesions – occurring in approximately 5%–10% of IBD patients within 1–3 weeks of initiating 5-ASA therapy [14]. Although rare, serious AEs such as fever, hepatotoxicity, pancreatitis, interstitial pneumonitis, myocarditis, pericarditis, or hemolytic anemia may occur with 5-ASA therapy [14]. Given the risk of nephrotoxicity, renal function should be assessed before and during treatment, particularly in elderly patients with chronic kidney disease [12]. Polypharmacy in elderly patients necessitates careful consideration of potential drug interactions since the relevant drugs are frequently used by the elderly. Combining 5-ASAs with thiopurines can lead to leukopenia due to increased levels of 6-thioguanine, the active metabolite of azathioprine and 6-mercaptopurine [12]. Mesalazine may enhance warfarin's anticoagulant effect [16], reduce digoxin's efficacy, and increase the serum concentrations and side effects of hydralazine and second-generation anti-tuberculosis drugs [17].

In 2024, the first genetic analysis to predict mild and severe AEs with 5-ASA therapy was conducted. Park et al. [14] identified new genetic biomarkers that predict 5-ASA-induced AEs in IBD patients in genomic-wide association study. These markers are rs12681590, rs10967320, rs78726924, and rs13898676, located near the genes *ASAP1*, *VLDLR*, *BNC2*, and *WSB2*, respectively. This discovery enhances crucial knowledge and offers opportunities to improve the efficacy and safety of 5-ASAs.

Corticosteroids

Corticosteroids were first used for IBD following a trial conducted in 1954 by Sidney Truelove, Lloyd Witts, and colleagues, which showed that 41.3% of UC patients on cortisone achieved remission after 6 weeks, compared to 15.8% on a placebo ($p < 0.001$). This established corticosteroids as the treatment of choice for moderate to severe UC and CD flare-ups [18]. Corticosteroids reduce inflammation in IBD by suppressing genes that limit lymphocyte migration to the gastrointestinal tract and inhibit pro-inflammatory cytokine secretion [19]. Contemporary guidelines emphasize the precedence of mesalazine over corticosteroids in the management of flare-ups. Oral or topical steroid administration should be reserved for cases that are refractory to treatment, exhibit allergic reactions, or demonstrate intolerance to mesalazine [18].

Corticosteroid therapy in elderly patients requires an "exit strategy" due to potential AEs [20], though clinical practice often deviates. A 2023 Indian cohort study showed similar corticosteroid use in adult and elderly-onset IBD [21], a pattern confirmed by a Danish nationwide study [22]. Additionally, elderly patients were less likely to discontinue steroids within 1 to 5 years [22].

This observation is thought-provoking given the increased susceptibility of the elderly to steroid-related AEs. Prolonged use in older patients poses higher risks of complications than in younger individuals [20]. Corticosteroid use and aging are established risk factors for severe infections [23]. A 2021 study of elderly men found that corticosteroids increased the risk of mild and severe infections, including pneumonia, compared to 5-ASA and VDZ [24]. Additionally, steroid therapy in elderly IBD patients worsened anxiety, sleep disturbances, and fatigue, and was linked to higher depressive symptoms compared to TNF-α inhibitors or immunomodulators [19]. Steroid therapy can affect glycemia, increasing the need for hypoglycemic agents, a particularly aspect important in elderly patients [18]. Moreover, prolonged corticosteroid use has been linked to an elevated risk of cardiovascular incidents, including thromboembolic events [25]. Research by Mebrahtu et al. [26] established a correlation between oral corticosteroid use in individuals with IBD and a higher incidence of hypertension across all age groups. Similarly, the findings of Segal et al. [16] indicate that corticosteroid use exacerbates hypertension, particularly in elderly patients. However, regarding cancer risk in individuals with elderly-onset IBD, a Chinese cohort study suggested that corticosteroid treatment may reduce the likelihood of disease progressing to malignancy in this population [27]. In elderly patients with IBD treated with corticosteroids, it is advisable to undergo dual-energy X-ray absorptiometry screening due to the heightened risk of osteoporotic fractures. Additionally, supplementation with calcium or vitamin D is recommended [20]. Other AEs associated with corticosteroid use in the elderly include venous thrombosis and psychiatric disorders such as depression and anxiety, as previously reported [23].

