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Is it time to include older adults in inflammatory bowel disease trials? A call for action

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The therapeutic management of older patients with inflammatory bowel disease (IBD) is challenging, particularly because of the absence of evidence-based guidelines for these patients, who seem to frequently be excluded from clinical trials. In this systematic review we investigated the exclusion of older patients with IBD from phase 3 studies registered on PubMed and ClinicalTrials.gov, by assessing the upper limit of age exclusion criteria and the percentage of patients older than 65 years included in the trials. Exclusion criteria other than age were also recorded, and comorbidities were analysed separately. Our review of 222 phase 3 studies shows that older patients are frequently excluded from IBD clinical trials because of their age, which was used as an exclusion criterion in 129 (58%) of the 222 assessed trials. Of the 32 trials that detailed the percentage of included patients who were 65 years or older, only 763 (5·4%) patients of the 14 124 patients included were older than 65 years. In addition to age, patients were also excluded because of comorbidities (mainly renal, hepatic, and cardiovascular, and used as an exclusion criterion in 76% of trials), a history of dysplasia (45% of trials), and previous treatment for IBD (19% of trials). We propose a three-step process that should enable the inclusion of all older patients in IBD clinical trials, regardless of their age, comorbidities, and frailty.

Introduction

Inflammatory bowel disease (IBD) encompasses ulcerative colitis and Crohn's disease, which are chronic inflammatory disorders of the gastrointestinal tract that were previously thought to affect mainly younger patients.[1] However, the incidence and prevalence of IBD are increasing and the general population is ageing.[2–5] Given the absence of curative treatment for IBD and its negligible effect on mortality, older patients now represent the largest-growing population of patients with the condition.[6,7] In 2010, patients aged 65 and older represented less than 20% of the overall population with IBD; however, current estimates suggest that they now represent more than a third of this population: 20% are older patients with adult-onset IBD, in which the patient was diagnosed at 60 years or younger and is now ageing with IBD, and 15% are patients with older-adult-onset IBD, defined by an IBD diagnosis when the patient was older than 60 years.[3,4,8–14]

The therapeutic management of older patients with IBD is challenging as it can be influenced by multiple concomitant factors, including age-related comorbidities, unpredictable consequences of long-term treatment (including infections), a higher risk of malignancy than in younger patients, polypharmacy, malnutrition, impaired physical and cognitive capacities, loss of autonomy, and social and financial issues faced by this population.[5,15–19] For older patients with IBD, disease progression and the need for surgery are similar to those of younger patients; however, surgery is associated with significantly higher postoperative mortality and complication rates in older patients.[20–23] Ensuring that older patients are not undertreated because of a fear of treatment-related complications is therefore important.[20,21] However, real-world studies have shown that the use of immunomodulators and biologics is lower in older patients than in younger patients with IBD.[5,18,24–26] The reluctance of IBD care providers to use steroid-sparing medications in older patients is largely driven by an absence of evidence regarding the safety and efficacy of these medications, because older adults are frequently excluded from clinical trials.[27]

In a recent systematic review that analysed the inclusion of older adults in clinical trials of approved IBD medications, Kochar and colleagues[27] found that patients 65 years and older represented fewer than 1% of participants in randomised clinical trials included in their analysis. In addition to age limits, comorbidities and a history of malignancy also contributed to the non-inclusion of older patients.[27] None of these studies assessed the functional status of the patient as an exclusion criterion.[27] However, the analysis was limited to 46 randomised controlled trials from four leading general medicine journals and four leading gastroenterology journals, and might therefore be subject to selection bias.[27]

In this systematic review, we assessed the upper limit of age exclusion criteria in all registered phase 3 IBD trials registered on PubMed and ClinicalTrials.gov. We then investigated the presence of comorbidities and how this influenced the exclusion criteria. We also assessed the relevance of frailty when assessing individual risk of adverse events. Finally, we propose some criteria and a three-step process to enable the inclusion of older patients in future IBD clinical trials.

