Clinical Medicine Insights: Geriatrics

REVIEW

Treatment of Ulcerative Colitis in the Elderly: A Systematic Review

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Abstract: Ulcerative colitis (UC) is increasingly recognized as a disease affecting the elderly. Approximately 10%–30% of the UC population is over the age of 60 years. Additionally, younger patients with UC are aging and thus comprise a second group of elderly IBD patients. To date, there have been no clinical trials that have evaluated treatment efficacy of UC in the elderly population. The aim of our study was to conduct a systematic review of all randomized controlled trials (RCTs) addressing treatment outcome in UC; we also sought to identify the elderly population, defined as age 60 years or older, represented in these studies, to see if pooled data would lead to meaningful conclusions regarding treatment efficacy and safety profile in the elderly. A search of the MEDLINE database via PubMed and the EMBASE database via Scopus was performed to identify all RCTs evaluating medical therapy for UC in humans, published within the English language through September 2012. Studies were grouped into three categories: biological agent (BA) therapy; immunosuppressant (IS) therapy; and 5-aminosalicylic acid (5-ASA) therapy. To estimate the number of elderly patients in each study, mean age plus 1 and 2 standard deviations (SD) was calculated to find the closest approximation to age 60. Of 876 studies, 112 RCTs were included in the final analysis—20 studies for BA, 20 for IS, and 72 for 5-ASA agents. While nearly all studies reported either a mean or median age, only 38% additionally reported the SD and age range. The mean composite age was 39.2 years for the BA studies, 38.5 years for the IS studies, and 42.8 years for the 5-ASA studies, consistent with a young middle-aged patient. We estimated that no more than 16% of patients per study would have qualified as elderly, and in most cases a much smaller percentage (<8%). Additionally, there were no BA or IS RCTs that reported results by age subgroup analysis. Four studies in the 5-ASA group report age-specific analyses and showed no difference in treatment efficacy by age. None of the 112 RCTs reported age sub-analyses of safety, tolerability, adverse events, or withdrawal rates. There is insufficient evidence to evaluate efficacy of treatment and adverse events from treatment for UC in the elderly. With the rising number of elderly patients with UC, there is a need for more clinical trials that specifically address UC treatment in this unique population.

Keywords: IBD (inflammatory bowel disease), UC (ulcerative colitis), elderly, treatment, safety

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Introduction

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory condition of the gastrointestinal tract with a relapsing, remitting course. While considered to be primarily a condition affecting young adults, UC can present at any age, including the elderly. Not only are new cases of UC diagnosed in older individuals, but given the negligible impact of inflammatory bowel disease (IBD) on mortality, younger patients with UC are also aging, and thus comprise a second group of elderly IBD patients.[1,2] Determining the true incidence of UC in the elderly is challenging for a variety of reasons. In addition to differences in populations studied, regional variations, case definitions of IBD, and the potential for misdiagnoses of ischemic colitis and nonsteroidal anti-inflammatory drug (NSAID)-induced colitis, there has been no standard definition of what age constitutes 'elderly'.[3–5] In several publications, the term was arbitrarily assigned to patient groups aged between 40–75.[6] Most developed world countries have accepted the chronological age of 65 years as a definition of 'elderly' or older person; however, the United Nations generally uses 60 years or greater to refer to the elderly population.[7]

The traditional view on IBD proposed a bimodal age distribution, with an initial peak between 20–30 years and a second, smaller peak occurring between the age of 60–80.[3,8–12] However, the existence of this second peak has not been reproduced in other studies, including the most recent epidemiologic survey from Olmsted County, Minnesota.[13–17]

The recognition of a growing elderly IBD population warrants a critical assessment of the literature used to guide treatment in this unique population. Factors potentially influencing optimal disease management include polypharmacy, drug interactions, comorbidity, and differences in disease location and severity.[18]

The goals for treatment of UC in the elderly remain the same as in younger patients, including induction and maintenance of clinical response and remission, reduction of disease related complications, improvement of quality of life, and minimizing short- and long-term toxicity. Early aggressive therapy along with combined therapy has been endorsed as a more favorable treatment strategy for the general IBD population. Although the commonly accepted perception is to be cautious when treating the elderly, the data behind these recommendations appears to be lacking. Ideally, there would be randomized controlled studies with the primary objective being the evaluation of treatment efficacy in elderly UC patients; however, this data does not yet exist. Therefore, the treatment algorithm for elderly IBD patients has been extrapolated from the same trials that have formed the basis for clinical practice recommendations and evidence-based guidelines for the management of IBD in general.[6]

Randomized controlled trials (RCTs) are recognized as the best approach available to study treatment outcome. By implementing strict study enrollment criteria, these trials aim to minimize the potential bias of confounding variables so as to preserve the internal validity of the study results. It is assumed that the findings obtained from RCTs carry a high level of external validity with applicability to general clinical practice.[19] However, using such stringent inclusion and exclusion criteria might actually limit the generalizability of the trial results. In a recent study, Ha et al found that only 26% of patients in their practice would qualify to participate in any of the 7 RCTs of biological therapy for UC that they reviewed. The applicability of published RCTs dealing with treatment of UC, specifically to elderly patients, is unknown.

In this systematic review of all randomized controlled trials addressing treatment outcome of UC, our aim was to identify the elderly population represented in these studies and to evaluate any subgroup analyses by age; we aimed to see if pooled data would lead to meaningful conclusions regarding treatment efficacy and safety profile in the elderly.

Methods

We performed a comprehensive computer-assisted literature search for treatment of ulcerative colitis; we used the MEDLINE database via PubMed, searching up to September 2012. MeSH terms were 'Colitis, Ulcerative/drug therapy' OR 'Colitis, Ulcerative/therapy'. Applied filters included randomized controlled trials, human species, and English language. A total of 531 citations were found. Additionally, the EMBASE database was searched via Scopus. The key term 'ulcerative colitis' was used in conjunction with all the active agents identified in our PubMed search. A total of 345 additional citations were found.

Titles and abstracts were assessed by one reviewer (BH) according to predetermined inclusion criteria. Studies were accepted if they were RCTs, patients had either active UC or remission of UC, and there was evaluation of an active agent in the treatment efficacy of UC. Active agents included in this study were biological agents (BA), immunosuppressants (IS) and 5-aminosalicylic acid (5-ASA) therapy. A total of 291 studies were immediately excluded because the active agent was not a BA, IS, 5-ASA therapy, or by review of title and abstract alone, were not RCTs. After this initial exclusion, 2 independent authors reviewed the remaining 240 studies (BH and BB). When differences existed, they were resolved by consensus; when needed, a third reviewer was consulted (AS). Relevant studies were identified from this group based on the inclusion and exclusion parameters. Outcome measures included response to therapy, remission rates, and relapse rates. We used the authors' definition of outcome for clinical remission, endoscopic remission, and response. When multiple comparisons were evaluated in a single study, the analysis was restricted to the most clinically appropriate or most effective dose. Since the patients in a given study are all randomized, the population characteristics of each treatment arm should be representative of the entire study population. After critical review, studies were further excluded if they were not RCTs or if they had primary outcomes other than those specified. Additional studies were excluded if the active agent was a rectal formulation alone, age data was not reported, included pediatric population only, reported on patient populations previously studied, and reported on both UC and Crohn's disease (CD) without separating age data and/or results. In total, 240 studies were included and grouped into three categories: BA, IS, 5-ASA related agents. A flow diagram describing the search and study selection strategies is shown in Figure 1.

Biological therapy was evaluated in 33 studies identified by the original search. Thirteen studies were excluded; four were not RCTs, 1 evaluated pediatric patients, 2 a previously studied population, 2 enema only studies, and 4 had outcomes other than induction or maintenance of remission. In total, 20 studies evaluating BA therapy for the treatment of UC were included.

Immunosuppressant therapy was evaluated in 68 studies identified by the original search. Six studies were not RCTs. Three studies evaluated pediatric patients, 24 rectal suppositories or enemas, 3 outcomes other than induction or maintenance of remission, and 4 previously studied populations. Two studies contained no age related data, 2 involved only patients with distal disease, and 2 evaluated patients with CD and UC, but did not report results by disease subset. One study did not evaluate an active agent but rather evaluated patient-led variable dosing. One study did not report sufficient results. These 48 studies were excluded, leaving 20 studies evaluating IS therapy for the treatment of UC included in this analysis.

5-ASA therapy was evaluated in 139 studies identified by the original search. Exclusion was because of the following reasons: 6 studies were not RCTs, 3 evaluated pediatric patients, 44 enemas or suppositories, 6 outcomes other than induction or maintenance of remission, 2 previously studied populations, 4 contained no age related data, 1 evaluated the effect of a tailored regimen rather than the effect of the active agent itself, and 1study evaluated patients with UC and CD, but did not report results by disease subset. A total of 72 articles evaluating 5-ASA therapy were included.

The EMBASE database results were combined with the original MEDLINE search. This yielded 201 citations. In a similar fashion one reviewer (BH) assessed the title and abstracts. 190 articles did not meet predetermined inclusion criteria. Of the 21 remaining articles, 15 were part of the original MEDLINE search; full text English version was not available in 'three of these. One article was a study reported in two unique journals and had already been included in the EMBASE search. Only 2 unique articles met our inclusion criteria. Both were excluded because they did not report adequate age data.