Budesonide, a newer corticosteroid, offers a safer profile than the traditional options. It is less likely to accumulate in the body, reaches deeper colonic segments, and causes less plasma cortisol suppression. Additionally, budesonide may have fewer AEs, making it a potentially better choice for elderly patients [19].

Thiopurines

Thiopurines, including azathioprine, mercaptopurine, and thioguanine, function as antimetabolites of purines [28]. These pharmacological agents were initially employed in the treatment of IBD during the 1970s. Monotherapy with thiopurines has demonstrated efficacy in sustaining clinical remission in patients with both UC and CD.

Studies on thiopurine use in elderly patients show mixed results. A 2017 cohort study found lower usage in elderly-onset CD and UC compared to other adults, though later studies both confirmed and contradicted these findings [29]. A 2020 study examined the switch to a second thiopurine in adult and elderly IBD patients previously treated with one. Elderly patients had a significantly shorter duration of exposure to the first thiopurine [30]. Of 1,278 patients, 173 (13%) were over 60, with 164 starting azathioprine and 9 mercaptopurine. Initiating mercaptopurine and advanced age were independent risk factors for AEs and intolerance to the second thiopurine. These findings had not been established in previous studies [30]. Regarding the discontinuation of thiopurines and the maintenance of remission, a 2021 study found that ceasing thiopurine treatment in elderly IBD patients who were in clinical and/or endoscopic remission led to sustained clinical remission in two thirds of the patients [31].

In terms of AEs, thiopurines are relatively safe for patients compared to therapies such as TNF-α inhibitors [32]. It is also worth noting that studies suggest thiopurines may help reduce the risk of venous thromboembolism, as in vitro findings indicate their ability to decrease platelet aggregation and inhibit platelet–leukocyte interactions [33]. Furthermore, a study conducted by Dheyriat et al. [33] demonstrated that the use of thiopurines in patients with IBD across all age groups was associated with a reduced risk of recurrent acute arterial event. The AEs of thiopurines encompass gastrointestinal toxicity, hepatotoxicity, myelotoxicity, certain types of cancer, and an increased risk of infections [27,29,30]. In the aforementioned 2020 study, the elderly patients were more likely than younger patients to discontinue thiopurine treatment due to hepatotoxicity, myelotoxicity, or gastrointestinal toxicity [30]. In contrast, the 2019 ENEIDA registry cohort found elderly patients had a higher risk of AEs, including non-infectious and non-neoplastic types [34]. AEs occurred in 43.4% of elderly patients, with thiopurine use linked to increased lymphoproliferative disorders, mainly non-Hodgkin lymphoma. The risk normalized after the cessation of treatment [32]. Thiopurine-treated elderly patients face an elevated risk of non-melanoma skin cancer, underscoring the importance of sun protection cream application and regular skin examinations as recommended preventive measures [32]. Finally, this cohort shows a higher incidence of infections due to immune response alterations from thiopurines, including primary viral infections and reactivation of latent ones. Notably, the risk of herpes zoster increases with age during thiopurine therapy, making elderly patients particularly vulnerable [32]. Preventive measures, such as herpes zoster vaccination, should be considered before starting treatment.

In general, thiopurines represent a viable option for elderly patients. However, the prescription of these medications should be accompanied by preventive measures and careful consideration.

Tumor necrosis factor α (TNF-α) inhibitors

TNF-α inhibitors (anti-TNFs) are effective agents in the treatment of IBD, although their immunosuppressive effects are also a source of AEs such as infections, skin cancer, and lymphoma [35]. This is especially concerning for elderly IBD patients as their age further increases the risk of infection and malignancies.

