



Ulcerative Colitis in Adulthood and in Older Patients: Same Disease, Same Outcome, Same Risks?

Walter Fries¹ · Maria Giulia Demarzo^{1,2} · Giuseppe Navarra³ · Anna Viola¹

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Abstract

The number of patients with inflammatory bowel disease (IBD) approaching an older age, together with the number of over-60-year-old patients newly diagnosed with IBD, is steadily increasing, reaching 25% of all patients. The present review focuses on late-onset ulcerative colitis (UC) and its initial disease course in comparison with that observed in younger adults in terms of extension at onset and the risk of proximal disease progression, medical treatment, surgery and hospitalization in the first years after diagnosis. We summarize the clues pointing to a milder disease course in a population which frequently presents major frailty due to comorbidities. With increasing age and thus increasing comorbidities, medical and surgical therapies frequently represent a challenge for treating physicians. The response, persistence, and risks of adverse events of conventional therapies indicated for late onset/older UC patients are examined, emphasizing the risks in this particular population, who are still being treated with prolonged corticosteroid therapy. Finally, we concentrate on data on biotechnological agents for which older patients were mostly excluded from pivotal trials. Real-life data from newer agents such as vedolizumab and ustekinumab show encouraging efficacy and safety profiles in the population of older UC patients.

Key Points

The number of older patients with ulcerative colitis is rising constantly, representing a challenge for physicians.

Immunomodulators and anti-TNF therapies may be burdened by a higher risk of adverse events including infections and malignancies in this age group.

Newer biological therapies and therapies with JAK inhibitors seem to be safer, but more data in older patients are needed.

1 Introduction

A large database including approximately 56 million US citizens reported increasing incidence data over a 10-year period (2005–2015), placing ulcerative colitis (UC) with onset at ≥ 60 years of age at the top of all IBD diagnoses with 16–22 cases/100,000 person-years, followed by adults (aged 26–59 years) with 12–20 cases/100,000 person-years [1]. In the Danish National registry, UC onset in older patients accounts for 21% of all IBD diagnoses [2] and in the Netherlands, the proportion of UC patients with an onset at age ≥ 60 years, diagnosed between 1991 and 2010, was 22.5% [3]. Incidence rates (IR) in Sweden reported an IR of 19 for UC onset in the population aged 60–79 years compared with an IR of 20 in the whole population [4]. In Canada, for the year 2030, a predicted prevalence of 0.69% (95% predictive interval [PI] 0.660–0.721) is estimated for the older UC population, including new diagnoses and already prevalent cases, with a forecasted average annual percentage change of 3% [5].

These epidemiological observations and estimates make it clear that UC onset over 60 years of age and older patients with UC represent, and will represent, a concrete challenge for health care planning today and in the near future. The purpose of the present review is to provide data on

✉ Walter Fries
fwalter@unime.it

¹ Gastroenterology and Chronic Bowel Diseases, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

² Gastroenterology Unit, Department of Internal Medicine, IRCCS Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy

³ Oncologic Surgery, Department of Human Pathology of Adult and Evolutive Age, University of Messina, Messina, Italy

differences between UC with onset in adulthood and in older patients in terms of disease location and behaviour, together with data on response and persistence to UC-specific therapies. Finally, we address the most common therapy-related adverse events such as infections, potentially life-threatening and debilitating in this age group, together with malignancies and mortality.

2 Presentation and Disease Course

2.1 Presentation of Disease at Diagnosis

Several attempts have been made in the past few years to define clinical presentation of late-onset UC and to determine if this variant may be different from adult forms.

Compared with adult-onset UC, more frequent weight loss but less frequent rectal bleeding and systemic symptoms like fever have been reported in older populations with UC onset [6–10]. In particular, UC onset in older patients requires a careful diagnostic work-up to differentiate between drug-induced colitis (e.g. non-steroidal anti-inflammatory drugs), segmental colitis associated with diverticular disease, ischemic or infectious colitis or even neoplastic disease [11], and this may lead to the significant diagnostic delay reported in late-onset disease [12, 13]. Concerning disease extension at diagnosis (Table 1), in a meta-analysis from 2016, left-sided colitis prevails in older-onset disease [14]. This finding was confirmed by subsequent studies [4, 15–17], whereas in other studies, extensive colitis [18] or proctitis [19, 20] were more frequent in late-onset UC. Some

studies found significant differences for disease extension at diagnosis between adult- versus late-onset UC [3, 4, 6, 8, 9, 16, 17, 21, 22], whereas others did not find such differences [15, 18–20]. Taken together, Fig. 1 depicts the most important studies in the past decade concerning disease extension at diagnosis including, where available, the corresponding figure of adult-onset UC.