Data Synthesis and Analysis

There is no standardized method for reporting age. Thus, age was reported in a variety of ways, including numbers for the total population enrolled versus subsets by treatment group. The variables for age assessment include a reported mean or median age with or without standard deviation (SD) or standard error of the mean (SEM). Age range was sometimes reported. Interquartile range was rarely included.

In this analysis, we define elderly as an age of 60 years or older. When age ranges were reported in

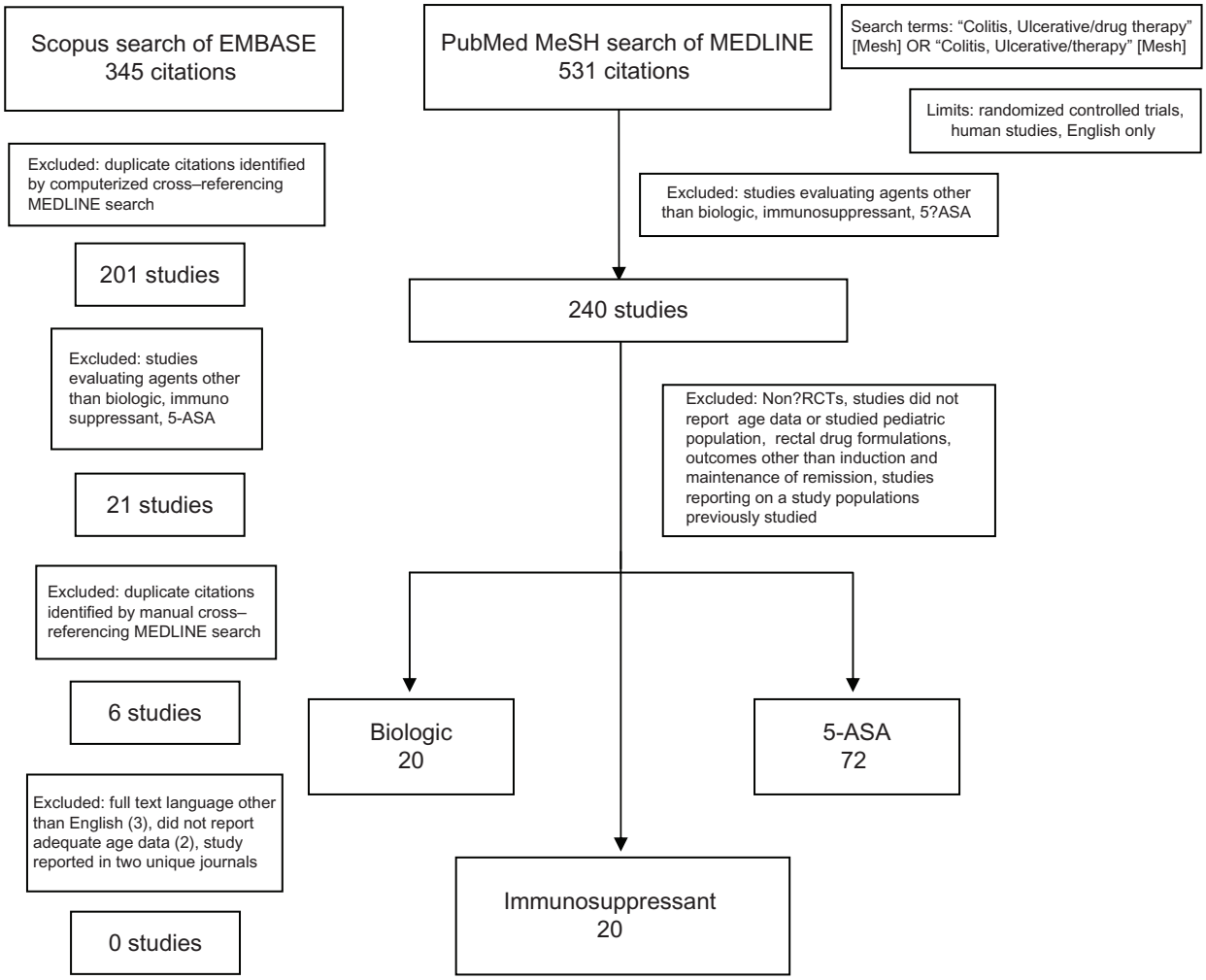

Figure 1.

the articles analyzed, one could determine if patients greater than 60 years of age were included in the study. When standard deviation was reported, estimation of the number of elderly patients in the study population could be calculated. Likewise, if the SEM was instead reported, it was converted to SD (calculation SEM $\times \sqrt{n}$ = SD). To estimate the number of elderly patients in each study, mean age plus 1 and 2 SD was calculated to find the closest approximation to age 60. Additionally, mean age plus 1 SD would represent approximately 16% of the study population, whereas mean age plus 2 SD would represent approximately 2.5% of the study population. Using these percentages, we then estimated the number of patients who were elderly in the study group. For example, in a study with 100 participants and mean age of 40 and a SD of 10, sixteen percent of the patients would be 50 years or older, and 2.5% would be 60 years or older. With a sample size of 100, that would mean 2–3 individuals would be elderly. Of note, there were a few studies that reported specific age subgroups, with number and percentage. When this was the case, we did not perform our own calculation but rather used what the study reported.

Results

Biological agents

Biological agents age summation

Twenty studies were included in this analysis and are summarized in Table 1.[20–38] All 20 studies reported a mean age. The composite mean age was 39.2 years with a mean range of 36.2 to 44 years. Thirteen studies reported SD of the mean age, 4 studies reported age range, 1 study reported interquartile range, and only 1 study reported both the SD and age range. When reported, the overall age range was 18–75, but in

Table 1.

	Author	Year	Total enrolled	Active agent	Active agent								Comparator	Results		
					N	Mean age	SD	Range	Mean age plus 1 SD	N ≥ mean plus 1 SD	Mean age plus 2 SD	N ≥ mean plus 2 SD		Study end-point	Study duration	Active agent vs. comparator
Infliximab	Rutgeerts	2005	364	ACT-1 Infliximab 5 mg/kg	121	42.4	14.3		56.7	19	71.0	3	Placebo	Induction remission	8 wks	38.8% vs. 14.9%
			364	ACT-2 Infliximab 5 mg/kg	121	40.5	13.1		53.6	19	66.7	3	Placebo	Induction remission	8 wks	33.9% vs. 5.7%
	Armuzzi	2004	20	Infliximab 5 mg/kg	10	36.2		24–50					Methylpredni-solone	Induction remission	2 wks	100% vs. 100%
	Ochsenkuhn	2004	13	Infliximab 5 mg/kg	6	31.0		21–44					Prednislone	Clinical response	13 wks	50% vs. 71.4%
	Probert	2003	43	Infliximab 5 mg/kg	23	41.0		35.5–50.5*					Placebo	Induction remission	8 wks	39% vs. 30%
	Sands	2001	11	Infliximab 5–20 mg/kg	7	38.0	12.6	20–63	50.6	1	63.2	0	Placebo	Treatment failure	2 wks	50% vs. 0%
Adalimumab	Sandborn	2012	494	Adalimumab 160/80/40 mg	248	39.6	12.5		52.1	40	64.5	6	Placebo	Induction/ maintenance remission	8, 52 wks	16.5% and 17.3% vs. 9.3% and 8.5%
	Reinisch	2011	390	Adalimumab 160/80/40 mg	130	36.5		18–75					Placebo	Induction remission	8 wks	18.5% vs. 9.2%
Tofacitinib	Sandborn	2012	194	Tofacitinib 15 mg	49	41.2	13.5		54.7	8	68.2	1	Placebo	Clinical response	8 wks	78% vs. 42%
Daclizumab	Van Assche	2006	159	Daclizumab 2 mg/kg	47	42.6	15.4		58.0	8	73.3	1	Placebo	Induction remission	8 wks	7% vs. 10%
Visilizumab	Sandborn	2010	127	Visilizumab 5 mcg/kg	84	40.4	12.9		53.3	13	66.2	2	Placebo	Induction remission	45 days	8% vs. 9%
	Baumgart	2010	73	Visilizumab 5–12.5 mcg/kg	73	38.8	11.4		50.2	12	61.6	2	None	Induction remission	30 days	50% vs. 71%
Basiliximab	Sands	2012	149	Basiliximab 20–40 mg	52	39.0	12.0		51.0	8	63.0	1	Placebo	Induction remission	8 wks	29% vs. 28%
Abatacept	Sandborn	2012	490	Abatacept 10 mg/kg	139	42.1	13.5		55.6	22	69.1	3	Placebo	Induction remission	12 wks	19% vs. 29.5%
Interferon	Pena-Rossi	2008	194	Interferon-beta-1a 44 mcg	65	39.9	14.0		53.9	10	67.9	2	Placebo	Induction remission	12 wks	29.5% vs. 23.4%
	Musch	2005	91	Interferon-beta-1a 3 MIU	32	38.0							Placebo	Clinical response	8 wks	56% vs. 34%

(*Continued*)

Table 1. (*Continued*)

Author	Year	Total enrolled	Active agent	Active agent								Comparator	Results		
				N	Mean age	SD	Range	Mean age plus 1 SD	N ≥ mean plus 1 SD	Mean age plus 2 SD	N ≥ mean plus 2 SD		Study end-point	Study duration	Active agent vs. comparator
	Tilg	2003	60	Pegylated interferon-alpha 0.5 mcg/kg	19	36.9	13.2		50.1	3	63.3	0	Placebo	Induction remission	12 wks	47% vs. 35%
	Nikolaus	2003	10	Interferon-beta-1a 22–88 mcg	10	42.2		32–68					Placebo	Induction remission	8 wks	50% vs. 14%
Integrin antibody	Feagan	2005	181	Alpha4Beta7 integrin Ab 0.5 mg/kg	58	41.6	14.7		56.3	9	71.0	1	Placebo	Induction remission	6 wks	33% vs. 14%
Rituximab	Leiper	2011	24	Rituximab 1 g	16	37.0	15.0		52.0	3	67.0	0	Placebo	Induction remission	4 wks	18.8% vs. 12.5%

Notes: Adalimumab 160 mg week 0, 80 mg week 2, then 40 mg every other week. *interquartile range.
Abbreviations: wks, weeks; SD, standard deviation.

many studies the age range was much smaller. Based on the age range data alone, 2 studies did not include elderly patients.[20,26] There were a total of 14 studies in which the estimated number of elderly patients could be calculated by adding 1 or 2 SD to the mean age, whichever provided the closest estimate to an elderly age. Using this method, approximately 16% of the study population had a mean age of 53.4 years (mean of 'mean plus 1 SD') or older. In most cases, a calculation of mean age plus 2 SD provided a closer approximation to an elderly age, with approximately 2.5% of the study population aged 66.9 years or older.