Defining older adults

A categorical definition of what constitutes older adults is arbitrary, and the term can be influenced by many factors including gender, culture, and country.[28] A chronological definition is commonly used but is contested, especially because in lower-income countries, where access to adequate health care can be restricted, people can be functionally old at a much younger age than those in higher-income countries.[28] WHO retains the age criterion of 65 years and older to define older adults, which is

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	Number of trials, n (%)
Published	127 (57%)
Pharmacological or non-pharmacological	
Non-pharmacological	9 (4%)
Pharmacological	213 (96%)
Diet	7 (3%)
Steroids	9 (4%)
5-Aminosalicylic acids	39 (18%)
Purines	4 (2%)
Anti-tumour necrosis factor	44 (20%)
Anti-integrins	15 (7%)
Anti-IL-12/IL-23	4 (2%)
Anti-IL-23	2 (1%)
Janus kinase inhibitors	8 (4%)
Inhibitors of sphingosine-1-phosphate	3 (1%)
Mesenchymal stem cells	6 (3%)
Antibiotics	7 (3%)
Probiotics	2 (1%)
Faecal transplantation	2 (1%)
Other IBD medications	34 (15%)
IBD medication class comparison	19 (9%)
Non-IBD medications	8 (4%)
Randomised/non-randomised	205 (92%)/17 (8%)
Double-blind/single-blind/open-label	168 (76%)/17 (8%)/37 (17%)
Monocentric/multicentric	23 (10%)/199 (90%)
Sponsorship	
Non-industrial	43 (20%)
Industrial	179 (81%)
Sample size	
1–50	28 (13%)
51–100	30 (14%)
101–500	111 (50%)
501–1000	41 (19%)
≥1001	11 (5%)
Missing	1 (1%)
Trial start year	
1995–2000	7 (3%)
2001–05	45 (20%)
2006–10	63 (28%)
2011–15	66 (30%)
2016–20	41 (19%)
Condition	
Ulcerative colitis	104 (47%)
Crohn's disease	107 (48%)
Ulcerative colitis and Crohn's disease	11 (5%)

IBD=inflammatory bowel disease. IL=interleukin. For published trials see references 37–151; details of unpublished trials are provided in the appendix (p 2–14).

***Table 1*: Characteristics of the 222 included trials**

See Online for appendix

considered in many countries as the official retirement age; although this is a pragmatic definition, it might no longer be relevant as life expectancy increases and, concomitantly, the age of retirement.[28] The same threshold value is used by the Centers for Disease Control and Prevention, the Agency for Healthcare Research and Quality, ClinicalTrials.gov, and the European Medicines Agency.

By contrast, geriatric medicine mostly uses the threshold of 75 years or even 80 years of age to define older adults. This choice is based on four considerations: first, the prevalence of age-related diseases and syndromes, frailty, and loss of autonomy, which all greatly increase after 80 years of age; second, the proportion of people within this age group is rapidly increasing in Europe—eg, between 1970 and 2020 the percentage of people older than 80 years in Europe increased from 2·4% to 7·9% for women and from 1·3% to 5·0% for men, and estimates suggest that, by 2024, more than 10% of the European population will be in this age group; third, life expectancy at age 80 years has increased by more than 50% during the past 50 years; and fourth, the evidence regarding the management of chronic diseases in this age group is very weak.[29,30]

For the population with IBD, the definition of older adults used in medical literature varies between 55 years and 70 years.[19] However, 60 years is the most widely accepted age limit, and is also the limit used to define older-adult-onset IBD, as agreed by the European Crohn's and Colitis Organisation in a 2016 topical review on IBD in older adults.[5,15,31] This difference in the definition of older adults compared with that of WHO is not surprising, as patients with IBD present a sterile low-grade inflammation leading to the senescence of cells, which, although not replicating, continue to produce pro-inflammatory cytokines including interleukin-6, C-reactive protein, and tumour necrosis factor, which are responsible for an acceleration of biological ageing and the earlier onset of geriatric syndrome.[32–34]