2.2 Disease Course of Ulcerative Colitis (UC) in Older and Adult-Onset Disease

The following variables are generally used to define a worse disease course and poor outcome: proximal disease extension over time, need for more intense medical treatments, hospitalizations, surgery, and extraintestinal manifestations (EIM).

Concerning proximal extension (i.e. a more widespread involvement of the colon surface over time), no differences compared with adult-onset disease were reported in late-onset UC, with figures for both age groups from 6.6 to 12.3% at 5 years after diagnosis and 9.4% to 20.8% at 10 years, respectively [3, 12, 17, 21], and stable disease in terms of extension was observed in 84% of patients [9] (Table 1).

Severity of disease at onset seems to be similar between adult- and late-onset UC [20, 22] with similar steroid needs at onset [3, 14–16]; in a former report, a more protracted first episode was found together with a shorter duration of remission compared with young adult-onset disease [23].

Hospitalizations were reported to be more frequent in late-onset UC, not only due to intestinal disease [3, 4] but also to comorbidities [17]. Apart from the disease itself, IBD

Table 1 Comparison of the main features of ulcerative colitis at diagnosis and follow-up over 5 years, between adulthood-onset and late-onset disease

	Adult onset	Onset \geq 65 years
Prevailing disease extent at diagnosis	E1 (4 studies) [8, 16, 20, 21] E2 (4 studies) [3, 15, 16, 23] E3 (2 studies) [4, 19]	E1 (2 studies) [8, 21] E2 (7 studies) [3, 4, 8, 15–17, 23] E3 (3 studies) [4, 18, 36]
Proximal disease extension first 5 years after diagnosis	8–14% [3, 12, 17, 23]	6.6–12.3% [3, 12, 17, 23]
Severity at diagnosis	Similar [22, 24]	Similar [22, 24]
Extraintestinal manifestations at diagnosis	10.7–23% [12, 17, 23]	7–9.7% [12, 17, 23]
Therapy in the first years		
Steroids	39.8–57% [3, 12, 23]	17–61% [3, 9, 17, 23]
Immunomodulators	11–54% [3, 4, 12, 17]	10–33% [3, 4, 9, 12, 17]
Biologics	2–20% [3, 4, 12, 17]	1–7% [3, 4, 9, 12, 17]
Hospitalizations at 3–5 years after diagnosis	16*–49% [3, 17]	24*–67% [3, 17]
Surgery	4–8% [3, 12, 17]	7–19% [3, 12, 17]
Mortality	No increased risk	Increased risk with frailty, steroid use, infections, surgery [24, 118, 119]