Efficacy of biological agents

Infliximab

Six RCTs have evaluated infliximab (IFX) for clinical improvement in patients with moderate to severely active UC. The primary outcome measure for these studies was induction of remission in 4 studies, clinical response in 1 and treatment failure in 1. Outcome assessment was performed at a range of 2–13 weeks. In an initial study by Sands, IFX was administered at doses ranging from 5 mg/kg to 20 mg/kg.[36] Eight patients received IFX, of which half responded to therapy. No patients receiving placebo achieved remission. In a second placebo controlled trial, Probert found that remission rates were not statistically different.[28] A 2004 study by Ochsenkuh showed IFX to be as effective as corticosteroids in the induction of remission;[26] a similar study by Armuzzi corroborated these results.[20] In the ACT-1 and ACT-2 trials completed by Rutgeerts et al, 121 patients in each of the two studies received IFX 5 mg/kg.[30] In comparison to placebo, remission induction rates for IFX were 38.8% and 33.9% versus 14.9% and 5.7% respectively. These results were statistically significant. The overall age range for these studies was 20–63 when reported. Two studies did not include elderly patients based on the reported age ranges.[20,26] The ACT-1 and ACT-2 trials reported mean age with SD.[30] In the ACT-1 trial the mean age was 42.4 and the mean age plus 1 and 2 SD was 56.7 and 71.0, respectively. Based off of these estimations, the number of patients enrolled in the active arm of the study was 19 patients over the age of 56.7 and 3 patients over the age of 71.0. In the ACT-2 trial, the mean age was 40.5 and the mean age plus 1 and 2 SD was 53.6 and 66.7, respectively. Thus in the ACT-2 trial, 19 patients in the IFX group were

over the age of 53.6 and 3 patients were over the age of 66.7. Sands reported both the SD and age range.[36] Based on this information the study contained one elderly patient. In Probert's study, mean age was 41 with an interquartile range 35.5–50.5.[28] There was no age subgroup analysis of the results in this study.

Adalimumab

Reinisch examined adalimumab (ADA) in moderate to severe UC.[29] Three hundred-ninety patients were enrolled, 130 receiving ADA at the optimal dose. Induction of remission was achieved in 18.5%, compared to 9.2% for placebo. Sandborn also evaluated ADA in moderate to severe UC.[34] In total, 494 patients were enrolled in this trial and 248 received ADA. Induction and maintenance of remission were considered co-primary outcomes. At 8 weeks, induction of remission was 16.5% in the ADA group as compared to 9.3% in the placebo group. Maintenance of remission at 52 weeks was 9.3% versus 8.5%, respectively. The mean age for these two studies was 36.5 years and 39.6 years.[29,34] The Reinisch study reported an age range of 18–75 years, but it did not report a SD of the mean; thus, no further age related information could be estimated.[29] Sandborn et al reported a mean age and SD. The mean age plus 1 SD was 52.1 years, and thus 40 patients were older than 52.1 years.[34] In this case mean age plus 2 SD was a closer estimate to an elderly age, 64.5 years. Using this calculation, 6 patients out of the 248 in the treatment arm were older than 64.5 years. There was no age subgroup analysis of the results in this study.

Tofacitinib

Sandborn evaluated tofacitinib in moderately to severely active UC.[33] One hundred ninety-four patients were enrolled, 49 receiving tofacitinib 15 mg. Clinical response at 8 weeks was seen in 78% versus 42% for placebo. The mean age was 41.2. Mean age plus 1 SD and 2 SD was 54.7 and 68.2, respectively. This study contained 23 patients over the age of 54.7 and 4 patients over the age of 68.2. There was no age subgroup analysis of the results in this study.

Daclizumab

Van Assche studied daclizumab 2 mg/kg compared to placebo for the induction of remission in 159 patients with moderate UC.[38] At eight weeks, remission rates were 7% and 10% respectively. The mean age was 42.6. The mean age plus 1 SD and 2 SD was 58.0 and 73.3 respectively. This study contained 8 patients over the age of 58.0 and 1 patient over the age of 73.3. There was no age subgroup analysis of the results in this study.

Visilizumab

Sandborn studied visilizumab in severe refractory UC. One hundred twenty-seven patients were enrolled and 84 received visilizumab.[31] Remission rates at day 45 were 8% for visilizumab and 9% for placebo. The results were not statistically significant. Baumgart examined visilizumab at varying doses in severe, steroid refractory UC.[21] Seventy-three patients were studied. Remission induction rates at day 30 were 71% at a dose of 12.5 mcg/kg. No placebo was used for comparison. Both studies reported mean age and SD. Baumgart et al reported a mean age of 38.8.[21] The mean age plus 1 and 2 SD was 50.2 and 61.6, respectively. The study contained 9 patients over the age 50.2 and 1 patient over the age 61.6. In the Sandborn trial, the mean age was 40.4 years, with a calculated mean age plus 1 and 2 SD of 53.3 and 66.2, respectively.[31] The study contained 13 patients over the age of 53.3 years and 2 patients over the age of 66.2 years in the active treatment group. There was no age subgroup analysis of the results in this study.

Basiliximab

Sands studied basiliximab versus placebo in patients with moderate to severe UC.[35] In this study, 149 patients were enrolled and 52 received basiliximab 40 mg. At eight weeks, induction of remission in patients receiving basiliximab was 29% versus 28% in those receiving placebo. The mean age was 39.0. The mean age plus 1 SD and 2 SD was 51.0 and 63.0, respectively. This study contained 8 patients over the age of 51.0 and 1 patient over the age 63.0. There was no age subgroup analysis of the results in this study.

Abatacept

Sandborn found that after 12 weeks of therapy, abatacept achieved clinical remission in 19% versus 29.5% in those treated with placebo.[32] The mean age of the abatacept group was 42.1. The mean age plus 1 SD and 2 SD was 55.6 and 69.1, respectively. This

study contained 22 patients over the age of 55.6 and 3 patients over the age of 69.1. There was no age subgroup analysis of the results in this study.

Interferon

Four studies evaluated interferon for the treatment of active UC. None showed any statistically significant clinical benefit. Nikolaus, Musch and Pena-Rossi studied interferon beta-1 and Tilg examined pegylated interferon alpha.[24,25,27,37] The mean age in these studies ranged was 36.9–42.2. One interferon-beta-1a study reported an age range of 32–68.[25] Two studies, one for interferon-beta-1a and one for pegylated interferon-alpha, reported SD.[27,37] The mean age plus 1 SD ranged from 50.1 to 53.9. The mean age plus 2 SD ranged from 63.28 to 67.9. One study, reported only the mean age of 38.[24] There was no age subgroup analysis of the results in this study.

Alpha4beta7 integrin

Feagan studied alpha4beta7 integrin for the induction of remission of moderate to severely active UC.[22] One hundred eighty-one patients were enrolled with 58 receiving 0.5 mg/kg. At 6 weeks, remission rates were 33% in comparison to 14% receiving placebo. The mean age was 41.6. The mean age plus 1 SD and 2 SD was 56.3 and 71.0, respectively. This study contained 9 patients over the age of 56.3 and 1 patient over the age of 71.0. There were no results reported by age subgroup analyses.

Rituximab

Leiper studied rituximab for the induction of remission.[23] Twenty-four patients were enrolled and 16 received rituximab. At 4 weeks, 18.8% of patients were in remission versus 12.5% receiving placebo. These results were not statistically significant. The mean age was 37.0. The mean age plus 1 SD and 2 SD was 52.0 and 67.0, respectively. This study contained 3 patients over the age of 52.0 and no patients over the age of 67.0. Again, there was no age subgroup analysis of the results in this study.

Safety of biological agents

All 20 RCTs reported side effects and adverse events. These measures were not the primary outcome in any of the studies, and were therefore exploratory findings. In general, the study agents were well tolerated. No study reported age related analysis with respect to safety, tolerability, AE, or withdrawal rates.