Methods

We conducted a systematic review in accordance with the Cochrane Handbook and the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analysis.[35,36] We searched PubMed and ClinicalTrials.gov for phase 3 clinical trials in IBD, registered from June 1, 1995 to August 1, 2021, and published in English. We used the following Medical Subject Heading terms, alone or matched with the Boolean operators "AND" or "OR": "phase III study", "ulcerative colitis" and "Crohn's disease". One author (SV) independently screened titles and abstracts to identify eligible studies. Full-text articles were examined for inclusion. In addition, the reference lists of selected manuscripts were searched manually to identify studies that were missed by the electronic search. After the identification of eligible studies, we extracted data (as of Nov 13, 2021) regarding the exclusion of participants on the basis of an arbitrary upper age limit and the percentage of patients older than 65 years who were included, when mentioned in the study. For studies in which patients older than 65 years were included, we

investigated whether the studies specified how many were older patients with adult-onset IBD and how many were patients with older-adult-onset IBD. For the studies for which the percentage of included patients older than 65 years was not reported, we tried to establish whether such patients were included or excluded. Exclusion criteria other than age were then recorded from protocols reported in ClinicalTrials.gov, and each comorbidity (ie, cardiovascular, pulmonary, renal, hepatic, endocrine, haematological, neurological, and gastrointestinal other than IBD) was analysed separately. Studies that excluded patients with a history of dysplasia or malignancy, cognitive impairment, functional limitations, and previous bowel resection or previous exposure to IBD treatment were also evaluated.

Results

Literature search

A summary of the search and selection process is shown in the appendix (p 1). Of the 430 phase 3 clinical trials we identified, we excluded 42 studies that were recruiting (n=37) or were registered but had not yet started recruitment (n=5), 39 studies that addressed only a paediatric population, 18 withdrawal trials, four studies that were registered twice in ClinicalTrials.gov, three studies that were not a phase 3 trial, and two studies that did not address patients with IBD. In addition, we excluded 65 maintenance trials that were an extension of an induction trial, 14 clinical trials that studied another endpoint of an included trial, and 21 pooled analyses of clinical trials included from PubMed.

Of the 222 phase 3 studies included in our analysis (169 identified from ClinicalTrials.gov, 15 identified from PubMed, and 38 identified in both), 127 (57%) have been published. We summarised the type of included study (pharmacological *vs* non-pharmacological, randomised *vs* non-randomised, double-blind *vs* single-blind *vs* open-label, industry-sponsored *vs* non-industry-sponsored), the type of medication, the trial start year, and the sample size (table 1).[37–151]

Exclusion of older adults from IBD trials

Almost two-thirds of the studies (n=129; 58%) excluded patients by using an upper age limit. This limit varied from older than 60 years to older than 130 years, and a limit of 75 years was the most common (table 2). Of the 222 studies included in the analysis, 20 studies excluded patients older than 65 years, and only 32 studies detailed the percentage of included patients who were 65 years or older. These 763 patients represented 5·4% of the 14124 participants in these 32 studies. None of these 32 studies specified whether these participants were older patients with adult-onset IBD or patients with older-adult-onset IBD. For the 170 remaining studies for which the percentage of people older than 65 years was not reported, we tried to establish whether these older patients were included or excluded. Unfortunately, the only information we obtained was the age of the patients who were included, but this was expressed in a heterogeneous way depending on the publication (eg, mean or median age, age of the whole cohort, or age according to the groups after randomisation), which made obtaining clear data impossible.

	Number of trials, n (%)
Upper age limit	129 (58%)
>60 years	2 (1%)
>65 years	18 (8%)
>70 years	21 (10%)
>75 years	50 (23%)
>80 years	32 (14%)
>85 years	1 (1%)
>90 years	1 (1%)
>95 years	0
≥99 years	4 (2%)
Comorbidities	168 (76%)
Generic term	75 (34%)
Cardiovascular	68 (31%)
Pulmonary	39 (18%)
Renal	82 (37%)
Hepatic	76 (34%)
Endocrine	43 (19%)
Haematological	41 (19%)
Neurological	46 (21%)
Gastrointestinal other than IBD	46 (21%)
Previous malignancy	99 (45%)
Previous bowel resection	36 (16%)
Previous exposure to IBD treatment	43 (19%)
Cognitive impairment or inability to give informed consent	12 (5%)
Disability	2 (1%)

IBD=inflammatory bowel disease.