*Estimates from Kaplan-Meier curves

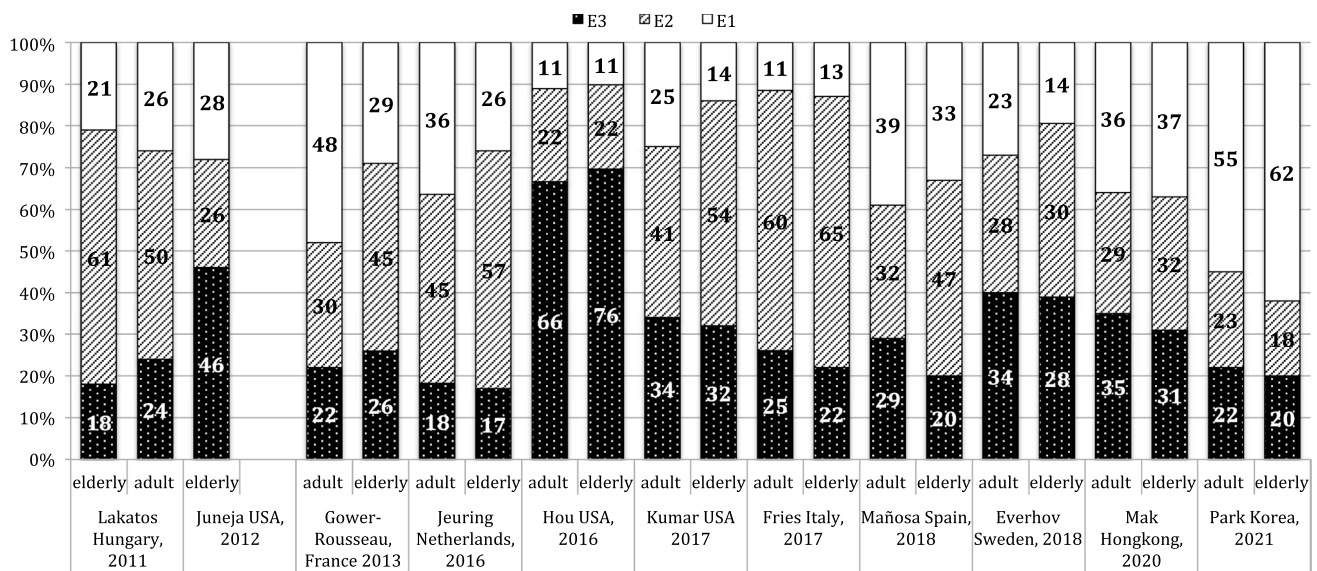


Fig. 1 Disease extension at diagnosis in late-onset ulcerative colitis (UC) according to the Montreal classification; *E1* proctitis; *E2* left sided; *E3* extensive; numbers refer to percentages

patients with an older age at onset present a higher risk for frailty which is associated with a higher risk for all-cause mortality compared with non-IBD patients [24].

Similar hospitalization rates were reported in a large retrospective US study during the first year of disease in late-onset UC compared with young adults; however, in follow-up, hospitalization rates declined in late-onset disease [25]. Conversely, more frequent infection-related hospitalizations were reported in the first year after diagnosis, especially due to *Clostridioides difficile* and cytomegalovirus, in a study from Hong Kong, China [26]. For older patients with UC diagnosed earlier in life, a worse outcome with higher hospitalization and mortality rates were reported, mostly due to comorbidities but not to surgery [27]. Higher mortality rates in hospitalized older UC patients including deaths due to surgery were confirmed by a Canadian nationwide study, and mortality as well as readmissions were associated with more comorbidities and being treated in low-volume centers, thus underlining the importance of specialized centers for the cure of fragile patients [28]. In other Canadian studies, the cumulative 5-year risk for colectomy was higher in late-onset compared with adult-onset UC (13.6% vs 10.3%) and this higher risk persisted for up to 10 years [29, 30]. Similar data come from a Spanish referral center cohort where the colectomy rate for older-onset UC compared with adult-onset disease was similar at 1 year from diagnosis, but significantly higher at 5 years (11% vs 5%, respectively) [17]. This finding was confirmed in a very recent Japanese study, although with much lower numbers (3.2% vs 1.1%) at 1 year after diagnosis [31]. In a meta-analysis [14], a higher risk for colectomy was reported in late-onset UC on pooled

data but subsequent reports showed no difference [3, 4, 15, 16, 19]. Of interest, elective colectomy was associated with better survival rates than medical therapy in patients over 50 years of age [32].

Concerning EIM that may precede or follow diagnosis of UC, with the exception of primary sclerosing cholangitis reported in (young) adult-onset UC, patients with UC in general are less likely to present with EIM compared with Crohn's disease patients, with more frequently occurring EIM in pancolitis rather than with proctitis [33]; overall, numerically less frequent EIM were reported in late-onset compared with adult-onset UC, although the difference did not achieve statistical significance in all studies [9, 15, 17].

Taken together, in terms of disease presentation and proximal disease extension, UC onset in older patients seems not to be very different from adult-onset disease. Colectomy rates are higher in late-onset disease, whereas hospitalizations, more frequently due to infections and comorbidities, are burdened by a worse outcome. EIM are less likely to occur in patients with UC onset at an older age.

