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REVIEW

Dose Escalation Patterns of Advanced Therapies in Crohn's Disease and Ulcerative Colitis: A Systematic Literature Review

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ABSTRACT

Introduction: Dose escalation is one of the treatment approaches studied and suggested in advanced therapies for Crohn's disease (CD) and ulcerative colitis (UC). This study aimed to identify and characterize the dosing escalation patterns of advanced therapies in CD and UC.

Methods: Two systematic literature reviews (SLRs) were conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. MEDLINE®, Embase®, and Cochrane Library were searched for articles published between January 2011 and October 2021 and limited to non-interventional studies in English language. Congress and bibliographic searches were also conducted. Articles were screened by two independent researchers. Dose escalation patterns were described and summarized considering the regional regulatory label recommendation (in North America [NA] or outside of North America [ONA]).

Results: Among 3190 CD and 2116 UC articles identified in the Ovid searches, 100 CD and 54 UC studies were included in the SLR, with more studies conducted ONA. Most studies reported an initial maintenance dose pattern aligned with the lower starting dose per local regulatory label; however, several ONA studies (n = 13 out

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of 14) reported ustekinumab every 8 weeks as starting maintenance pattern in CD. In ONA studies, the median within-guideline escalation rates in CD and UC were 43% in ustekinumab (CD only), 33% and 32% for vedolizumab; 29% and 39% for adalimumab; and 14% and 10% for infliximab. Evidence regarding dose escalation patterns for tofacitinib, certolizumab pegol, and golimumab was limited. Some dose escalation patterns outside of label recommendations were observed including ustekinumab every 8 weeks to every 4 weeks and vedolizumab every 8 weeks to every 6 weeks.

Conclusion: Dose escalation strategies are widely documented in the literature. The reported dose escalation patterns and escalation rates vary by region and by CD and UC. Most escalation patterns reported were aligned with regulatory recommendations while some reported more diverse or aggressive dose escalation.

Prospero Registration: CRD42021289251.

Keywords: Crohn's disease; Ulcerative colitis; Dose escalation; Advanced therapies; Biologics

Key Summary Points

In this systematic review, most identified studies reported initial maintenance dosages aligned with local regulatory label indications for CD and UC, except for ustekinumab in countries ONA, where the majority of studies reported initial maintenance doses of 90 mg every 8 weeks

In ONA studies, the median within-guideline escalation rates in CD and UC were 43% in ustekinumab (CD only); 33% and 32% for vedolizumab; 29% and 39% for adalimumab; and 14% and 10% for infliximab

Some dose escalation patterns outside of label recommendations were observed including ustekinumab every 8 weeks to every 4 weeks and vedolizumab every 8 weeks to every 6 weeks

The most commonly reported reason for dose escalation in identified studies was a loss of response

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, relapsing-remitting inflammatory disease that includes Crohn's disease (CD) and ulcerative colitis (UC) [1–3]. Presenting symptoms of IBD most commonly include mild to moderate diarrhea and abdominal pain, nausea, and vomiting [1, 4–6]. CD impacts the entire digestive tract and is broadly characterized by the presence of a patchy network of transmural inflammatory lesions, whereas UC is an idiopathic disease of the colon and rectum characterized by mucosal inflammation and ulceration [1, 5–8].

IBD may occur at any age, yet peak diagnosis is typically between the ages of 15 and 35 for both CD and UC [5, 6, 9]. In 2017 alone, > 6.8 million cases of IBD (age-standardized prevalence: 84.3 per 100,000) were reported globally [4]. Though IBD is typically regarded as a disease with the greatest impact in developed countries, incidence rates have either declined or stabilized over the past two decades [4, 8]. In contrast, IBD incidence in developing countries continues to rise [5, 6, 8].

IBD is associated with significant impairment to the patient's physical and emotional quality of life [9–12]. Characterized by intermittent periods of gastrointestinal inflammation and remission, uncontrolled IBD increases a patient's risk of developing complications, frequently leading to a higher risk of oncogenesis and higher rates of mortality than the general population [9, 11, 12]. As there is no cure for CD or UC, the primary goal of treatment involves symptom resolution, inflammation reduction, and improvements in long-term prognostic outcomes and quality of life [1, 5, 6, 13].