***Table 2*: Frequencies of exclusion criteria that might negatively affect the inclusion of older individuals in the 222 included trials**

Looking beyond age: comorbidities

When considering older patients, other factors such as comorbidities, frailty, and functional status are arguably more important than age itself. Several comorbidities have been proposed to be related to IBD, including cardiovascular disease, neuropsychological disorders, and metabolic syndrome.[152] An assessment of frailty is important in patients with IBD and could help to identify those at higher risk of complications.[153]

In the included studies, the most common exclusion criteria were those based on comorbidities (168 [76%] of 222 trials). A total of 75 studies (34%) excluded patients in generic terms (ie, any condition that, in the investigator's opinion, makes the subject unsuitable for study participation). We detail exclusion by specific non-malignant comorbidities (table 2), of which renal, hepatic, and cardiovascular comorbidities were the most common

non-malignant exclusion criteria. History of cancer or dysplasia (99 [45%] of 222 trials), as well as previous bowel resection (36 [16%] of 222 trials) and exposure to previous IBD treatment (43 [19%] of 222 trials), both of which are more common in older patients with adult-onset IBD, can also contribute to the non-inclusion of patients.[18] We found few studies with cognitive impairment (12 [5%] of 222) as an exclusion criterion, and only two studies used functional limitation.

Frailty in IBD trials

Frailty is defined as a state of decreased general health reserve, resulting from a decline in the physiological capacity of multiple organ systems that ultimately increases vulnerability to stress, exposes the individual to adverse health outcomes, and influences the risk–benefit ratios of several medical and surgical treatments.[154–158] Although chronological age and comorbidities are often used in risk stratification tools, recent data suggest that frailty might be a better comprehensive assessment of an individual's risk of adverse health outcomes.[159–162] The prevalence of frailty increases with age, and patients who are frail present with more comorbidities; however, advanced chronological age, multimorbidity, and frailty are not synonyms.[163]

Proinflammatory cytokines have a role in the pathophysiology of frailty, which is particularly relevant to consider in chronic inflammatory diseases such as IBD.[164] However, frailty is probably undiagnosed in patients with IBD; a cohort study of 135 patients with IBD who were older than 65 years reported that 30 patients (22%) had increased vulnerability and 44% showed impairment during frailty testing.[165,166] This frailty, after adjustment for age and comorbidities, confers an increased risk of treatment-related infectious complications, with an increased risk for anti-tumour necrosis factor use (adjusted odds ratio [aOR] 2·05 [95% CI 0·7–3·93]) and immunomodulator use (1·81 [1·22–2·70]).[163] Regarding mortality and hospitalisation, Kochar and colleagues[167] showed, in a cohort of 11 000 patients, that frailty—independent of age and comorbidities—was associated with mortality (OR 2·90 [95% CI 2·29–3·68]). Similar results were found in two large-scale studies[168,169] showing that patients with IBD who are frail have a higher risk of readmission to hospital after discharge (adjusted hazard ratio [aHR] 1·21 [95% CI 1·17–1·25] in the study by Qian and colleagues and relative risk [RR] 1·16 [95% CI 1·14–1·17] in Faye and colleagues), a higher risk of mortality (aHR 1·57 [1·34–1·83] in Qian and colleagues, RR 1·12 [1·02–1·23] in Faye and colleagues), spend more days in hospital annually (4 extra days per year in the study by Qian and colleagues), had an average longer hospital stay (3 days in the study by Faye and colleagues), and higher hospitalisation-associated costs (US$17 791 [$8368–$38 942] *vs* $10 924 [$5571–$22 632] in Qian and colleagues; $20 916 *vs* $13 539 in Faye and colleagues) than patients with IBD who were not frail. Frailty also seems to be a stronger predictor than age for postoperative morbidity in both ulcerative colitis (in which frailty was associated with an increased risk of septic and cardiopulmonary complications) and Crohn's disease.[170,171]

These consequences of frailty, in the context of IBD, are a relatively new consideration and some issues still need to be addressed, such as identifying the most appropriate frailty-assessment tool for predicting adverse outcomes in patients with IBD, evaluating whether frailty can be improved by treatment (because an inflammatory state in patients with older-adult-onset IBD could trigger or worsen underlying geriatric deficits) or by individually targeted interventions (eg, physical rehabilitation, nutritional supplementation, and cognitive training), and assessing whether treatment response is affected by the degree of frailty.[168,172–175]