3 Medical Therapy—Effectiveness and Persistence

Every type of drug, from mesalazine through steroids, immunomodulators, and biotechnological therapies, used in adult UC are also indicated in older patients with UC; limitations and contraindications depend on coexisting comorbidities. There is a lack of specific studies addressing efficacy of mesalazine, steroids, especially low bioavailability

Table 2 Effectiveness of and persistence in therapies in patients with late-onset ulcerative colitis (UC) and with long-standing UC in comparison with younger adult patients unless otherwise indicated

	Effectiveness		Persistence	
	Late-onset UC	Older patients with long-standing UC	Late-onset UC	Older patients with long-standing UC
Mesalazine	No data	No data	No data	No data
Steroids	<ul style="list-style-type: none"> • Similar refractoriness (474) [8] • Similar response (100) [15] • Better (95) [21] • Lower response to IV steroids(83) [36] 	<ul style="list-style-type: none"> • Lower response to IV/oral steroids (73) [37] 		
Thiopurines	No data	No data	No data	<ul style="list-style-type: none"> • Higher discontinuation rate (1888) [44]
Methotrexate	No data	No data	No data	
Anti-TNF agents	<ul style="list-style-type: none"> • Lower steroid-free remission at 8 wks (55) [47] 	<ul style="list-style-type: none"> • Lower response at 10 wks (66)* [49] • Similar response at 8 wks (25) [47] • Similar response and remission rate (231) [48] 	No data	<ul style="list-style-type: none"> • Higher discontinuation rate (54)* [50] • Higher discontinuation rate (41) [53] • Similar LOR rate (939)* [51] • Higher discontinuation rate (81)* [52]
Vedolizumab	No data	<ul style="list-style-type: none"> • Similar to IFX (103)* [60] • Similar response, remission and steroid-free remission at 14 wks (62) [55] • Similar steroid-free remission at 6–12 mo (77) [54] • Similar to Crohn's (84) [59] • Similar mucosal healing rates (25) [57] • Similar steroid-free remission at 6–12 mo (103) [56] 	No data	<ul style="list-style-type: none"> • Similar persistence (77) [54] • Similar to Crohn's (84) [59] • Similar persistence (103) [56] • Better persistence compared with anti-TNF (108)* [61]
Ustekinumab	No data	No data	No data	No data
Tofacitinib	No data	No data	No data	No data

Numbers in brackets refer to patient numerosity of the corresponding study

discont. discontinuation, *IFX* infliximab, *IV* intravenous, *LOR* loss of response, *TNF* tumor necrosis factor

*Pooled data on UC and Crohn's disease

steroids, or immunomodulators in the older UC population. As shown by Kochar et al. in a recent systematic review [34], <1% of patients included in randomized clinical trials were ≥65 years. The evidence reported in literature in real-life studies concerning effectiveness of available therapies and persistence in therapy is therefore summarized in Table 2, divided into late-onset and older patients with long-standing disease (in the assumption that late-onset UC may represent a distinct entity).

3.1 Mesalazine (5-ASA)

5-ASA is the most common drug employed in late- as well as in adult-onset UC, reaching >90% of all patients in the first year after diagnosis. Thereafter, this percentage declined by approximately 20% in a study from Italy [15]; a similar pattern but with lower numbers was reported from Sweden [4],

whereas in Northern France treatment with 5-ASA showed an inverse pattern starting with 65% and reaching 84% 10 years after diagnosis [9]. In other reports, percentages of 5-ASA use were comparable in late-onset versus adult-onset UC, ranging from 75% versus 71% [20] to 84% versus 74%, respectively [35].

3.2 Corticosteroids

In both young adult and older patients, conventional systemic steroids were employed in 20–50% of UC patients at diagnosis or in the following years depending on disease severity [3, 4, 8, 15, 17], and the use of steroids, with few exceptions, did not differ between the age groups.

Conflicting results were reported on response to steroids, ranging from a better outcome in late-onset UC compared with young adults in achieving steroid-free remission at

1 year after diagnosis [21] to similar response to steroids including low-bioavailability steroids [15], or even lesser response to intravenous (IV) steroids [36] or IV/oral steroids in longstanding UC [37].

Other studies found a more frequent and more prolonged use of steroids in patients with late-onset UC, with chronic steroid treatment in 31% of patients [34]; this figure rose to 40% in a study on older IBD patients [38].