Immunosuppressants

Immunosuppressant age summation

Twenty studies were included in this analysis and are summarized in Table 2.[39–58] All 20 studies reported a mean age. The composite mean age was 38.5 years, with a mean range of 30.5 to 46.4 years. Nine studies reported SD of the mean age, 1 reported SEM, 5 reported age range, and 5 reported both the SD/SEM and age range. When reported, the overall age range was 15–75, but in many studies, the age range was much smaller. Based on age range alone, 2 studies did not include elderly patients.[47,48] There were a total of 15 studies in which the estimated number of elderly patients could be calculated by adding 1 or 2 SD to the mean age, whichever provided the closest estimate to an elderly age. Using this method, approximately 16% of the study population had a mean age of 52.1 years (mean of 'mean plus 1 SD') or older. In most cases, a calculation of mean age plus 2 SD provided a closer approximation to an elderly age, with 2.5% of the study population aged 65.3 years (mean of 'mean plus 2 SD') or older.

Efficacy of Immunosuppressant agents

Corticosteroid

There were 10 studies evaluating the efficacy of corticosteroids for the treatment of UC. Rhodes et al found that in patients with active UC, prednisolone metasulfobenzoate achieved remission in 46% compared to 41% of patients receiving oral prednisolone after 8 weeks of treatment.[52] The mean age was 44.5. The mean age plus 1 SD and 2 SD was 58.7 and 72.9, respectively. This study contained 9 patients over the age of 58.7 and 1 patient over the age of 72.9. Bossa et al found that in the treatment of severe UC attacks, there was no difference in clinical response between treatment with continuous infusion and treatment with bolus administration of intravenous methylprednisolone.[40] The mean age in this study was 39.2. The mean age plus 1 SD and 2 SD was 53.9 and 68.6, respectively. This study contained 5 patients over the age of 53.9 and 1 patient over the age of 68.6. Sood et al found that in patients with moderately active UC, patients receiving prednisolone had a better response (63.2%) compared to methylprednisolone

Table 2.

	Author	Year	Total enrolled	Active agent	Active agent								Comparator	Results		
					N	Mean age	SD	Range	Mean age plus 1 SD	N ≥ mean plus 1 SD	Mean age plus 2 SD	N ≥ mean plus 2 SD		Primary end-point	Study duration	Active agent vs. comparator
Corticosteroid	Rhodes	2008	181	Prednisolone metasulfoben-zoate 40 mg	59	44.5	14.2		58.7	9	72.9	1	Prednisolone	Induction remission	8 wks	46% vs. 41%
	Bossa	2007	66	Methylpredni-solone 1 mg/kg, continuous	34	39.2	14.7	15–75	53.9	5	68.6	1	Methylpred-nisolone, bolus	Complete response	1 wks	50% vs. 50%
	Sood	2002	40	Methylpredni-solone acetate 80 mg IM	21	31.7	14.7		46.4	3	61.1	1	Prednisolone	Therapeutic response	1 wks	23.8% vs. 63.2%
	Hawthorne	1993	205	Fluticasone propionate 5 mg	73	41.0		18–72					Prednisolone	Investigator's overall assessment	4 wks	25.5% vs. 29%
	Meyers	1983	66	Hydrocortisone 100 mg	19	38.6	12.2	21–58	50.8	3	63.0	0	ACTH	Treatment success	10 days	53% vs. 25%
Budesonide	D'Haens	2010	32	Budesonide-MMX 9 mg	17	44.5	12.6		57.1	3	69.7	0	Placebo	Induction remission	4 wks	47% vs. 33%
	Lofberg	1996	72	Budesonide taper	34	33.0		18–67					Prednisolone taper	Endoscopic remission	4 wks	12.9% vs. 16.7%
Beclometasone	Campieri	2003	177	Beclomethasone dipropionate 5 mg	90	41.1	15.2		56.3	14	71.5	2	5-ASA	Induction remission	4 wks	63% vs. 62.5%
	Rizzello	2002	119	Beclomethasone dipropionate 5 mg	58	43.1	14.5		57.6	9	72.1	1	5-ASA	Induction remission	4 wks	58.9% vs. 34.4%
	Rizzello	2001	57	Beclomethasone dipropionate 5 mg	19	36.7	10.5	18–70	47.2	3	57.7	0	5-ASA	Responders	4 wks	47.4% vs. 36.8%
Methotrexate	Oren	1996	67	Methotrexate 12.5 mg	30	38.3	14.9		53.2	5	68.1	1	Placebo	Clinical remission	36 wks	46.7% vs. 48.6%
MMF	Orth	2000	24	Mycophenolate Mofetil 20 mg/kg	12	42.4		23–70					AZA	Maintenance remission	52 wks	88% vs. 100%
Tacrolimus	Ogata	2006	63	Tacrolimus trough 10–15 ng/mL	19	33.3	10.3		43.6	3	53.9	0	Placebo	Clinical improvement	2 wks	68.4% vs. 10%
Cyclosporine	Van Assche	2003	73	Cyclosporine 4 mg/kg	38	39.0	14.0		53.0	6	67.0	1	Cyclosporine 2 mg/kg	Clinical response	8 days	84.2% vs. 85.7%
	D'Haens	2001	30	Clyclosporine 4 mg/kg	14	36.7	10.5	20–67	47.2	2	57.7	0	Methypredni-solone	Clinical improvement	8 days	64% vs. 53%
	Lichtiger	1994	20	Cyclosporine 4 mg/kg	11	34.0		18–60					Placebo	Clinical response	2 wks	82% vs. 0%

(*Continued*)

Table 2. (*Continued*)

Author	Year	Total enrolled	Active agent	Active agent						Comparator	Results		
				N	Mean age	SD	Range	Mean age plus 1 SD	N ≥ mean plus 1 SD		Primary end-point	Study duration	Active agent vs. comparator
Azathioprine	Ardizzone	2006	72	Azathioprine 2 mg/kg	36	43.0	14.0	18–72	57.0	6	71.0	1	5-ASA	Maintenance remission	24 wks	53% vs. 21%
	Mantzaris	2004	70	Azathioprine 2.2 mg/kg	34	35.0		20–55					AZA + 5-ASA	Maintenance remission	2 years	81% and 82%
	Sood	2002	35	Azathioprine 2.5 mg/kg + coricosteroid and sulfasalazine	17	39.6	14.1		53.7	3	67.7	0	Cortico-steroids and sulfasalazine	Maintenance remission	52 wks	76.5% vs. 44.4%
	Sood	2000	50	Azathioprine 1 mg/kg + sulfasalazine and prednisolone	25	35.2	11.4		46.6	4	58.0	1	Placebo + sulfasalazine and prednisolone	Maintenance remission	52 wks	56% vs. 40%

Abbreviations: wks, weeks; SD, standard deviation.

intramuscularly (23.8%).[57] The mean age was 31.7. The mean age plus 1 SD and 2 SD was 46.4 and 61.1 respectively. This study contained 3 patients over the age of 46.4 and 1 patient over the age of 61.1. Hawthorne et al compared oral fluticasone to prednisolone taper in patients with active left sided or pancolitis.[44] Clinical remission, as judged by the investigator's overall assessment, was seen in 25.5% of fluticasone patients and 29% receiving placebo. The mean age was 41 and the age range 18–72 years. SD was not reported and further age related information could not be ascertained. The study by Meyers et al found that hydrocortisone treatment for 10 days achieved treatment success in 53% of patients versus 25% of patients treated with ACTH.[48] This study did not include any elderly patients based on mean age of 38.6 and the age range 21–58 years.

D'Haens et al evaluated oral budesonide compared to placebo in patients with active left-sided UC.[43] Thirty-two patients were enrolled and 17 received budesonide. At 4 weeks, remission induction was 47% versus 33% respectively. This result was not statistically significant. The mean age was 44.5. The mean age plus 1 SD and 2 SD was 57.1 and 69.7, respectively. In the budesonide group, there were 3 patients over the age of 57.1 and no patients over the age of 69.7 years. There were 3 studies evaluating beclomethasone as compared to 5-ASA, for the treatment of mild to moderately active UC. The Campieri et al and Rizzello et al studies found no difference between the 2 medications with similar remission rates;[41,54] however, Rizzello et al found that at 4 weeks, patients treated with beclomethasone achieved clinical remission in 58.9% versus 34.4% of patients treated with the 5 ASA agent.[53] The mean age for these 3 studies was 40.3 years. Based on mean age plus SD, there were no elderly patients in the Rizzello 2001 study, and less than 16% in the other two studies. None of these corticosteroid studies reported results by age subgroup analyses.

Methotrexate

Oren et al studied methotrexate (MTX) versus placebo in patients with chronic active UC.[50] Sixty-seven patients were enrolled and 30 received MTX. At 36 weeks, clinical remission was seen in 46.7% of MTX patients versus 48.6% for those receiving placebo. The authors concluded that MTX was not

beneficial in induction of remission. The mean age was 38.3. The mean age plus 1 SD and 2 SD was 53.2 and 68.1, respectively. This study represented 5 patients over the age of 53.2 years and 1 patient over the age of 68.1 years. There were no results reported by age subgroup analyses.

Mycophenolate mofetil

Orth et al evaluated mycophenolate mofetil (MMF) as compared to azathioprine (AZA) in moderate to severe UC.[51] Twenty-four patients were enrolled and 12 received MMF. Remission rates at one year were 88% (MMF) and 100% (AZA). These results were statistically significant. The mean age was 42.4 and range 23–70. No SD was reported. There were no results reported by age subgroup analyses.

Tacrolimus

Ogata et al reported that at 2 weeks, tacrolimus given at a dose to achieve a high trough (10–15 ng/mL) induced remission in 68.4% of patients as compared to 10% in patients on placebo.[49] The mean age was 33.3. The mean age plus 1 SD and 2 SD was 43.6 and 53.9, respectively. This study contained 3 patients over the age of 43.6 and no elderly patients. There were no results reported by age subgroup analyses.