Patients with mild symptoms are often treated with anti-inflammatory medications, yet more aggressive cases require lifelong use of advanced therapies, including infliximab, adalimumab, golimumab, vedolizumab, or ustekinumab as well as small molecular therapies such as tofacitinib, filgotinib, or ozanimod [5, 6, 14]. Healthcare costs for patients with IBD vary based upon disease severity, yet generally

cost three times that of the general population [13, 15–18].

In the United States (US), total lifetime healthcare costs were $622,056 and $405,496 (2016 US dollars [USD]) per CD and UC patient, respectively [19]. IBD also imposes a considerable societal burden due to loss of schooling, work absenteeism, short-term disability, and early retirement [4, 15, 18, 20]. Indirect costs in patients with IBD account for 30–50% of all healthcare expenditure in the US, with recent estimates totaling $5.1 and $4.9 billion annually for CD and UC patients, respectively [4, 15, 18].

Even in the era of widespread advanced therapy availability, up to 65% of patients will experience treatment failure within 12 months of maintenance therapy initiation [16, 21–24]. Dose escalation has been observed as a common treatment strategy, even in the range outside of regulatory recommendations, to maintain or regain response [16, 21, 25, 26]. Though effective, dose escalation also comes at a cost to the healthcare systems and patients [17].

In the European Medicines Agency (EMA) label of advanced therapies in CD/UC, dose escalation is usually allowed if patients lose their response to the initial lower dose of the regimen (e.g., increase in dosing frequency from 90 mg every 12 weeks to every 8 weeks in ustekinumab), although, in the US and certain countries like Canada, dose escalation may not be allowed in the regulatory label recommendation. It is unclear to what extent the maintenance dose or the dose escalation regimen is aligned with the label.

The objective of this study was therefore to identify and characterize dosing patterns of advanced therapies for CD and UC through a comprehensive assessment of the data from real-world (RW) evidence studies.

METHODS

Two systematic literature reviews (SLRs), one in patients with CD and the other in patients with UC, were conducted and registered with PROSPERO (trial registration: CRD42021289251). The searches were done per Centre for Reviews and Dissemination (CRD), Cochrane Collaboration, and National Institute for Health and Care Excellence (NICE) guidelines on October 26, 2021.

Each SLR focused on non-interventional studies to capture all dosing pattern analyses conducted in RW settings. To reflect current CD/UC clinical practices, studies were restricted to those conducted between January 2011 and October 2021 and limited to English language studies of adults with active CD/UC undergoing advanced therapy maintenance treatment. Advanced therapies include infliximab, adalimumab, vedolizumab, ustekinumab, and certolizumab pegol in CD; infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, ustekinumab, and ozanimod in UC. The full scope of each SLR was defined in terms of the patient population, intervention, comparators, outcome measures, and study design (PICOS) statement for study inclusion and exclusion (Table 1).

Search Strategy

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The Ovid platform was used to conduct searches of MEDLINE® (Medical Literature Analysis and Retrieval System Online), Embase® (Excerpta Medica Database), and Cochrane collaboration. Secondary searches were conducted in EconLit, MEDLINE® Epub Ahead of Print, and In-Process to identify relevant economic studies or non-indexed citations. Studies, systematic reviews, and meta-analyses identified through the database searches underwent bibliography review to identify relevant studies and capture articles or papers not identified during the initial search. All publication types, including conference abstracts and pre-prints, were considered for inclusion. Conference abstracts from the past two years, and those indexed via Ovid, were searched to retrieve the latest studies. Please refer to the Supplementary Material for CD and UC search strategies.

Table 1 PICOS for SLR of Crohn's disease and ulcerative colitis

PICOS criteria	CD	UC	Exclusion criteria
Patient population	Adults with moderate-to-severe active CD undergoing either induction or maintenance treatment	Adults with active UC undergoing either induction or maintenance treatment	Non-human Non-active disease Pediatric (< 16 years)
Interventions	Ustekinumab Vedolizumab Certolizumab pegol Adalimumab Infliximab	Ozanimod Tofacitinib Ustekinumab Vedolizumab Golimumab Adalimumab Infliximab	Studies not including any interventions of interest
Outcome Measures	Prevalence or proportion of varying dosing frequencies/intervals and therapeutic schedules Presence and/or magnitude of dose escalation or intensification Treatment Patterns Average dose over specific time point(s) Median treatment duration (before and/or after dose escalation) Reasons for dose escalation or intensification (i.e., loss of response, etc.) Any efficacy and/or safety outcomes in the context of dose intensification or escalation	Prevalence or proportion of varying dosing frequencies/intervals and therapeutic schedules Presence and/or magnitude of dose escalation or intensification Treatment patterns Average dose over specific time point(s) Median treatment duration (before and/or after dose escalation) Reasons for dose escalation or intensification (i.e., loss of response, etc.) Any efficacy and/or safety outcomes in the context of dose intensification or escalation	No exclusion criteria