A lower rate of steroid-dependency in late-onset UC compared with younger adults was reported in a Spanish referral center study [17], whereas similar rates of steroid dependency and refractoriness were found in a French population-based study [8].

3.3 Immunomodulators

With the exception of two recent Asiatic studies [31, 39], almost all previous epidemiological studies investigating the use of immunomodulators (mainly thiopurines) in late-onset UC in comparison with younger age groups reported a minor use of these therapies in older patients [3, 4, 8, 15, 19, 22], and this observation was interpreted as these patients having a more benign disease course. While in younger adults diagnosed with UC, immunomodulators were commenced in 5–27% to 18–53%, 1 and 5 years after diagnosis, respectively, only 2.5–15% to 10–36% of patients with late-onset UC were reported to start such therapy [3, 4, 8, 17]. A switch to a second thiopurine in the case of intolerance or adverse event with the first one (in general, azathioprine) was also deemed safe in older patients [40].

Recent investigations, however, showed that the age of patients was the main hindrance for the prescription of these medications [41], whereas a retrospective study identified comorbidities as the main factor for not prescribing immunomodulators [42]. When administered, thiopurines showed a similar efficacy in late- compared with young adult-onset UC [15] and a more prolonged treatment with thiopurines (>12 months) was associated with a lower risk for colectomy [43]. However, in older IBD patients, thiopurines showed a higher discontinuation rate due to adverse events compared with younger patients [44].

3.4 Biotechnological Therapies

3.4.1 Anti-Tumor Necrosis Factor (Anti-TNF) Therapies

In late-onset UC studies, whether referral center- or population-based, anti-tumor necrosis factor (anti-TNF) therapies were administered in the first 3–5 years to a minority (5–12%) of older patients with UC compared with 14–16% of patients with adult-onset disease [4, 15, 17], whereas a similar use of anti-TNF was reported in older UC patients with longstanding disease [45, 46].

Lower steroid-free remission rates at 8 weeks compared with young adults were recently reported in late-onset UC [47], whereas the same authors reported a similar response to younger adults in older patients with longstanding disease. An analysis from randomized trials showed no difference in response and remission rates in older UC patients [48]. Previous reports indicated a lower response to anti-TNF therapy in older longstanding IBD populations [49, 50] but in the longer term, a similar effectiveness of anti-TNF was reported in a mixed IBD population in older patients [51]. Finally, higher discontinuation rates of anti-TNFs were reported in older patients with UC in comparison with younger adult patients due to loss of response or to adverse events [52, 53].

3.4.2 Vedolizumab

Comparable clinical response and remission rates including steroid-free and endoscopic remission were reported with the use of vedolizumab, an $\alpha 4\beta 7$ anti-integrin antibody, in older versus adult patients with UC, with about 50% of patients already exposed to anti-TNFs [54, 55] with similar persistence in therapy [54, 56] and mucosal healing rates [57].

In biologically naïve older UC patients, steroid-free remission at 52 weeks was reported in 40–60% together with good persistence in therapy over time (75% at 52 weeks) [58, 59]. A retrospective multicenter comparison between anti-TNF and vedolizumab in older UC patients did not find any difference at 6 and 12 months [60]. In contrast, a single-center retrospective study showed an advantage for vedolizumab compared with anti-TNF agents with respect to drug persistence and endoscopic remission in a mixed IBD cohort over 60 years of age [61].

3.4.3 Ustekinumab

Ustekinumab, an antibody targeting the common p40 subunit of interleukin-12/23, has been introduced very recently to the range of therapeutic options for UC [62]. To date, no data on older patients with UC or patients with late-onset UC are available but its safety profile seems promising.

3.5 Small Molecules

3.5.1 Tofacitinib

Tofacitinib is a Janus kinase (JAK) inhibitor recently approved for UC. Similar to ustekinumab, no specific data on efficacy in older UC patients were available. In a global analysis, no difference for safety was reported in 77 patients ≥ 65 years of age [63].