Cyclosporine

Van Assche et al studied 2 doses of cyclosporine (2 mg/kg and 4 mg/kg) in the acute treatment of severe UC.[58] Seventy-three patients were enrolled. Clinical response at 8 days was seen in 84% and 85% in the high and low dose groups, respectively. The mean age was 39. The mean age plus 1 SD and 2 SD was 53.0 and 67.0, respectively. This study contained 6 patients over the age of 53.0 and 1 patient over the age of 67.0. D'Haens et al studied cyclosporine in comparison to intravenous corticosteroids for severe UC.[42] Thirty patients were enrolled and 14 received cyclosporine. Clinical improvement at day 8 was seen in 64% of patients on cyclosporine versus 53% on placebo. These results were not statistically significant. The mean age was 36.7. The mean age plus 1 SD and 2 SD was 47.2 and 57.7, respectively. This study contained 2 patients over the age of 47.2 and no elderly patients. Lichtiger et al studied cyclosporine versus placebo in patients with severe steroid refractory UC.[45] Twenty patients were studied and 11 received cyclosporine. At two weeks, clinical response was seen in 82% of patients on cyclosporine versus 0% on placebo. The mean age was 34 and age range 18–60. There were no results reported by age subgroup analyses.

Azathioprine

Ardizzone et al and Mantzaris et al both studied AZA in comparison to 5-ASA in patients with steroid dependent UC.[39,47] In Ardizzone et al's study, seventy-two patients were enrolled and 36 received AZA.[39] At 6 six months, maintenance of remission was 53% versus 21%. These results were statistically significant. The mean age was 43.0. The mean age plus 1 SD and 2 SD was 57.0 and 71.0, respectively. This study contained 6 patients over the age of 57.0 and 1 patient over the age of 71.0. Mantzaris et al enrolled seventy patients and 34 received AZA.[47] Maintenance of remission at two years was 81% versus 82%. The mean age was 35.0 and range 20–55. No elderly patients were included. Sood et al performed 2 similar studies in 2000 and 2002, comparing a 5-ASA/corticosteroid regimen with and without AZA for the treatment of severe UC.[55,56] Both studies showed results favoring the AZA/5-ASA/corticosteroid regimen over the 5-ASA/corticosteroid only regimen. Mean ages for the two studies were 39.6 years and 35.2 years, respectively. In the 2000 study, there was 1 patient estimated to be over the age of 58 and in the 2002 study, there were no patients over the age of 67.7, with only 3 over the age of 53.7. None of these AZA studies looked at results by age subgroup analyses.

Safety of Immunosuppressant agents

All 20 IS RCTs reported side effects and adverse events. As in the BA studies, these measures were not the primary outcomes. Study agents were generally well tolerated. No study reported age related analysis with respect to safety, tolerability, AE or withdrawal rates.

5-ASA

5-ASA age summation

Seventy-two studies were included in this analysis and are summarized in Table 3.[59–131] Of these, 65 reported a mean age, 5 reported a median age, and 2 reported neither; instead these 2 specified age range by subgroups. The composite mean age (counting the

Table 3.

Author	Year	Total enrolled	Active agent	Active agent								Study reported "elderly" age range	N elderly (%)	Comparator	Results		
				N	Mean/ median age	SD	Age range	Mean age plus 1 SD	N ≥ mean plus 1 SD	Mean age plus 2 SD	N ≥ mean plus 2 SD				Primary outcome	Study duration	Results of primary outcome
Induction–mesalamine																	
Gross	2011	343	Salofalk 3 g once daily	166	43.5	14.1	18–75	57.6	27	71.7	4			Budesonide 9 mg daily	Clinical remission	8 wks	54.8% vs. 39.5%
Hiwatashi	2011	123	Mesalazine 4 g/d (2 g BID)	59	NR	NR	15–64					60–64	2 (3.4%)	Mesalazine 2.25 g/d (0.75 g TID)	Clinical response	8 wks	76.3% vs. 45.8%
Lichtenstein	2011	391	Asacol 4.8 g/d (1600 mg TID)	213	43.4	NR	18–75					64–75	19 (8.9%)	Asacol 2.4 g/d (800 mg TID)	Mucosal healing	6 wks	80% vs. 68%
Ito	2010	229	Ascacol 3.6 g/d (1.2 g TID)	64	41.6	10.4	16–64	52.0	10	62.4	2			Asacol 2.4 g/d (0.8 g TID), Pentasa 2.25 g/d (0.75 g TID) and placebo	Clinical remission	8 wks	45.3% vs. 30.3% (Asacol 2.4 g/d), 28.6% (Pentasa 2.25 g/d) and 9.4% (placebo)
Sandborn	2009	672	Asacol 4.8 g/d (1.6 g TID)	389	44.1	NR	18–75					65–75	34 (8.7%)	Asacol 2.4 g/d (0.8 g TID)	Treatment success	6 wks	70% vs. 66%
Kruis	2009	381	Salofalk 3 g once daily	191	41.8	14.0	18–75	55.8	31	69.8	5			Salofalk 1 g TID	Clinical remission	8 wks	79.1% vs. 75.7%
Hanauer	2007	301	Asacol 4.8 g/d (1.6 g TID)	147	45.9	NR	18–75					65–75	14 (9.5%)	Asacol 2.4 g/d (0.8 g TID)	Treatment success	6 wks	56% vs. 51%
Lichtenstein	2007	280	Lialda 4.8 g daily	89	41.8	13.6	≥18	55.4	14	69.0	2			Lialda 2.4 g/d (1.2 g BID) and placebo	Complete remission	8 wks	29.2% vs. 34.1% (Lialda 1.2 g BID) and 12.9% (placebo)
Kamm	2007	343	Lialda 4.8 g daily	85	44.6	13.1	≥18	57.7	14	70.9	2			Lialda 2.4 g/d, Asacol 2.4 g/d (0.8 g TID) and placebo	Complete remission	8 wks	41.2% vs. 40.5% (Lialda 2.4 g/d, 32.6% (Asacol 2.24 g/d) and 22.1% (placebo)

Gibson	2006	258	Mesalazine Eudragit L 3 g/d (1 g TID)	131	40.0	NR	18–69							Mesalazine ethylcellulose-coated 3 g/d (1 g TID)	Clinical remission	8 wks	69% vs. 69%
D'Haens	2006		Lialda 2.4 g/d	14	39.0	NR	23–74							Lialda 1.2 g/d and 4.8 g/d	Clinical remission	8 wks	31% vs. 0% (Lialda 1.2 g/d) and 18% (Lialda 4.8 g/d)
Hanauer	2005	268	Asacol 4.8 g/d (1.6 g TID)	129	42.0	NR	18–75				3	65–75	11 (8.5%)	Asacol 2.4 g/d (0.8 g TID)	Treatment success	6 wks	72% vs. 59%
Prantera	2005	79	Lialda 3.6 g/d (1.2 g TID)	40	41.1	14.4	≥18	55.5	6	69.9	1			Asacol enema 4g/100 mL daily	Clinical remission	8 wks	60% vs. 50%
Forbes	2005	90	Ipocol 2.4 g/d (0.8 g TID)	46	47.9	15.3	≥18	63.2	7	78.5	1			Asacol 2.4 g/d (0.8 g TID)	Clinical remission	8 wks	26.1% vs. 28.6%
Marakhouski	2005	233	Mesalazine Eudragit L pellets 1.5 g/d (0.5 g TID)	114	41.9	NR	18–70				3			Meslazine Eudragit L tablets 1.5 g/d (0.5 g TID)	Clinical remission	8 wks	67% vs. 68%
Raedler	2004	362	Mesalazine micropellets 3 g/d	179	NR	NR	18–75				4	≥65	10 (5.6%)	Mesalazine tablets 3 g/d	Clinical resmission	8 wks	67% vs. 62.9%
Kruis	2003	321	Mesalamine Eudragit L pellets 4.5 g/d (1.5 g TID)	106	41.5	NR	19–69				3			Mesalamine Eudragit L pellets 1.5 g/d (0.5 g TID) and 3 g/d (1 g TID)	Clinical remission	8 wks	55% vs. 50% (Eudragit-L 1.5 g/d) and 66% (Eudragit-L 3 g/d)
Paoluzi	2002	149	Asacol po 2.4 g/d + Asacol enema 2 g/d × 4 wks	73	42.0	16.0	≥18	58.0	12	74.0	2			Asacol po 2.4 g/d + Asacol enema 2 g/d × 8 wks	Clinical remission	8 wks	55% vs. 64%
Farup	2001	227	Pentasa 4 g/d (2 g BID)	227	43.0	NR	17–77				6			Pentasa 4 g/d (1 g QID) and Mesalazine 4 g/d (1 g QID)	Clinical response	8 wks	39% vs. 37% (Pentasa 1 g QID) and 31% (Mesalazine 1 g QID)

(*Continued*)

Table 3. (*Continued*)