A study by de Jong et al. [36] compared the safety and efficacy of anti-TNF therapy in three age cohorts: <40, 40–59, and ≥60 years. Patients at least 60 years of age were defined as elderly. Of 895 IBD patients, 81 were ≥60 years old. After 6 months, drug survival was 84.3% in patients <40 years and 71.8% in those ≥60. In the <40 cohort, treatment was stopped due to a lack of effectiveness (40.5%) or AEs (27.1%), whereas in the elderly group, these reasons applied in 42.4% and 39.4% of cases, respectively. Serious infections occurred more frequently in the elderly (61.2 vs. 16.0 per 1,000 patient-years). This study shows that starting anti-TNF therapy in elderly patients is linked to higher rates of serious infections and treatment failure.

A study on anti-TNF therapy persistence and safety in IBD patients <60 and ≥60 years old included 114 elderly and 330 younger patients [37]. At 12 months, significantly fewer elderly patients had achieved corticosteroid-free remission (31% vs. 67%, $p < 0.001$). While primary non-response rates were similar, treatment discontinuation due to loss of response, AEs, infections, or tumors was more common in the elderly.

A meta-analysis conducted by Hahn et al. [38] provides dissimilar evidence. The researchers investigated the comparative safety of anti-TNF, VDZ, and UST in elderly IBD patients. Data from 12 peer-reviewed papers and 3 abstracts was included. Their analysis showed that the rates of AEs and infections were not significantly different for the biologics they examined. Infusion/injection reactions were more common for anti-TNFs ($p = 0.02$), while malignancy rates were higher for VDZ and UST ($p = 0.01$). The findings are insufficient to propose the sequencing of biologics in elderly IBD patients; however, the study does suggest that the rates of AEs and infections are comparable for anti-TNFs, VDZ, and UST.

The use of TNF-α inhibitors in elderly patients with IBD has been associated with a significantly higher risk of developing herpes zoster, as demonstrated by Santella et al. [39]. This finding is particularly concerning given the heightened severity and frequency of complications in immunocompromised individuals. Additionally, anti-TNF therapy necessitates careful monitoring of cardiac function due to potential links to heart failure, though further research is needed to establish this association conclusively [40,41]. Moreover, TNF-α inhibitors may also contribute to an increased risk of depression and anxiety, underscoring the need for comprehensive patient assessment and monitoring during treatment [42].

The anti-TNFs seem to be less effective and riskier in the treatment of IBD if the patient is elderly. However, the aforementioned meta-analysis does indicate the comparable safety profile of anti-TNFs when compared with VDZ and UST. While anti-TNFs are an effective form of treatment for patients with IBD, their efficacy and safety may be lower for the elderly population. Even though these agents may be comparable to other biologics in terms of the rates of AEs and infections, further research is warranted to estimate which type of biological drugs are most suited for elderly IBD patients.

Vedolizumab

VDZ is a humanized antibody that selectively limits the inflammation of the gastrointestinal tract by binding to α4β7 integrin, which allows memory T lymphocytes to migrate into the gut [11]. VDZ was found to be effective in treating IBD; its high selectivity to the digestive tract reduces the risk of potential AEs associated with systemic immunological suppression [43]. Treatment with VDZ only rarely causes infusion--related reactions, autoimmune reactions, or enteric infections. Moreover, it seems to not increase the risk of serious or opportunistic infections, nor malignancy in IBD patients [44].

The efficacy of VDZ was examined in a retrospective cohort study comparing steroid-free remission rates achieved with VDZ treatment during a 6–12-month period in patients <60 years and ≥60 years old [45]. The researchers enrolled 289 patients into the younger group and 279 patients into the elderly group; in total, 568 persons suffering from IBD were included, 316 of which were taking steroids when VDZ therapy was initiated. From those 316, the percentage of patients who achieved steroid-free remission and were still on VDZ during said period was 46.8% for the younger group and 40.1% for the elderly group ($p = 0.2374$). Stratifying the numbers based on IBD phenotype produced similar results. Additionally, the rates of IBD-related hospitalizations, IBD-related surgeries, and endoscopic improvement showed no significant differences between the two age groups. However, the study did find that CD patients in the older group were more likely than the younger patients to stop the treatment due to the "loss of response," with "no response" used as a reference (OR = 3.23, 95% CI = = 1.33–7.81, $p = 0.009$). The correlation was not found in patients with UC. The efficacy of VDZ treatment was comparable in both age groups. Combined with the fact that the rates of discontinuation due to AEs were low (2.5% and 2.4% for the younger and elderly groups, respectively), VDZ seems to be an effective steroid-sparing agent for elderly IBD patients.