Table 1 continued

PICOS criteria	CD	UC	Exclusion criteria
Study design	Real-world evidence studies including:	Real-world evidence studies including:	Reviews
	Prospective observational studies	Prospective observational studies	Editorials
	Retrospective studies	Retrospective studies	Notes
	Registry analyses	Registry analyses	Comments
	Database analyses	Database analyses	Letters
	Any non-interventional studies	Any non-interventional studies	Interventional studies
	Systematic reviews and meta-analyses (to check for relevant RCTs)	Systematic Reviews and meta-analyses (to check for relevant RCTs)	Case reports
			Case series
Restrictions	English language	English language	Non-English language studies
	2011 to October 26, 2021	2011 to October 26, 2021	Before to 2011

CD, Crohn's disease; *RCTs*, randomized controlled trials; *UC*, ulcerative colitis

Search Results and Screening

The Ovid searches identified 3190 CD and 2116 UC publications. Upon completion of database and bibliographic searches, all publications underwent an abstract/title review resulting in 1809 CD and 1233 UC records being excluded based upon PICOS criteria. Three hundred eighty-one CD and 323 UC publications were retained for full-text review by two independent researchers (**Stacy Grieve and Rhiannon Campden**). Based upon the SLR's inclusion/exclusion criteria, 100 studies in CD and 54 in UC met the inclusion criteria (Figs. 1a, b) and were fully extracted. Fully extracted studies were those that contained information on proportions of individuals on any dose escalation, escalated maintenance patterns, or any reports of re-induction and/or de-escalation.

Data Extraction

All data were extracted into a pre-defined Excel-based template by one independent reviewer (Stacy Grieve) and cross-checked by a second senior reviewer (Rhiannon Campden) in compliance with CRD's guidelines for Undertaking Reviews in Healthcare. A third reviewer was consulted to resolve any disagreements and/or make final decisions (Sharada Harricharan). Search findings are presented in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagrams and systematic review reports.

Risk of Bias Assessment

The Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I) tool was utilized to address any possible biases introduced by studies that did not randomize participants into comparison groups. Overall estimates of bias were calculated based on the seven domains of bias addressed by the ROBINS-I tool.

Outcomes

All treatment patterns were evaluated by disease (CD or UC) and treatment. A cross-sectional view of the regimen dose at the beginning of