Author	Year	Total enrolled	Active agent	Active agent								Study reported "elderly" age range	N elderly (%)	Comparator	Results		
				N	Mean/ median age	SD	Age range	Mean age plus 1 SD	N ≥ mean plus 1 SD	Mean age plus 2 SD	N ≥ mean plus 2 SD				Primary outcome	Study duration	Results of primary outcome
Vecchi	2001	130	Salofalk 4 g/d po (2 g BID)	67	43.0	14.0	21–74	57.0	11	71.0	2			Salofalk po 2 g/d (1 g BID) + Salofalk enema 2 g/d	Clinical remission	6 wks	82% vs. 87%
Munakata	1995	118	Pentasa 1.5 g/d (0.5 g TID)	52	34.0	NR	≥16							Sulfasalazine 3 g/d (1 g TID)	Clinical response	4 wks	63% vs. 62%
Hanauer	1993	374	Pentasa 2 g/d (0.5 g QID)	97	40.1	14.6	>18	54.7	16	69.3	2			Pentasa 4 g/d (1 g QID) and Placebo	Treatment success	8 wks	57% vs. 59% (Pentasa 1 g QID) and 36% (Placebo)
Sninsky	1991	158	Asacol 1.6 g/d	53	43.3	14.4	25–74	57.7	8	72.1	1			Asacol 2.4 g/d and Placebo	Clinical response	6 wks	43% vs. 49% (Asacol 2.4 g/d) and 23% (Placebo)
Rachmilewitz	1989	220	Mesasal 1.5 g/d	115	38.7	12.9	18–70	51.6	18	64.5	3			Sulphasala-zine 3 g/d	Clinical remission	8 wks	71% vs. 66%
Riley	1988	61	Asacol 1200 mg BID	21	34.0	NR	23–76							Asacol 400 mg BID andSalazopy-rin 1 g BID	Treatment success	4 wks	81% vs. 75% (Asacol 400 mg BID) and 47% (Salazo-pyrin 1 g BID)
Schroeder	1987	88	Asacol 4.8 g/d (1.2 g QID)	38	42.5	13.0	21–68	55.5	6	68.5	1			Placebo	Clinical response	6 wks	24% vs. 5%
Maintenance–mesalamine																	
Kruis	2011	648	Salofalk 3 g once daily	217	45.2	14.0	18–75	59.2	35	73.2	5			Salofalk 1.5 g daily and 0.5 g TID	Clinical remission	52 wks	75% vs. 61% (1.5 g daily) and 69% (0.5 g TID)

Lichtenstein	2010	305	Apriso 1.5 g daily	209	47.0	14.0	≥18	61.0	33	75.0	5			Placebo	Clinical remission	36 wks	78.9% vs. 58.3%
Sandborn	2010	1027	Asacol 1.6–2.4 g/d given once daily	512	50.4	14.6	≥18	65.0	82	79.6	13	≥65	103 (20.1%)	Asacol 1.6–2.4 g/d given in divided doses BID	Clinical remission	52 wks	85.4% vs. 85.4%
Ito	2010	131	Ascacol 2.4 g/d (0.8 g TID)	65	43.4	12.0	16–64	55.4	10	67.4	2			Pentasa 2.25 g/d (0.75 g TID)	Clinical remission	48 wks	76.9% vs. 69.2%
Dignass	2009	362	Pentasa 2 g daily	175	48.7	15.0	19–80	63.7	28	78.7	4			Pentasa 1 g BID	Clinical remission	52 wks	70.9% vs. 58.9%
Prantera	2009	334	Lialda 2.4 g once daily	162	45.5	14.1	18–74	59.6	26	73.7	4			Asacol 2.4 g/d (1.2 g BID)	Clinical remission	52 wks	68% vs. 65.9%
Kamm	2008	459	Lialda 2.4 g once daily	225	42.4	12.1	NR	54.5	36	66.6	6			Lialda 1.2 g BID	Clinical remission	52 wks	64.4% vs. 68.5%
Paoluzi	2005	156	Asacol 2.4 g/d (0.8 g TID)	80	47.7	14.2	≥18	61.9	13	76.1	2	>40	48 (60%)	Asacol 1.2 g/d (0.4 g TID)	Clinical remission	52 wks	30% vs. 26%
Kane	2003	22	Mesalamine once daily dosing	12	46.2	13.4	NR	59.6	2	73.0	0			Mesalamine “conventional dosing” (BID or TID)	Clinical remission	36 wks	91.7% vs. 90%
Hanauer	1996	264	Asacol 1.6 g/d	87	42.1	13.5	18–75	55.6	14	69.1	2			Asacol 0.8 g/d and placebo	Clinical remission	36 wks	70.1% vs. 63.3% (Asacol 0.8 g/d) and 48.3% (placebo)
Ardizzone	1995	88	Claversal 0.5 g BID	44	32.0	NR	18–61							Sulfasalazine 1 g BID	Clinical remission	52 wks	38.4% vs. 51%
Miner	1995	205	Pentasa 4 g/d (1 g QID)	103	39.0	11.0	≥18	50.0	16	61.0	3			Placebo	Clinical remission	52 wks	64% vs. 38%
Fockens	1995	169	Pentasa 3 g/d (1 g TID)	82	45.0	14.5	16–74	59.5	13	74.0	2			Pentasa 1.5 g/d (0.5 g TID)	Relapse rate	52 wks	33% vs. 46%
Rutgeerts	1989	334	Claversal 0.75 g/d	131	41.5	13.5	18–72	55.0	21	68.5	3			Sulphasa-lazine 1.5–2 g/d	Relapse rate	52 wks	28% vs. 23%
Mulder	1988	75	Pentasa 1.5 g/d (500 mg TID)	41	43.3	15.6	18–79	58.9	7	74.5	1			Salazopyrin 3 g/d (1 g TID)	Clinical remission	52 wks	72% vs. 46%

(*Continued*)

Table 3. (*Continued*)

Author	Year	Total enrolled	Active agent	Active agent								Study reported "elderly" age range	N elderly (%)	Comparator	Results		
				N	Mean/ median age	SD	Age range	Mean age plus 1 SD	N ≥ mean plus 1 SD	Mean age plus 2 SD	N ≥ mean plus 2 SD				Primary outcome	Study duration	Results of primary outcome
Riley	1988	100	Asacol pre-trial dose of sulfasalazine converted, where 1 g SSZ = 400 mg 5ASA	48	42.1	15.5	NR	57.6	8	73.1	1			Salazopyrin continued at pre-trial dose	Relapse rate	48 wks	37.5% vs. 38.6%
Dew	1983	67	5ASA, Eudragit-S 2.4–4.4 g/d	32	48.6	16.2	NR	64.8	5	81.0	1			Sulphasalazine 2–4 g/d	Relapse rate	36 wks	22% vs. 20%
Dew	1982	72	5ASA, Eudragit-S, pre-trial dose of sulfasalazine converted, where 1 g SSZ = 400 mg 5ASA	32	44.9	15.3	NR	60.2	5	75.5	1			Sulphasalazine continued at pre-trial dose	Relapse rate	16 wks	26% vs. 18%
Induction–olsalazine																	
Kruis	1998	172	Dipentum 3 g/d (1 g TID)	88	41.9	14.7	18–75	56.6	14	71.3	2			Mesalazine, Eudragit-L 3 g/d (1 g TID)	Endoscopic remission	12 wks	52.2% vs. 48.8%
Zinberg	1990	15	Olsalazine 750 mg QID	7	37.0	NR	18–75							Placebo	Clinical response	4 wks	57% vs. 25%
Feurle	1989	105	Dipentum 2 g/d (500 mg QID)	52	42.9	15.8	18–75	58.7	8	74.5	1			Placebo	Endoscopic remission	4 wks	52.2% vs. 48.8%
Rao	1989	39	Olsalazine 2 g/d (500 mg QID)	20	46.0	NR	19–77							Sulphasalazine 3 g/d (750 mg QID)	Clinical response	4 wks	89% vs. 77%
Ewe	1988	41	Dipentum 1.5 g/d	20	42.9	17.7	22–73	60.6	3	78.3	1			Sulphasalazine 3 g/d	Clinical response	4 wks	55% vs. 37.5%
Willoughby	1988	56	Dipentum 3 g/d	26	41.0	NR	22–68							Sulphasalazine 3 g/d	Clinical response	5 wks	57% vs. 68%

Meyers	1988	66	Dipentum 3 g/d	15	43.0	12.7	22–61	55.7	2	68.4	0			Dipentum 0.75 g/d, 1.5 g/d and Placebo	Clinical response	3 wks	50% vs. 29% (Dipentum 0.75 g/d), 27% (Dipentum 1.5 g/d) and 16% (placebo)
Hetzel	1988	30	Dipentum 1 g BID	15	45.0	NR	NR							Placebo	Clinical response	6 wks	40% vs. 13%
Selby	1985	40	Olsalazine 2 g/d (500 mg QID)	20	42.0	NR	19–67							Placebo	Clinical response	2 wks	65% vs. 40%
Maintenance–olsalazine																	
Kruis	1995	162	Olsalazine 2 g/d (666 mg TID)	35	40.0	NR	16–72							Olsalazine 0.5 g/d, 1.25 g/d and Sulphasala-zine 2 g/d	Relapse rate	36 wks	24% vs. 36% (Olsalazine 0.5g/d),49% (Olsalazine 1.25 g/d) and 32% (Sulphasala-zine 2 g/d)
Nilsson	1995	329	Olsalazine 1 g/d (500 mg BID)	161	41.8	11.9	19–69	53.7	26	65.6	4			Sulphasala-zine 2 g/d (1 g BID)	Relapse rate	52 wks (mean)	54.7% vs. 47.2%
Travis	1994	198	Dipentum 2 g/d	62	49.0	12.0	NR	61.0		73.0	2			Dipentum 0.5 g/d and 1 g/d	Clinical remission	52 wks	78% vs. 60% (Dipentum 0.5 g/d) and 70% (Dipentum 1 g/d)
Courteny	1992	100	Dipentum 500 mg BID	50	40.7	NR	16–72							Asacol 600 mg BID	Relapse rate	52 wks	24% vs. 46%
Kiilerich	1992	227	Dipentum 500 mg BID	114	41.4	NR	20–79							Sulphasala-zine 1 g BID	Relapse rate	52 wks	46.9% vs. 42.4%
Rijk	1992	49	Olsalazine 1 g BID	23	36.0	NR	16–76							Sulfasalazine 2 g BID	Relapse rate	48 wks	26.1% vs. 30.4%
Jewell	1988	82	Olsalazine 500 mg BID	82	49.0	NR	18–75							Sulphasala-zine 1 g BID	Relapse rate	36 wks	20% vs. 12%
Induction–balsalazide																	
Scherl	2009	250	Balsalazide 3.3 g BID	166	43.6	13.4	≥18	57.0	27	70.4	4	≥65	2 (7.2%)	Placebo	Clinical response	8 wks	55% vs. 40%