Safety and effectiveness were also investigated in a retrospective-prospective Italian study, which examined matched groups of elderly and non-elderly IBD patients [46]. It included 198 patients ≥65 years old and 396 matched patients aged 18–64 years old. The incidence rates of AEs were comparable in both age groups, and the most common AEs were infections. Nevertheless, the researchers found that the rate

of withdrawal among elderly patients was significantly higher than that of the non-elderly (47.9% vs. 38.6%, p = 0.029). Furthermore, in UC patients, the non-elderly had significantly higher rates of clinical remission, steroid-free clinical remission, and biochemical remission. In CD patients only the biochemical remission rate was nonsignificantly higher in non-elderly patients. Contrary to the aforementioned research, this study suggests that while VDZ can be a safe treatment option for elderly IBD patients, its effectiveness may be lower when treating UC in the elderly compared to younger patients.

Another retrospective cohort study aimed to investigate the influence of patients' age on the efficacy of VDZ treatment [47]. The researchers included 144 patients aged over 60 (82 with CD and 62 with UC) and 140 patients aged under 40 years old (83 with CD and 57 with UC) – a total of 284 patients. In both the CD and UC patients, there were no significant differences in the rates of clinical response or remission between the young and the elderly. However, the multivariate analysis found that the patient's exposure to anti-TNF in the past was an independent predictor of poor treatment response to VDZ, which is especially true for the elderly.

Furthermore, data from 11 studies concerning VDZ utilization in elderly IBD patients was a subject for a meta-analysis in a systematic review from 2024 [48]. It included 3,546 IBD patients, 1,314 of which were elderly. The researchers found that the safety and effectiveness of VDZ for clinical and endoscopic remission were similar in elderly and younger populations, while the younger persons were significantly more likely to achieve steroid-free remission. Moreover, the infection rates were comparable for both age groups.

The evidence indicates that VDZ is a promising agent for treatment of elderly IBD patients, with a favorable safety profile and effectiveness.

Ustekinumab

UST is a monoclonal antibody to the p40 subunit of IL-12 and IL-23. It is an effective agent for induction and maintenance therapy for moderate-to-severe CD and UC [41,42]. UST seems to be comparably effective for elderly and non-elderly CD patients. The study conducted by Casas-Deza et al. [49] examined the efficacy and safety of UST for CD patients >60 years old compared to patients <60 years. The researchers included 212 elderly (>60 years) patients and matched each with two controls under 60 years of age, analyzing data from 648 patients in all. Rates of persistence, steroid-free remission, AEs, and severe infection showed no significant differences between the two age groups. Furthermore, the analysis showed no differences in C-reactive protein or fecal calprotectin levels depending on age. The safety of the treatment was similar for both young and elderly patients, apart from the higher risk of de novo neoplasms observed in the elderly group. The influence of UST is difficult to estimate, however, as age itself is a factor that predisposes one to oncogenesis. Additionally, a different study demonstrated that the efficacy and safety profile of UST in treating elderly CD patients was similar to that of VDZ [50].

It is also worth noting that the studies demonstrated that the use of UST is associated with a risk of infections, postoperative complications, and a higher rate of infusion reactions. However, these risks are comparable between younger and elderly patients [51,52]. Another possible, though rare AE associated with UST is depression or anxiety [42].