In summary, 5-ASA, although not supported by specific studies, remains the mainstay in mild to moderate UC in

Table 3 Potential therapy-related risks, actions to reduce risks, and potential/known drug interactions per pharmacological principle in patients with ulcerative colitis (UC)

	Potential risks	Clinical approach	Potential/known drug interactions
Mesalazine	Renal damage	Check renal function	Thiopurines
Steroids	Hypertension	Therapy courses as short as possible	
	Osteoporosis/fractures	Vitamin and calcium supplements; check bone mineral density	
	Infections due to immunosuppression	Vaccinations where available	
Thiopurines	Cataracts, glaucoma		
	Infections due to myelosuppression	Vaccinations where available	Allopurinol
	Lymphoproliferative disorders	Reduce exposure	Warfarin
	Urinary tract neoplasia	Reduce exposure	Mesalazine
Methotrexate	NMSC	Annual dermatologic surveillance; solar protection (UVA)	Trimethoprim/sulfamethoxazole
	Hepatotoxicity	Switch to 6-MP may be considered	ACE inhibitors
	Infections due to myelosuppression	Vaccinations where available	Cimetidine
Anti-TNF agents	Hepatotoxicity	Check HBV, HCV infection, control liver enzymes	Sulphasalazine
	Infections	Vaccinations where available, HBV, HCV status	
	Melanoma risk	Annual dermatologic surveillance	Not reported
	TBC risk	Interferon-release assay prior to treatment	
Wedolizumab	Heart failure	Check heart status	
	URT infections	Vaccinations where available	Not reported
Ustekinumab	No specific risk identified		Not reported
Tofacitinib	Infections (<i>H. zoster</i>)	Vaccinations where available	CYP3A4 inhibitors e.g. ketoconazole
	Thromboembolism	Avoid or reduce to 5 mg BID in induction	CYP2C19 inhibitors, e.g. fluconazole
	Cardiac events	Check heart status	OAT3 inhibitors, e.g. valsartan
	Malignancies?		

ACE angiotensin converting enzyme, *CYP2C19* cytochrome P-450 2Cq19, *CYP3A4* cytochrome P-450 3A4, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *NMSC* non-melanoma skin cancer, *OAT3* human organic anion transporter 3 (see ref. [40, 51, 65–71]), *TBC* tuberculosis, *TNF* tumor necrosis factor, *URT* upper respiratory tract infections, *UVA* ultraviolet A rays, *6-MP* 6-mercaptopurine

older patients but, if necessary, the use of immunomodulators in fit patients may be indicated on a case-by-case basis. Among the biological therapies, the more recent drugs, vedolizumab and ustekinumab (the latter lacks UC-related data in older patients), may represent the drugs of choice in late-onset and in older patients with longstanding, more aggressive UC. Evidence for tofacitinib, although promising, is still awaiting data on safety (see section 4).

4 Therapy-Related Risks in Older Patients with UC

Potential risks due to therapy, possible preventive actions, and known drug–drug interactions are summarized in Table 3. Polypharmacy is frequently reported in older IBD patients [34, 64] and for potential interactions please refer to ref. [65–68].

In this section, we will focus on risks associated with the disease itself in older UC patients and induced or enhanced by therapies approved for the treatment of UC. With the exception of well-known specific risks of drug categories, such as osteoporosis, fractures, hypertension, and diabetes due to steroids [69, 70] or bone marrow and liver toxicity due to immunomodulators [71, 72], we will consider infections, in part potentiated by combination therapies, the risk of malignancies, thromboembolism, and mortality. Frequently, these studies have been carried out on older mixed IBD populations but, whenever possible, peculiar aspects in UC patients will be addressed.

4.1 Infections

Except for mesalazine (5-ASA), all conventional treatment options for UC carry a risk for infections and, generally speaking, this risk increases in older patients. These may be

opportunistic infections from viruses, fungi or bacteria or may be due to well-known pathogens such as pneumococcus and Herpes zoster (*H. zoster*). Besides the therapy-induced risk for infections, there are infections that are increased in IBD patients regardless of current therapies, such as pneumococcal disease and infections from *H. zoster* and *C. diff.*, and this risk increases further when patients are exposed to immunosuppressive agents. Cofactors that potentiate immunosuppression do exist and are represented by malnutrition, advanced age, frailty and comorbidities (especially diabetes), chronic lung disease and alcoholism [42, 73]. Finally, the risks due to the recent SARS-CoV-2 pandemic in immunosuppressed and older patients will be examined.