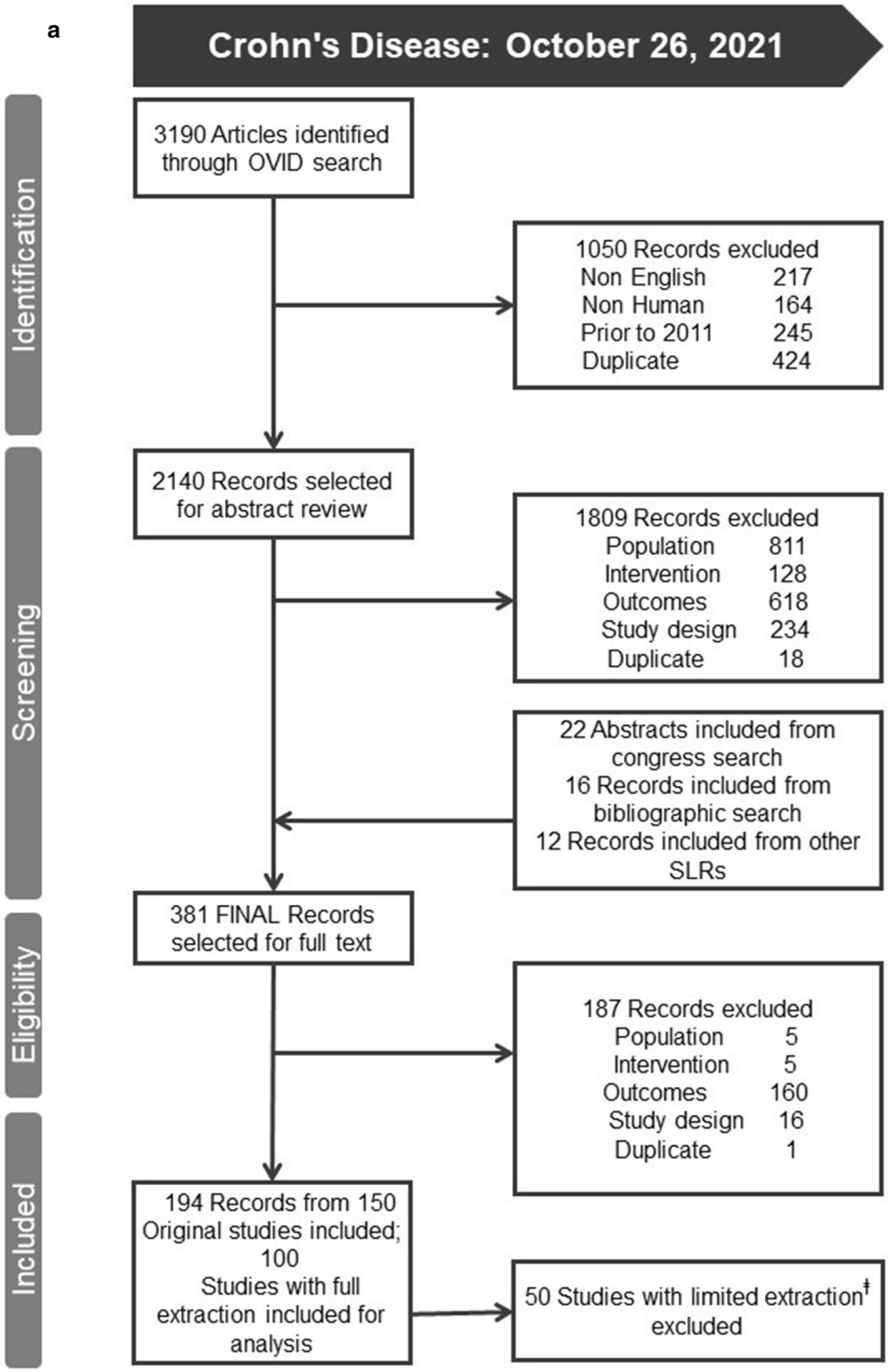


Fig. 1 **a** PRISMA diagram for Crohn's disease SLR. **b** PRISMA diagram for ulcerative colitis SLR. *SLRs*, systematic literature reviews. ‡Studies that did not record the type of dose escalation were excluded from the analysis