Risankizumab

Risankizumab is a specific IL-23p19 antagonist effective in the treatment of CD [53]. It has also been shown to be more effective than a placebo in inducing remission in UC [54]. There is a scarcity of data concerning the differences in treating elderly versus non-elderly IBD patients with risankizumab. However, the influence of age on the effectiveness and safety of risankizumab was examined for patients with plaque psoriasis; the results were comparable for younger and elderly patients [55]. The safety concerns of risankizumab therapy include malignancies, infections, myocardial infarction, thrombosis, and hypertension [56,57].

Janus activated kinase inhibitors

The family of JAK inhibitors includes tyrosine kinases such as JAK1, JAK2, JAK3, and tyrosine kinase-2 (TYK2). Their primary function is to facilitate intracellular communication between cytokine receptors and nuclear signals. It is noteworthy that numerous inflammatory cytokines are overexpressed in UC pathogenesis [58]. JAK inhibitors differ from other biologics by providing a gradual and reversible effect, making them more favorable than biologics, which induce strong, long-lasting cytokine inhibition [59]. Representatives of this group of drugs are tofacitinib, filgotinib, and upadacitinib. They differ in selectivity for the different JAK subtypes and have a quick onset of action and a very short half-life (5–6 h).

Due to the risk of severe AEs, the European Medicines Agency recommends cautious use of JAK inhibitors, particularly in individuals aged 65 years or older, those at higher cardiovascular risk, current or former long-term smokers, and those with an elevated cancer risk. They should only be used when no other alternatives are available [60]. The principal AEs of JAK inhibitors include venous thromboembolism, malignancy, and non-melanoma skin cancer [23]. There is also a significant exacerbation of dyslipidemia [61] and an increased risk of cardiovascular events, pulmonary embolism, and death associated with its use [16]. Furthermore, patients receiving treatment with JAK inhibitors are at an increased risk of herpes zoster infection, although this typically affects only one

dermatome. It is recommended that patients undergoing JAK inhibitor therapy receive vaccination, as the vaccine is inactivated [12].

Tofacitinib

Tofacitinib primarily targets the JAK1 and JAK3 enzymes. Its therapeutic efficacy extends beyond IBD, having been established in conditions such as rheumatoid arthritis, psoriatic arthritis, and polyarticular course juvenile idiopathic arthritis [62]. Tofacitinib is an oral agent. Its efficacy has been demonstrated in the treatment of UC, although it has not shown effectiveness in CD. It is typically utilized in the management of moderate to severe cases of UC. Notably, tofacitinib undergoes hepatic metabolism [61]. Studies show that tofacitinib is more effective than a placebo in all age groups. The risk of AEs increases with age [23,49]. It is also worth noting that treatment with tofacitinib carries a risk of hypertension [63].

Upadacitinib

Upadacitinib is an oral JAK1 inhibitor with a favorable safety profile, which may enhance its tolerability in patients with concomitant diseases [61]. It is used for the treatment of moderate-to-severe UC in individuals who have an inadequate response or intolerance to anti-TNF agents [55]. Uniquely, upadacitinib is effective in treating both UC and CD, unlike tofacitinib, which is limited to UC treatment [64]. The study by Sandborn et al. [65] demonstrates that upadacitinib can achieve long-term remission in CD patients who are resistant to other treatments. In clinical studies, major adverse cardiovascular events, venous thromboembolisms, and cancer were rare among patients treated with upadacitinib. However, the incidence of herpes zoster was higher than in patients receiving other JAK inhibitors [66].

Filgotinib

Filgotinib, an oral JAK1 inhibitor, is primarily eliminated through urinary excretion, necessitating caution when administering it to individuals with severe kidney disease. It has received approval for patients with moderate-to-severe active UC [67]. However, it has shown superiority over a placebo in CD and has demonstrated the ability to induce long-term remission [68]. Regarding tolerability, there is no discernible variance based on age; however, a higher incidence of AEs in elderly patients has been observed. Notably, filgotinib presents a lower risk of serious infection compared to other JAK inhibitors; nevertheless, vigilance regarding venous thromboembolism remains imperative [56,57].