4.1.1 Respiratory Tract Infections and Pneumonia

In a large retrospective cohort (<64 years of age) of mixed IBD patients (database: LifeLink™ Health Plan Claims Database; IMS Health Inc, Norwalk, CT, USA), 4856 patients were diagnosed with bacterial pneumonia and compared with non-IBD controls (ratio 1:4). For these IBD patients, an annual incidence for pneumonia was calculated with 138 cases/10,000, compared with 76/10,000 in the non-IBD cohort. Among the most important risk factors, the authors identified the use of steroids and narcotics with an adjusted odds ratio (OR) of 1.91 (95% CI 1.72–2.12) and 2.28 (95% CI 2.09–2.48), respectively [74]. In a nationwide Danish study, the risk for invasive pneumococcal disease was investigated in 75,156 IBD patients [75] and was found to be twofold higher among patients with UC within 1 year after diagnosis. In this study, the use of thiopurines was also associated with a higher risk for invasive pneumococcal disease in UC patients (hazard ratio [HR] 2.38; 95% CI 1.00–5.67). Interestingly, the risk for pneumococcal disease was also found to be increased in the 12 months before the diagnosis of IBD was established, pointing to an IBD-specific risk for pneumococcal disease. In a cohort with late (≥ 66 years) disease onset, respiratory tract infections represented 37.8% of all infections with an adjusted relative risk of 4.0 (95% CI 2.5–6.6) for all serious bacterial infections in concurrent steroid users [76]. Of interest, the risk remained elevated for 3 months after the last prescription of steroids.

An increased risk for infections (mainly pulmonary) and mortality was reported in older IBD patients treated with anti-TNF compared with older patients without biologic treatment [77]. Toruner et al. [78] showed that the odds ratios for opportunistic infection including pneumonia rose with every single immunosuppressive agent (steroids, thiopurines, anti-TNFs) by a risk factor of 3, whereas the combination of these agents was associated with a risk factor of 14.5, with higher relative risks in patients aged >50 years.

4.1.2 Clostridioides difficile

Infections due to *C. diff.* have been steadily increasing over the past decades, especially in IBD patients [79–81]. Known risk factors for *C. diff.* infection in the general population are the use of antibiotics, living in communities, and the use of proton pump inhibitors [82, 83]. In IBD, no age-specific risk has yet been identified with the exception of comorbidities [84]. IBD patients have a threefold to fivefold risk for *C. diff.* infections compared with non-IBD patients with higher hospitalization rates, longer in-hospital stays, and greater mortality. Moreover, especially in UC patients, an increased long-term risk for colectomy was reported [85]. The impact of therapy on the development of *C. diff.* infections in IBD remains controversial. There is a consistent body of evidence that immunosuppressive treatment including steroids, immunomodulators and anti-TNF agents is associated with *C. diff.* infection [80, 81, 84, 86], but in the most recent systematic review with meta-analysis no association between steroids or immunomodulators and *C. diff.* infections was identified [87].

4.1.3 Herpes zoster

A higher risk of *H. zoster* compared with non-IBD subjects was reported in a retrospective analysis in the prebiologic era (1988–1997) in a cohort of approximately 20,000 IBD patients with an increased incidence rate ratio in UC (1.21; 95% CI 1.05–1.40) [88]. Steroids (OR 1.5; 95% CI 1.1–2.2) and thiopurines (OR 3.1; 95% CI 1.7–5.6) were both associated with *H. zoster*. In the aforementioned LifeLink™ database [74], an increased *H. zoster* risk was reported for IBD patients compared with non-IBD controls and in patients aged >60 years. Assessing risk factors, all types of medications except 5-ASA (thiopurines: OR 1.68, 95% CI 1.30–2.16; steroids: OR 1.96, 95% CI 1.60–2.40; and anti-TNFs: OR 2.36, 95% CI 1.47–3.79) were independently associated with an increased risk for *H. zoster* in UC patients [89]. The highest risk was reported for combination therapies (OR 4.79, 95% CI 1.84–12.45). An association with *H. zoster* has similarly been reported for methotrexate [90]. A more recent US study investigating the association between different pharmacologic strategies for IBD in terms of an increased *H. zoster* risk showed an association between short-term and cumulative steroid use, use of thiopurines, and of combination therapies but not for anti-TNF monotherapy [91]. The highest risk showed in patients aged >60 years on combination therapies with an annual incidence of 2%. As an additional risk factor, disease flare was identified.