Proposal for inclusion of older adults in IBD trials before drug approval

As early as 1989, the US Food and Drug Administration stated: "There is no good basis for the exclusion of patients on the basis of age alone, or because of the presence of any concomitant illness or medication, unless there is a reason to believe that the concomitant illness or medication will endanger the patient or lead to confusion in interpreting the results of the study."[176] In oncology, in which the inclusion of older people in clinical trials has been widely studied, setting upper age limits in clinical trials is generally considered to be rarely justified, and in many cases, ethical review fails to highlight the issue of excluding patients on the basis of age.[177] We propose to include both older patients with adult-onset IBD and patients with older-adult-onset IBD in clinical trials, regardless of their age.

If the age limit is abolished, considering the functional status of patients is important as it seems to be a better determinant of negative health outcomes than age. Abolishing age limits, better differentiation between patients who are fit and those who are frail, and reducing other exclusion criteria could improve the enrolment of older patients into IBD trials.[161,162]

Several tools have been used in IBD to assess frailty, such as Frailty Risk Score, International Classification of Diseases codes, Fried frailty phenotype criteria, the simplified Frailty Index score, and the Hospital Frailty Risk Score; however, these indices are based on cumulative deficits and do not incorporate a comprehensive assessment of the different domains of functional capacities.[155,163,167,178–181] Simple, fast, and effective tools are needed to enable a more standardised geriatric assessment. The development and validation of such indices would take time. We could, while waiting for these, evaluate patients with IBD by building on the Comprehensive Geriatric Assessment proposed by Asscher and colleagues[181,182] which explores different geriatric domains reflecting a patient's health, including

the somatic, functional, and mental domains.

We summarise a proposal for the inclusion of older adults with IBD in clinical trials (panel), which we hope will be further investigated. On the basis of the tools proposed by Asscher and colleagues,[181] we propose, as a first step, to include patients with preserved somatic function in clinical trials. These patients could be identified by: the absence of malnutrition risk or a score of more than 11 on the Mini-Nutritional Assessment short form;[183] a low Charlson Comorbidity Index, which considers the number and severity of 16 predefined comorbidities[184] (as higher Charlson Comorbidity Indices are associated with higher risk of infection[185] in patients with IBD, and increased post-colonoscopy hospitalisation[186]); and the absence of polypharmacy—preferably five or fewer non-IBD prescription medications[187] (as polypharmacy, which is frequent in patients with IBD,[188,189] can lead to drug–drug interactions that could affect the efficacy and safety of IBD medication and can affect a patient's adherence to treatment[18]).

An assessment of the functional domain—which reflects daily living activities and physical capacity—is important before the inclusion of older patients in clinical trials, not only to assess the ability of patients to attend outpatient appointments but also because clinical trials often require serial endoscopy, which could be made difficult by the functional limitations of older patients.[190,191] Patients to be included in trials should probably have no impairment of daily living activities, which could be defined as having a Katz Index of Independence in Activities of Daily Living[192] score or a Lawton Instrumental Activities of Daily Living scale (sex-adjusted)[193] score of less than 1, and preserved physical capacities, as evaluated by isometric hand-grip strength (assessed by three measures with the dominant hand) with a Jamar hand dynamometer[194] (stratified by sex and body-mass index, according to Fried and colleagues[155]) and 4-m gait speed.[195]

Assessment of the mental domain is also important during screening, because participation in a clinical trial requires sufficient cognitive function to understand the information provided; patients who are selected must be able to make decisions, but also adhere to the treatment and evaluation tests (eg, questionnaires, blood, stool samples, and endoscopies). A score of fewer than 8 points in the Six-Item Cognitive Impairment Test (a short cognition test with a maximum score of 28 points) could be an indication of a good cognitive function.[196]

As well as the somatic, functional, and mental domains, which integrate the overall level of frailty, other patient-related criteria should be considered so as to appropriately select an older patient for a clinical trial, including a definitive diagnosis of IBD. Such a definitive diagnosis can be challenging given the wide-ranging differential diagnoses and misdiagnoses, which can occur in up to 60% of older patients.[15,197] Specifically, conditions such as ischaemic and infectious colitis, segmental colitis associated with diverticular disease, radiation damage secondary to gynaecological or prostate cancers, solitary rectal ulcer syndrome, and NSAID-induced ulcers can mimic IBD and could therefore influence the assessment of the response to treatment.[198,199] Older patients also have a higher risk of malignancy than younger patients, whether it is a recurrence of a previous cancer or the occurrence of a new disease, which justifies a certain caution for their inclusion in therapeutic trials. Although there are already many recommendations regarding the use of immunosuppressants in patients with a history of cancer, caution is required in the use of lesser-known molecules or those under investigation, for which there