CONCLUSIONS

In this review article, we discussed and juxtaposed modern medications available for the treatment of IBD, including 5-ASAs, corticosteroids, thiopurines, TNF-α inhibitors, risankizumab, UST, VDZ, and JAK inhibitors, as well as their advantages and disadvantages when used for treatment of elderly patients. Currently, there is no consensus among researchers regarding which of these treatments is most suitable for this age group. All of the examined drugs function by suppressing the immune system. In terms of administration methods, 5-ASAs, corticosteroids, thiopurines, and JAK inhibitors are administered orally, while VDZ, UST, and risankizumab are administered through parenteral routes.

With respect to safety, 5-ASAs are among the safest options, causing mostly mild AEs. VDZ is also considered safe due to its localized influence within the gastrointestinal tract. However, UST is slightly less favorable due to a potential risk of de novo neoplasms. In elderly patients, JAK inhibitors carry a higher risk of non-melanoma skin cancer, venous thromboembolism, and pulmonary embolism, while TNF-α inhibitors have been linked to an increased risk of skin cancer and lymphoma. Corticosteroids raise the risk of osteoporosis and venous thrombosis and may be more likely to lead to infection compared to the other drugs discussed. Thiopurines are distinguished by gastrointestinal, hepatic, and bone marrow toxicity, as well as higher risk of cancer. Unfortunately, limited data is available regarding the safety profile of risankizumab. Renal function should be closely monitored when administering 5-ASAs and filgotinib. Given the increased vulnerability of elderly patients to many AEs, assessing individual risk, including comorbidities and risk factors, is essential when choosing a treatment. It is also important to note that not all possible AEs were specified in this review; Table I presents selected ones. We recommend clinicians to carefully consider detailed product specifications for a complete understanding of the risks associated with particular drugs.

In terms of efficacy, 5-ASAs are well tolerated long-term in mild-to-moderate IBD. Corticosteroids should be used for moderate-to-severe flare-ups, but mesalazine is first-line mainly in mild-to-moderate UC. Medications that have shown poorer treatment outcomes in the elderly include thiopurines, TNF-α inhibitors, and JAK inhibitors. VDZ and UST have demonstrated the best efficacy in studies, showing the most promising results in the elderly, which may indicate their potential as the future of IBD treatment. VDZ may not be as effective as UST in achieving steroid-free remission; however, further research is necessary to establish which one is more favorable.

While treatment of elderly people suffering from IBD proves to be more challenging in comparison to younger patients, the development of innovative drugs and a growing understanding of the pathophysiology of these diseases opens the way to improve the situation. Further research is warranted to further refine the therapeutic options for IBD as a whole, as well for the elderly population in particular, which as of now is underrepresented in clinical trials.

Table I. Health risks associated with inflammatory bowel disease drugs in the elderly

Elderly-related disease	Drug							
	5-ASAs	Cortico-steroids	Thiopurines	TNF-α inhibitor	VDZ	UST	Risanki-zumab	JAK inhibitors
Cancer	–	–	+	+	–	+	+	+
Infections	–	+	+	+	–	+	+	+
Herpes zoster infection	–	+	+	+	–	+	–	+
Cardiovascular events	+	+	–	+	–	–	+	+
Venous thrombosis	–	+	–	–	–	–	+	+
Hypertension	–	+	–	–	–	–	+	+
Depression or anxiety	–	+	–	+	–	+	–	–
Osteoporosis	–	+	–	–	–	–	–	–
Diabetes	–	+	–	–	–	–	–	–

5-ASAs – 5-aminosalicylates; TNF-α – tumor necrosis factor alpha; VDZ – vedolizumab; UST – ustekinumab; JAK – Janus activated kinase;
+ The use of this drug may increase the risk of developing the listed disease or complication (adverse effect) in the elderly population.
– No significant impact of this drug on the risk of developing the listed disease or complication in the elderly population is known.