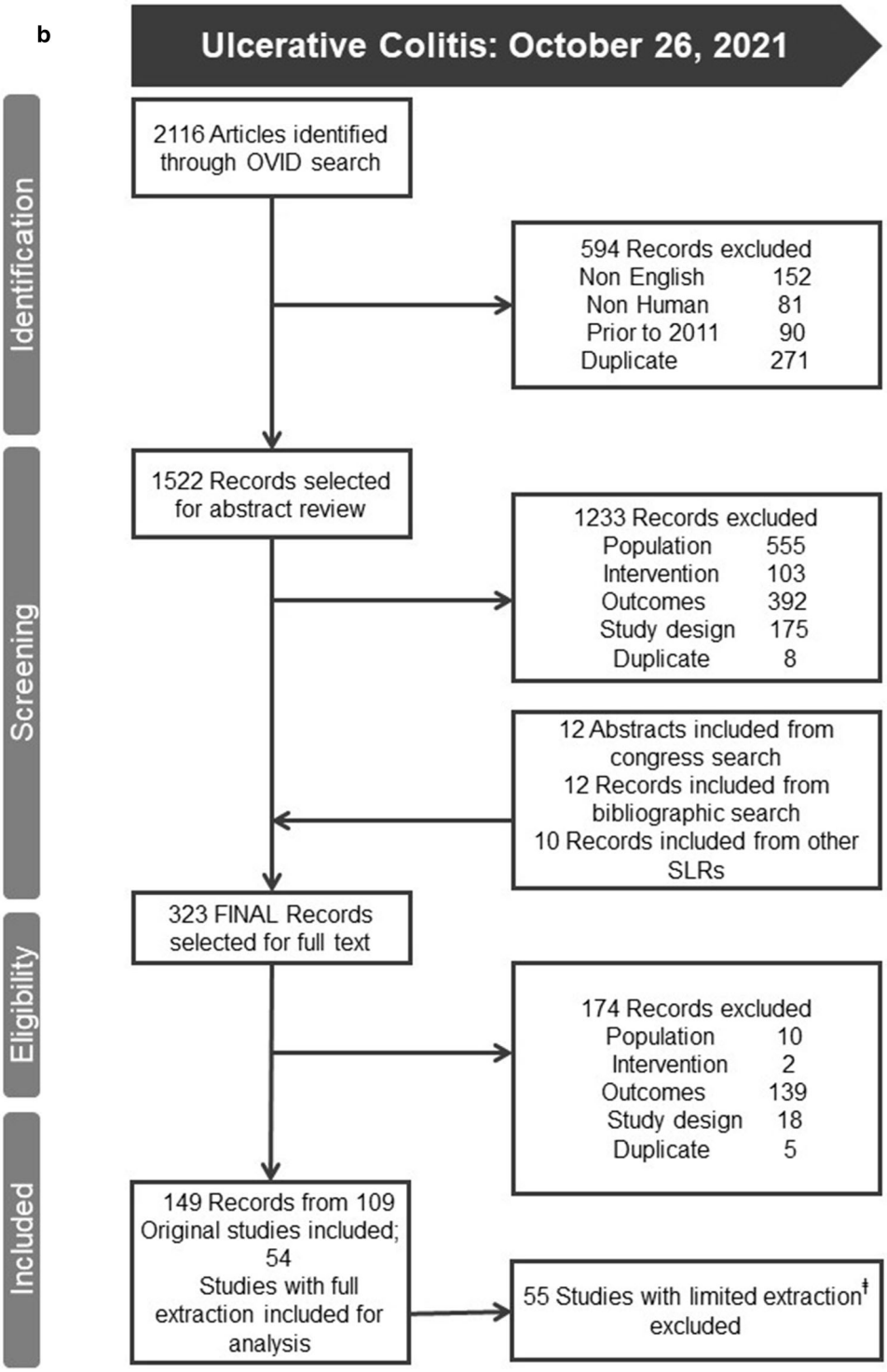


Fig. 1 continued

the maintenance therapy and the last dose at the end of follow-up were recorded. Dose escalation was categorized into shortening of the interval/frequency or increase in dosage/strength through a longitudinal view of the initial starting dose and the dose to which the regimen later escalated. For a given treatment pattern, a dose escalation median rate was reported. Given the variation of regulatory recommendations in maintenance dose (Table 2) and allowance of dose escalation, results were reported by region as the US and Canada (e.g., North America [NA]) and outside of North America (ONA) for all other studies.

RESULTS

Study Characteristics and Patient Characteristics

The included CD/UC studies were conducted in the US, Canada, Europe, Australia (CD only), Israel, Japan, and Korea. Overall, interval shortenings were most often reported in patients treated with ustekinumab, vedolizumab, and adalimumab (CD/UC), while infliximab (CD/UC) and golimumab (UC) treatment were more commonly associated with dose strength increases (Table 3).

The CD study populations ranged from 10 to 2904 patients with a mean age range of 25–-48.5 years. The proportion of males varied widely (25–85.4%) between studies, as did the proportion of smokers (3.5–52.4%). The mean disease duration ranged from 3.2 to 32.5 years. Population size for the UC studies ranged from 18 to 2968 patients; the mean age ranged from 31.5 to 49.8 years. The proportion of males varied between 25% and 73.1% across studies, with the proportion of smokers ranging from 3% to 25%. The mean disease duration ranged from 4.1 to 11.2 years.

Results in CD

Overview

In 69 studies reporting reasons for dose escalation, the most common reason was related to partial response, no response, or loss of response; some were related to low drug serum levels (Supplementary Material) [27–87]. The most common initial maintenance doses (Fig. 2), dose escalation patterns (Fig. 3), and last dose pattern at the end of follow-up (Fig. 4) are described by region below, with full details in the Supplementary Material.