***Panel*: Proposal for the inclusion of older patients with IBD in clinical trials**

Patient-related considerations

- Include older patients with adult-onset IBD and patients with older-adult-onset IBD, regardless of their age
- Identify suitably fit patients taking into account the following:

Somatic domain

- Malnutrition (Mini Nutritional Assessment score >11)
- Comorbidities (low Charlson Comorbidity Index)
- Polypharmacy (<5 non-IBD medications)

Functional domain

- Daily living activities (Katz Index of Independence in Activities of Daily Living score <1; Lawton Instrumental Activities of Daily Living score <1, corrected for sex)
- Physical capacity (hand-grip strength; 4-m gait speed)

Mental domain

- Cognitive function (Six-Item Cognitive Impairment Test <8 points)

Other criteria

- Definitive diagnosis of IBD
- No previous malignancy or dysplasia history
- Up-to-date dysplasia screening colonoscopy
- Normal life expectancy

Trial-related considerations

- Validate the use of patient-reported outcomes and biomarkers
- Define appropriate clinical endpoints
- Define the ideal time at which to assess the clinical response

Research team-related considerations

- Collaborate closely with a geriatrician and their team
- Recruit a nurse specialised in caring for and communication with older adults
- Expand the research team or implement extra working hours for the current team
- Carry out some of the consultations at patients' homes

IBD=inflammatory bowel disease.

is less experience with oncogenic risks.[200,201] Moreover, because older patients with IBD have a higher risk of colonic dysplasia related to the long duration of their disease, patients should be up to date with dysplasia screening colonoscopy before inclusion in a trial.[202]

In addition to the selection of suitable patients in terms of somatic, functional, and mental capacity, there are several issues that need to be resolved before including older patients with IBD in clinical trials. First, further research is needed to assess how symptoms, especially those included in patient-reported outcomes, and biomarkers (C-reactive protein and faecal calprotectin) can be affected by the range of non-specific conditions found in older populations (such as pelvic floor dysfunction and incontinence) and to validate their use in the prediction of disease activity in the population of older patients with IBD.[203,204] Second, appropriate clinical endpoints (symptom control *vs* objective) should be considered for clinical trials in the older population. Although mucosal healing remains an ideal treatment target, this needs to be weighed against the risk of therapy escalation in this vulnerable population with a shorter lifespan.[205] Moreover, the ideal time to assess clinical response should also be studied, as some studies have suggested that the time to treatment effect is prolonged in older patients.[206] Finally, examining whether older patients should be included in the same clinical trials as their younger counterparts or be the subject of separate studies would be of interest. Several studies suggest that older patients with IBD have a poorer response to treatment, even after adjusting for duration of disease and altered pharmacokinetics (absorption, distribution, metabolism, and elimination are affected by ageing), and that the inclusion of older patients in clinical trials could lead to poorer outcomes than expected and adversely influence drug prescription.[206–208]

The inclusion of older patients with IBD in clinical trials will probably require adaptations for the research team, such as working more closely with geriatricians and their teams, recruitment of a nurse specialised in caring for and communication with older adults, expansion of the research team (or a requirement for the existing staff to work extra hours) because caring for older adults might take more time, and, eventually, potentially carrying out some consultations in patients' homes.[209]