(*Continued*)

Table 3. (*Continued*)

Author	Year	Total enrolled	Active agent	Active agent								Study reported "elderly" age range	N elderly (%)	Comparator	Results		
				N	Mean/ median age	SD	Age range	Mean age plus 1 SD	N ≥ mean plus 1 SD	Mean age plus 2 SD	N ≥ mean plus 2 SD				Primary outcome	Study duration	Results of primary outcome
Levine	2002	154	Balsalazide 6.75 g/d (2.25 g TID)	49	42.3	12.6	18–80	54.9	8	67.5	1			Balsalazide 2.25 g/d (0.75 g TID) and Asacol 2.4 g/d (0.8 g TID)	Rectal bleeding improve-ment	8 wks	65% vs. 35% (Balsalazide 2.25 g/d) and 53% (Asacol 2.4 g/d)
Pruitt	2002	173	Balsalazide 6.75 g/d (2.25 g TID)	84	41.6	13.5	12 to 80	55.1	13	68.6	2			Asacol 2.4 g/d (0.8 g TID)	Clinical remission	8 wks	46% vs. 44%
Green	2002	57	Balsalazide 6.75 g/d	28	43.0	13.7	≥18	56.7	4	70.4	1			Sulfasalazine 3 g/d	Clinical remission	12 wks	75% vs. 59%
Mansfield	2002	50	Balsalazide 6.75 g/d	26	46.0	14.9	21–69	60.9	4	75.8	1			Sulfasalazine 3 g/d	Complete remission	8 wks	50% vs. 38%
Green	1998	101	Balsalazide 6.75 g/d	50	39.7	12.7	23–76	52.4	8	65.1	1			Asacol 2.4 g/d	Complete remission	12 wks	62% vs. 37%
Maintenance–balsalazide																	
Green	1998	99	Balsalazide 3 g/d	49	43.4	12.5	20–70	55.9	8	68.4	1			Mesalazine, Eudragit S 1.2 g/d	Relapse rate	52 wks	58% vs. 58%
Green	1992	108	Balsalazide 3 g/d	54	46.0	NR	21–78							Balsalazide 6 g/d	Clinical remission	52 wks	77% vs. 68%
Giaffer	1992	133	Balsalazide 4 g/d	68	46.0	NR	16–79							Balsalazide 2 g/d	Relapse rate	52 wks	36% vs. 55%
McIntyre	1988	79	Balsalazide 1 g BID	79	49.0	NR	19–79							Sulphasala-zine 1 g BID	Clinical remission	36 wks	51% vs. 63%
Induction–sulfasalazine																	
Fleig	1988	43	Benzala-zine 0.72 g TID	22	42.4	16.2	19–75	58.6	4	74.8	1			Sulfasalazine 1 g TID	Treatment success	6 wks	86% vs. 95%
Maintenance–sulfasalazine																	
Dickinson	1985	32	Sulfasala-zine 2 g/d (continued from induction)	10	35.0	NR	28–54							Sulfasalazine 3 g/d × 14 days	Relapse rate	52 wks	30% vs. 39%

Abbreviation: NR, not reported.

median values as a mean) was 42.8 years with a mean range of 32 to 50.4 years. Forty-one studies reported standard deviation of the mean age and 3 reported standard error of the mean. Specific age range was reported in 65 studies; however, 13 of these did not report an upper limit to the range. Composite age range was from 12–80 years.

Of the initial 72 studies, one reported only a mean age without a SD or age range, and thus further age related information could not be ascertained.[83] Another study did not include elderly patients based on the reported age range of 28–54 years.[64] Of the remaining 70 studies, 26 did not report a SD/SEM, one of which also did not report an upper limit to the age range, so no further age related information could be estimated.[108] In the other 25 studies, since no SD was provided, an estimate of the number of elderly patients could not be performed. However, based on their reported age range, they presumably included a percentage of elderly subjects. Nine studies (6 not reporting SD) reported age subgroups, generally with subdivision of age 65 or older, which was representative of 8% of the study population.[81,82,84,101,110,116,122–124] One of these studies only reported on age > 40, with a mean age of 47.7.[110] Therefore, in the remaining 41 studies, the estimated number of elderly patients in each study was calculated by adding 1 or 2 SD to the mean age, whichever provided the closest estimate to an elderly age. Using this method, approximately 16% of the study population had a mean age of 57.2 years or older. In 4 studies, a calculation of 2 SD provided a closer estimate to an elderly age, with 2.5% of the population aged 64.4 years or older.

Efficacy of 5-ASA agents

Mesalamine-containing preparations—induction

Twenty-six RCTs specifically evaluated mesalamine containing preparations (Asacol®, Lialda®, Pentasa®, Salofalk®, Mesasal®, Ipocol®, Eudragit L unspecified and mesalazine not otherwise specified) for the induction of clinical efficacy in patients with mild to moderately active UC. The primary outcome measures were induction of remission in 15, clinical response in 5, treatment success in 5, and mucosal healing in 1. Study duration ranged from 4–8 weeks. Most studies compared a certain mesalamine formulation to a different mesalamine preparation or to placebo; however, there were also comparisons with sulfasalazine and budesonide. The active agent was evaluated for superiority, non-inferiority, dose-ranging studies, and frequency scheduling regimens. Of these 26 studies, 4 reported age subgroups, but did not report results stratified by these age subdivisions.[82,84,101,116] There were 3 studies, however, that did present age subanalysis of the results. In 1987, Schroder et al reported that when compared to placebo, Asacol® 1.2 g QID achieved clinical response at week 6 in 24% versus 5% of patients respectively.[125] The authors report that analysis by age subdivisions, with age ranges of 15–30, 31–45 and >45, had no significant effect on clinical outcomes. In 1993, Hanauer et al compared Pentasa® in doses of 2 g/d and 4 g/d to placebo and found treatment success in 57%, 59%, and 36% respectively.[80] Again, subgroup analysis showed no outcome difference. In 2009, in their ASCEND III study, Sandborn et al found that in patients with moderately active UC, Asacol® at a dose of 4.8 g/d achieved treatment success in 70% of patients after 6 weeks of treatment compared with 66% for those treated with 2.4 g/d.[123] However, subgroup analysis showed a trend towards improved outcomes in patients 65 years and older receiving the lower mesalamine dose of 2.4 g/d.

Mesalamine-containing preparations—maintenance

Eighteen studies evaluated these same mesalamine containing preparations (Asacol®, Lialda®, Pentasa®, Salofalk®, Apriso®, Claversal®, Eudragit-S, and mesalamine not otherwise specified) for the maintenance of remission and prevention of relapse over a 6–12 month period. In general, findings from these studies proved the superiority or non-inferiority of mesalamine preparations in the maintenance of remission as compared to sulfasalzine preparations and placebo. Studies looking at dose escalation found that a higher total dose/day is most effective. Finally, frequency studies found that once daily dosing was as effective, if not more effective, than conventional dosing of BID or TID regimens. Four studies performed age subanlyses.[70,106,110,122] Sandborn et al report that in patients with clinical remission of UC, once-daily dosing of Asacol® at doses of 1.6–2.4 g/d, when compared to the same daily doses but given as BID, was as effective for the maintenance of clinical remission over a 12 month period, with remission rates of 85.4% in

both groups.[122] Furthermore, treatment outcomes were consistent between age subgroups younger or older than 65 years. Paoluzi et al found that, compared to 1.2 g/d, Asacol® 2.4 g/d maintained remission in 30% vs. 26% of patients after 12 months of treatment, with no difference in outcomes when stratified by age.[110] Miner et al compared Pentasa® 4 g/d to placebo and found a significantly higher remission rate of 64% versus 38%, with no difference in outcome in the age subgroup analysis.[106] Lastly, a 1995 study by Fockens et al found that in 169 patients, compared to 1.5 g/d, Pentasa® given at a dose of 3 g/d was associated with fewer relapses over a 12-month period, 33% vs. 46% respectively.[70] However, they report that an inverse relation between relapse rate and age of the patient was detected in both treatment arms. The relapse rate for ages 16–34 was 53%, ages 35–49 was 40%, and ages 50–79 27%.