Ustekinumab

Most studies conducted within the US and Canada ($n = 10$) reported initial dosing in alignment with local regulatory guidelines (e.g., 90 mg every 8 weeks) in a median of 100% of patients (range: 74–100%) [27, 30, 31, 34, 39, 88–97]. Among studies ONA that reported an initial maintenance dose ($n = 14$), six reported a median of 29% of patients (range 9–100%) started on every-12-week dosing, while 13 out of 14 studies reported a median of 100% (range 63–100%) of patients initially started on every-8-week maintenance dosing (Fig. 2) [28, 29, 33, 35–37, 40, 41, 98–104]. The EMA recommendation, however, is to start with a lower dose regimen (e.g., 90 mg every 12 weeks) [105].

During follow-up, interval shortening to 90 mg every 4 weeks was reported in a median patient proportion of 27% (range 17–77%) in NA and 24% (range 11–33%) in studies ONA when started on every-8-week dosing (Fig. 3) [29–31, 33, 35, 39, 40, 88, 89, 92–94, 96, 98, 100–104]. Dose strength increases were reported in two studies and ranged from 108 to 180 mg every 8 weeks in 18% to 23% of patients in NA studies [90, 91, 97].

Vedolizumab

All studies conducted within NA ($n = 3/3$) [46, 47, 106, 107] or ONA ($n = 8/8$) [42–45, 48, 49, 51, 52, 103, 108–110] reported initial maintenance dosing of 300 mg every 8 weeks with a median proportion of 100% (Fig. 2). The most common dose escalation pattern observed during follow-up was from 300 mg every 8 weeks to every 4 weeks [median proportion: 18% (range 8–27%) in NA studies; 33% (range 12–79%) in studies ONA] (Fig. 3) [44–49, 51, 52, 103, 106, 107, 109–111].

Certolizumab Pegol

The initial maintenance pattern reported in one study was 400 mg every 4 weeks, per US Food & Drug Administration (FDA) guidelines, in 88% of patients (Fig. 2) [86, 87]. Dose escalation of certolizumab pegol in one study was reported as an interval shortening to 400 mg every 2 weeks in 17% of patients from 400 mg every 4 weeks (Fig. 3) [86, 87]. The study also reported a dose strength increase, from 200 mg every 2 weeks to 400 mg every 2 weeks, in 18% of patients (Supplementary Material) [86, 87].

Adalimumab

Most studies reported an initial maintenance dose of 40 mg every other week (EOW): four NA studies with a median proportion of 100% [69, 90, 91, 112–114] and 17 ONA studies with a median of 100% (range 38–100%) [53–56, 59–68, 70, 115–123] (Fig. 2). Follow-up escalation patterns in NA and ONA were most commonly interval shortenings to 40 mg every week (EW) dosing from 40 mg EOW in a median proportion of 43% (range 40–45%) and 29% (range 14–77%) of patients, respectively (Fig. 3) [53, 54, 59–70, 112, 113, 115–123].

Infliximab

An initial maintenance dose of 5 mg/kg every 8 weeks was used (Fig. 2), per FDA/EMA recommendations, in three NA studies (median proportion: 100%; range 76–100%) and 17 studies ONA (median proportion: 100%; range 100–100%) [53, 54, 63, 64, 66, 68, 71–80,

Table 2 Recommended maintenance dose and dose escalation by regulatory body

Treatment	FDA label dose	FDA label dose if inadequate response	EMA label dose	EMA label dose if inadequate response
Crohn's disease				
Ustekinumab	90 mg q8w	n/a	90 mg q12w	90 mg q8w
Vedolizumab	300 mg q8w	n/a	300 mg q8w	300 mg q4w
Certolizumab pegol	400 mg q4w	n/a	Not approved in the EU	Not approved in the EU
Adalimumab	40 mg EOW	n/a	40 mg EOW	40 mg EW or 80 mg EOW
Infliximab	5 mg/kg q8w	10 mg/kg q8w	5 mg/kg q8w	10 mg/kg q8w
Ulcerative colitis				
Tofacitinib	5 or 10 mg BID	n/a	5 mg BID	10 mg BID
Ustekinumab	90 mg q8w	n/a	90 mg q12w	90 mg q8w
Vedolizumab	300 mg q8w	n/a	300 mg q8w	300 mg q4w
Golimumab	100 mg q4w	n/a	50 mg q4w, if < 80 kg	100 mg q4w, if < 80 kg
			100 mg q4w, if > 80 kg	200 mg q4w, if > 80 kg
Adalimumab	40 mg EOW	n/a	40 mg EOW	40 mg EW or 80 mg EOW
Infliximab	5 mg/kg q8w	n/a	5 mg/kg q8w	10 mg/kg q8w