Future outlook

This systematic review shows that older adults are frequently excluded from IBD clinical trials because of their age, but also because of comorbidities, a history of dysplasia or cancer, and, in the case of older patients with adult-onset IBD, exposure to previous IBD treatment. Few phase 3 studies have used functional status as an exclusion criterion, although the assessment of frailty and functional capacities seems to be a better approach than screening by age to stratify the risk of adverse events. A three-step process should be considered. First, we propose including older patients with IBD in phase 2–3 clinical trials according to the suggested inclusion criteria, and suggest stratification according to age. Second, after drug approval, real-world studies should be done to assess the effect of age, comorbidities, and frailty on the feasibility, safety, and efficacy of the use of these new compounds in older patients who are frail and who have comorbidities. A favourable benefit–risk ratio could support proceeding to a third step, involving clinical trials that include all older people with IBD—with or without comorbidities and who are frail or not—to better reflect the true population of patients with IBD and to enable the development of evidence-based guidelines for the use of these new compounds in clinical practice for older patients with IBD with different levels of frailty. The exclusion criterion for these trials could be the inability to attend outpatients appointments or to conduct the examinations needed according to each study protocol. Pending results from such trials, data from phase 2–3 clinical trials that include older patients with IBD should not be extrapolated to older adults with comorbidities, who are frail, or both.

Contributors

LP-B conceived the study. SV wrote the article and created the tables and appendix. BC, VJ, AB, SD, EL, and LP-B critically reviewed the content of the manuscript, which was approved by all authors.

Declaration of interests

BC reports lecture fees from AbbVie, Amgen, Ferring Pharmaceuticals, Janssen Pharmaceuticals, and Takeda; and consulting fees from Celltrion and Janssen Pharmaceuticals. VJ has received consulting and advisory board fees from AbbVie, Alimentiv (formerly Robarts Clinical Trials), Arena Pharmaceuticals, Asahi Kasei Pharma, Asieris Pharmaceuticals, Bristol Myers Squibb, Celltrion, Eli Lilly, Ferring Pharmaceuticals, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genentech, Gilead Sciences, Janssen Pharmaceuticals, Merck, Mylan, Pandion, Pendopharm, Pfizer, Protagonist Therapeutics, Reistone Biopharma, Roche, Sandoz, Second Genome, Takeda, Teva Pharmaceuticals, and Topivert Pharma; and speaker's fees from AbbVie, Ferring Pharmaceuticals, Galapagos, Janssen Pharmaceuticals, Pfizer, Shire, and Takeda. SD has served as a consultant for Schering-Plough, AbbVie, Actelion, Alphawasserman, AstraZeneca, Cellerix, Cosmo Pharmaceuticals, Ferring Pharmaceuticals, Genentech, Grünenthal, Johnson & Johnson, Millennium Takeda, Merck Sharp & Dohme, Nikkiso Europe, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, UCB Pharma, and Vifor; and as a speaker for Pfizer, Takeda, AbbVie, and Janssen Pharmaceuticals. EL reports research grants from Janssen Pharmaceuticals, Pfizer, Ferring Pharmaceuticals, Dr Falk Pharma, AbbVie, and Takeda; educational grants from AbbVie, Janssen Pharmaceuticals, Fresenius Kabi, and Takeda; speaker's fees from AbbVie, Dr Falk Pharma, Ferring Pharmaceuticals, Janssen Pharmaceuticals, Pfizer, Galapagos, and Takeda; advisory board membership of AbbVie, Celgene, Ferring Pharmaceuticals, Janssen Pharmaceuticals, Bristol Myers Squibb, Pfizer, Takeda, Galapagos, Gilead Sciences, Arena Pharmaceuticals, and Eli Lilly; and has served as a consultant for AbbVie. LP-B reports personal fees from Galapagos, AbbVie, Janssen Pharmaceuticals, Genentech, Ferring Pharmaceuticals, Tillots Pharma, Pharmacosmos, Celltrion, Takeda, Boerhinger Ingelheim, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Alma Bio Therapeutics, Sterna Biologicals, Nestlé, Inotrem, Enterome, Allergan, Merck Sharp & Dohme, Roche, Arena Pharmaceuticals, Gilead Sciences, Hikma Pharmaceuticals, Amgen, Bristol Myers Squibb, Vifor Pharma, Norgine, Mylan, Eli Lilly, Fresenius Kabi, Oppilan Pharma, Sublimity Therapeutics, Applied Molecular Transport, OSE Immunotherapeutics, Enthera, Theravance, and Pandion Therapeutics; grants from AbbVie, Merck Sharp & Dohme, Takeda, and Fresenius Kabi; and stock options for Clinical Trials Mobile

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