Olsalazine—induction

Olsalazine is a compound consisting of 2 molecules of 5-ASA linked together by an azo bond, eliminating the sulphapyridine. The majority of adverse events associated with sulphaslazine have been attributed to this sulphapyridine component. There have been 9 RCTs, between 1985–1998, which have evaluated Dipentum® or olsalzine not otherwise specified for the induction of clinical response or endoscopic remission. Outcome assessment was performed at a range of 2 to 12 weeks. Five studies compared olsalazine to placebo, all with findings of statistically significant clinical improvement in the olsalazine treatment groups.[68,83,105,126,131] When compared to sulphasalzine, all 3 studies showed non-inferiority of olsalazine.[66,117,130] There was one study that compared olsalazine 3 g/d to Eudragit-L mesalazine 3 g/d and found similar rates of endoscopic remission.[94] There was one last study that looked at dose response of olsalazine, with findings favoring the higher dose (3 g/d) versus 0.75 g/d and 1.5 g/d.[105] In this group of RCTs, there was no age subgroup analysis of the results.

Olsalazine—maintenance

Seven RCTs looked at the use of olsalazine for the maintenance of remission or prevention of relapse. Five of these compared olsalazine to sulphasalzine, 1 to Asacol®, and 1 was a dose-escalation trial. Duration of the studies was 6 to 12 months. All 5 studies comparing olsalazine to sulphasalzine found comparable results.[87,91,96,109,118] The study by Courtney et al in 1992 found that in patients with clinical remission, olsalazine 500 mg BID compared to Asacol® 1.2 g/d was superior in maintaining remission over a 12 month period, with failure rate of 24% versus 46% respectively.[60] Travis et al was the only RCT to evaluate dose escalation therapy, finding that a dose of 2 g/d was the optimal dose for maintaining remission, with 78% achieving remission at 12 months compared to 60% of those on a dose of 0.5 g/d and 70% on a dose of 1 g/d.[128] There was no age subgroup analyses reported in any of these studies.

Balsalazide—induction

Balsalazide is a prodrug where 5-ASA is azo bound to 4-aminobenzoyl-β-alanine (4-ABA), which is unique from olsalazine in that both the pro-drug and 4-ABA are pharmacologically inert, thus delivering 99% of 5-ASA compound to the colon. There are 6 RCTs evaluating the efficacy of balsalazide in the treatment of active UC. The primary outcome measures were induction of remission in 4, clinical response in 1, and improvement in rectal bleeding 1. Study duration was 8–12 weeks. When compared to placebo, balsalazide was superior in achieving clinical response.[124] This same finding was reported in the 2 studies comparing balsalazide with sulphasalazine.[76,102] Three studies compared balsalazide 6.75 g/d to Asacol® 2.4 g/d, with results favoring balsalazide.[75,98,114] While the Scherl et al study in 2009 did provide age subdivisions, there was no age subgroup analysis.[124]

Balsalazide—maintenance

Four studies evaluated balasalazide as a maintenance medication. Green et al in 1998 and 1992 looked at balsalazide 3 g/d versus Eudragit S mesalazine 1.2 g/d and balsalazide 6 g/d respectively, finding comparable results over a 2 month period.[74,77] In 1992 Giaffer et al compared balsalazide 4 g/d to 2 g/d and found fewer relapse rates with the 4 g/d regimen over 52 weeks.[72] McIntyre et al found similar efficacy between balsalazide 2 g/d versus sulphasalazine 2 g/d

over a 6 month follow-up period.[104] There were no age subgroup analyses in these studies.

Sulfasalazine—induction

Dating back to the 1960s, sulfasalazine was found to be effective in the treatment of UC; it has been the mainstay of treatment for years. Interestingly, there was a paucity of RCTs looking at the efficacy of sulfasalazine for the induction of clinical remission. In fact, there was only 1 RCT that met our inclusion and exclusion criteria, performed by Fleig WE et al in 1988.[69] The authors report that benzalazine 0.72 g TID, compared to sulfasalazine 1 g TID, had similar efficacy achieving clinical improvement at week 6. There was no age related results.

Sulfasalazine—maintenance

The last RCT from Dickinson et al in 1985 found that in patients with clinical remission of UC, sulfasalazine given as 2 g/d "continued" from induction versus given as a 14 day burst of 3 g/d at the start of symptom recurrence ("on-demand") after induction had been achieved, had similar relapse rate at a 12 month follow-up period, 30% versus 39% respectively.[64] Unfortunately, this study did not include any elderly patients, based on the stated age range of 28–54 years.

Safety of 5-ASA agents

Of the 72 RCTs, 4 did not discuss safety and/or tolerability profiles. Of the remaining 68 studies, while safety, tolerability, AE and withdrawal rates were discussed, none of these studies reported by age subanalysis.

Discussion

To date, there have been no clinical trials that have directly evaluated treatment efficacy of UC in the elderly population. The approach to treating UC in this unique population has been based on expert opinion and extrapolated data from clinical trials that may or may not have included elderly patients. Evidence based guidelines generally emerge from RCTs, with the assumption that the findings obtained will be applicable to general clinical practice. The elderly population, independent of functional status, is often excluded due to co-morbidities and polypharmacy and concern for drug interactions; it is therefore under-represented in the RCT population. This systematic review is, to the best of our knowledge, the first attempt to review all of the RCTs addressing the treatment outcome of UC in the elderly, defined as age 60 years or older.

In total, 112 RCTs were included in the final analysis and were grouped by medication therapy: BA, IS or 5-ASA. While nearly all studies reported either a mean or median age, only 38% additionally reported the SD and age range. The mean composite age for the BA studies was 39.2 years, 38.5 years for IS, and 42.8 years for the 5-ASA studies, consistent with a young middle-aged patient. Our estimation of the percentage of patients per study that would have qualified as elderly was no more than 16% of the study population, and in most cases a much smaller percentage (<8%). This is a gross underrepresentation of the proportion of elderly patients currently seen in general clinical practices. As an example, based on our clinical experience, 80% of the IBD patients seen at the Minneapolis Department of Veterans Affairs are in fact elderly.

None of the BA or IS studies presented analyses of the data by age subgroups. In the 5-ASA group, there were 4 studies that provided age sub-divisions; however, they did not report any analysis of the data stratified by these age subgroups. There were an additional 4 studies that reported no difference in efficacy outcomes by age subgroup analysis, but they did not provide supporting data in the paper and did not specify what age subgroups they evaluated. Notably, there were 4 studies that did present age-specific analyses, all of which evaluated the efficacy of mesalamine. In the ASCEND III trial, the study conclusion was that Asacol® at a dose of 4.8 g/d achieved better clinical results than the 2.4 g/d dose; however, there was a non-significant trend favoring the lower dose in patients 65 years or older.[123] In the Paoluzi et al study, they found that a dose of 2.4 g/d was more effective in maintaining remission than a 1.2 g/d, with no difference in outcomes when stratified by age.[110] In a dosing study by Sandborn et al, once daily dosing was found to be as effective as BID dosing and no difference in outcome seen in patients < 65 years or 65 years and older.[122] Finally, Fockens et al reported that Pentasa® 3 g/d was more

effective in maintaining remission than a dose of 1.5 g/d, but interestingly found that older age was associated with a lower relapse rate. If one were to extrapolate data from these 4 studies, it would appear that mesalamine at a dose of 2.4 g/d is most effective in an elderly patient and that once daily dosing is a reasonable frequency schedule.[70] Additionally, relapse rates may be less frequent in the elderly. However, caution should be advised when interpreting these results, as the trends, while noteworthy, are not conclusive. Interestingly, none of the 116 RCTs reviewed reported adverse events or safety profile by age subgroup.

Physicians caring for this elderly IBD population are faced with multifaceted problems, including misdiagnoses, late presentation, management of comorbid diseases, and polypharmacy with potential for drug interactions and adverse events. While general geriatric treatment principles apply to IBD patients, there are some notable IBD specific considerations. Early aggressive therapy along with combined therapy has been endorsed as a more favorable treatment strategy for the general IBD population; on the other hand, there is no consensus on whether this translates to the elderly population as well. Katz and Feldstein published a comprehensive review of the pharmacokinetics and drug interactions that are commonly seen in elderly patients with IBD.[18] They note that while recognition of the drug type, elimination patterns, drug metabolism enzymes, and GFR are important, 'frailty' may actually be more important than age in drug elimination and pharmacokinetics. Age alone, therefore, should not exclude a certain class of drugs. They suggest distinguishing between the 'fit elderly' and the 'frail elderly' when making decisions about treatment. Elderly are also more susceptible to adverse events. For example, osteoporosis is already a concern for the elderly population, making corticosteroids a less appealing adjunctive medication. While there is no evidence that the efficacy of biological therapy is altered by age, there have been some non-RCT reports suggesting a trend towards more severe infections in patients older than 70 years.[132]

At this time, the treatment considerations of UC in the elderly are similar to younger patients. However, there is insufficient evidence in our current literature to evaluate the efficacy of treatment for UC specifically in the elderly. Additionally, the unknown safety profile in this population warrants further study. With the rising number of elderly patients with UC, there is a tremendous need for more clinical trials—ideally RCTs—that specifically address UC treatment in the elderly population.

Author Contributions

Conceived and designed the experiments: BH, BB, AS. Analyzed the data: BB, BH, AS. Wrote the first draft of the manuscript: BB, BH, AS. Contributed to the writing of the manuscript: BA, BH, AS. Agree with manuscript results and conclusions: BH, BB, AS. Jointly developed the structure and arguments for the paper: BB, BH, AS. Made critical revisions and approved final version: BB, BH, AS. All authors reviewed and approved of the final manuscript.

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Competing Interests

Author(s) disclose no conflicts of interest.

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