The recently approved JAK inhibitor tofacitinib was reported to carry a high risk for *H. zoster*, especially in older patients, underlining the importance of vaccinations against *H. zoster* in these high-risk patients [63, 92].

4.1.4 SARS-CoV-2

In several studies, older age and a higher Charlson-Comorbidity index were associated with an increased risk for severe SARS-CoV-2 infections, and these risk factors, together with active intestinal disease, were found to be significantly associated with SARS-CoV-2-related death [93, 94]; immunosuppressive therapy was not associated with an increased risk for SARS-CoV-2 infection [95] and it appears that UC patients had a lower risk for severe viral disease, possibly due to the lower rate of smokers among UC patients [96].

Taken together, besides drug-specific adverse events, infection risk remains a major problem when treating older UC patients, especially with corticosteroids. Thus, vaccination programs with recombinant vaccines, where available, for preventable diseases (e.g. pneumococcal pneumonia, *H. zoster*, influenza, etc.) are mandatory to reduce such risk, even in patients already under immunosuppressive treatment.

4.2 Thromboembolism

Patients with IBD are at increased risk for arterial [97] and venous thromboembolic events with an important impact on in-hospital mortality in older patients [98]. The risk persists even after discharge, especially in surgical UC patients [99]. International guidelines recommend prophylaxis in hospitalized and especially in surgical patients [100].

Only one medication approved for UC (tofacitinib) appears to increase the risk for venous thromboembolic events, with an induction regimen of 10 mg twice daily [101] with US Food and Drug Administration (FDA) [102] and European Medicines Agency (EMA) warnings [103], especially in patients aged >65 years.

4.3 Malignancies

It is well known that older IBD patients are at increased risk for malignancies, such as colorectal cancer (CRC), especially in patients with longstanding disease, or leukemia in UC patients [87, 104]. This section focuses mainly on therapy-related malignancy risk modulation observed in the older IBD population.

Firstly, thiopurines have been recognized as carrying an increased risk of malignancies, especially for lymphoproliferative disorders [105], non-melanoma skin cancer [106], urinary tract disease [107], and for new cancers or cancer recurrence [108]. Of interest, the risk for skin cancer persists even after drug withdrawal, making lifetime dermatologic controls mandatory. On the other hand, the use of thiopurines has been associated with a reduced risk for CRC [109].

Biotechnological therapies have been discussed over the last decade with respect to cancer risk, but no conclusive

data are available yet, especially for lymphoproliferative disorders [110, 111] and melanoma [112, 113]. No increased risk of new or recurrent cancers with anti-TNF or vedolizumab in patients with prior malignancy has been reported [114]. Other therapies such as ustekinumab [115] or tofacitinib [116] appear to be safe but an in-depth evaluation by the EMA including all JAK inhibitors is underway.

4.4 Mortality

Independently from age, mortality in UC after the first year from diagnosis appears to be similar to that of the general population [117], but frailty [24], steroid use [118], infections [119], and surgery-related complications [27] remain the major drivers for adverse outcomes.

5 Conclusions

UC onset at an older age is becoming more and more frequent, exceeding the incidence of adult-onset disease in some studies and, together with patients with longstanding disease, those >65 years of age represent a consistent proportion of the UC population.

In late-onset disease, disease presentation and initial course seem comparable to those of adulthood, an observation confirmed by the need for steroids and surgery, but some indicators point to a more benign disease course, such as the need for immunosuppression and biologics, the rate of proximal extension, as well as the less frequent occurrence of EIM in late-onset UC. These apparently favourable factors are outweighed by age- and therapy-related risks for adverse events including infections, thromboembolic events, and malignancies in older UC patients either with long-standing disease or with recent onset. Vaccination-preventable infections such as pneumonia or *H. zoster* must be addressed both in adult and, especially, in older patients as outcomes may be worse in the latter. More data on newer biological drugs (i.e. ustekinumab and vedolizumab) and the recently introduced JAK inhibitor, tofacitinib, are warranted in older patients, including those with new-onset disease as well as patients with longstanding disease.

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