Appendix A

1. **Search string for PubMed:**
   ("Inflammatory Bowel Diseases"[Mesh] OR "Crohn Disease"[Mesh] OR "Colitis, Ulcerati-ve"[Mesh]
   OR "inflammatory bowel disease"[tiab] OR "Crohn*"[tiab] OR "ulcerative colitis"[tiab])
   AND
   ("Aged"[Mesh] OR elderly[tiab] OR "older adult*"[tiab] OR senior*[tiab])
   AND
   ("5-aminosalicylic acid"[Mesh] OR mesala-mine[tiab] OR sulfasalazine[tiab] OR olsalazine[tiab] OR balsalazide[tiab]
   OR "Adrenal Cortex Hormones"[Mesh] OR corticosteroid*[tiab] OR prednisone[tiab] OR budesonide[tiab]
   OR azathioprine[tiab] OR mercaptopurine[tiab] OR thiopurine*[tiab]
   OR infliximab[tiab] OR adalimumab[tiab] OR certolizumab[tiab] OR golimumab[tiab] OR "Tumor Necrosis Factor-alpha"[Mesh]
   OR ustekinumab[tiab] OR risankizumab[tiab] OR vedolizumab[tiab]
   OR tofacitinib[tiab] OR upadacitinib[tiab] OR filgotinib[tiab] OR "Janus Kinase Inhibi-tors"[Mesh])
   AND
   (remission[tiab] OR "disease severity"[tiab] OR persistence[tiab] OR "therapy persistence"[tiab]
   OR "adverse event*"[tiab] OR safety[tiab])
2. **Search string for Embase:**
   ('inflammatory bowel disease'/exp OR 'crohn disease'/exp OR 'ulcerative colitis'/exp OR 'inflammatory bowel disease':ti,ab OR 'crohn*':ti,ab OR 'ulcerative colitis':ti,ab)
   AND
   ('aged'/exp OR elderly:ti,ab OR 'older adult*':ti,ab OR senior*:ti,ab)
   AND
   ('5 aminosalicylic acid'/exp OR mesalamine:ti,ab OR sulfasalazine:ti,ab OR olsalazine:ti,ab OR balsalazide:ti,ab
   OR 'corticosteroid'/exp OR corticosteroid*:ti,ab OR prednisone:ti,ab OR budesonide:ti,ab
   OR 'azathioprine'/exp OR azathioprine:ti,ab OR mercaptopurine:ti,ab OR thiopurine*:ti,ab
   OR infliximab:ti,ab OR adalimumab:ti,ab OR certolizumab:ti,ab OR golimumab:ti,ab OR 'tumor necrosis factor alpha'/exp
   OR ustekinumab:ti,ab OR risankizumab:ti,ab OR vedolizumab:ti,ab
   OR tofacitinib:ti,ab OR upadacitinib:ti,ab OR filgotinib:ti,ab OR 'janus kinase inhibitor'/exp)
   AND
   (remission:ti,ab OR 'disease severity':ti,ab OR persistence:ti,ab OR 'therapy persistence':ti,ab
   OR 'adverse event*':ti,ab OR safety:ti,ab)

3. **Search string for Scopus:**

TITLE-ABS-KEY(
("inflammatory bowel disease" OR "crohn*" OR "ulcerative colitis")
AND
(elderly OR "older adult*" OR senior*)
AND
("5-aminosalicylic acid" OR mesalamine OR sulfasalazine OR olsalazine OR balsalazide
OR corticosteroid* OR prednisone OR budesonide
OR azathioprine OR mercaptopurine OR thiopurine*
OR infliximab OR adalimumab OR certolizumab OR golimumab OR "tumor necrosis factor alpha"
OR ustekinumab OR risankizumab OR vedolizumab
OR tofacitinib OR upadacitinib OR filgotinib OR "janus kinase inhibitor*")
AND
(remission OR "disease severity" OR persistence OR "therapy persistence" OR "adverse event*" OR safety)
)

Conflict of interest statement

The authors declare no conflicts of interest.

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Use of AI tools statement

During the preparation of this manuscript, the authors used ChatGPT-4o for the purposes of superficial text editing. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

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