BID, twice daily; *EMA*, European Medicines Agency; *EOW*, every other week; *EW*, every week; *FDA*, US Food and Drug Administration; *kg*, kilogram; *mg*, milligram; *n/a*, not applicable; *q4w*, every 4 weeks; *q8w*, every 8 weeks; *q12w*, every 12 weeks

Table 3 Study setting and reported escalation patterns in the studies included in the SLR

Intervention	Studies (N)	Study designs	Source/setting(s)	Number of patients median (range)	Follow-up median (range)	Studies with interval shortenings (N)	Studies with dose increases (N)	Variations in interval	Variations in dose
Crohn's disease									
Ustekinumab	32	Retrospective (n = 25); Prospective (n = 5); Multicenter (n = 11); *Other (n = 2)	Hospital (n = 12); Chart Review/EHR (n = 1); Registry (n = 1); Clinic/Center (n = 6); Database (n = 4); Research Institute (n = 2); NR (n = 5)	102 (12–993)	12.0 months (3.7–28)	24	2	q2w–q8w	45 mg– > 180 mg
Vedolizumab	13	Retrospective (n = 8); Prospective (n = 4); Multicenter (n = 3); Single-Center (n = 5); *Other (n = 1)	Hospital (n = 6); Registry (n = 1); Clinic/Center (n = 2); Research Institute (n = 2); NR (n = 5)	85 (30–294)	12 months (3–37.3)	11	0	q4w– < q8w	300 mg
Certolizumab pegol	2	Retrospective (n = 2); Single-Center (n = 1)	Hospital (n = 1); Database (n = 1)	140.5 (23–258)	26.2 months	1	1	q2w–q4w	200 mg–600 mg
Adalimumab	32	Retrospective (n = 20); Prospective (n = 7); Multicenter (n = 11); Single-Center (n = 10); *Other (n = 4)	Hospital (n = 16); Clinic/Center (n = 4); Database (n = 6); Research Institute (n = 5); NR (n = 2)	110 (4–2742)	18 months (2.8–96)	18	4	EW–q10d	> 20 mg–80 mg
Infliximab	32	Retrospective (n = 27); Prospective (n = 5); Multicenter (n = 10); Single-Center (n = 7)	Hospital (n = 22); Chart Review/HER (n = 1); Clinic/Center (n = 1); Database (n = 6); Research Institute (n = 2); NR (n = 3)	18 (3–582)	18 months (< 12–41)	17	19	q4w–q8w	> 5 mg/kg–22.5 mg/kg
Ulcerative colitis									
Tofacitinib	1	Prospective (n = 1)	Registry (n = 1)	113	10.1 months	0	1	BID	10 mg
Ustekinumab	4	Retrospective (n = 3); Multicenter (n = 1); Single-Center (n = 2)	Hospital (n = 2); Registry (n = 1); Clinic/Center (n = 1); Research Institute (n = 1)	53.5 (19–108)	7.3 months (7.1–7.6)	3	0	q4w–q8w	90 mg

Table 3 continued

Intervention	Studies (N)	Study designs	Source/setting(s)	Number of patients median (range)	Follow-up median (range)	Studies with interval shortenings (N)	Studies with dose increases (N)	Variations in interval	Variations in dose
Vedolizumab	13	Retrospective (n = 10); Prospective (n = 1); Multicenter (n = 2); Single-Center (n = 5); *Other (n = 1)	Hospital (n = 3); Chart Review/EHR (n = 1); Registry (n = 1); Clinic/Center (n = 4); Database (n = 1); Research Institute (n = 2); NR (n = 1)	71 (18–119)	18.8 months (6.9–37.3)	10	1	q4w–q7w	300 mg
Golimumab	6	Retrospective (n = 4); Prospective (n = 1); Multicenter (n = 4); *Other (n = 1)	Hospital (n = 2); Clinic/Center (n = 2); Database (n = 1); NR (n = 1)	85 (27–186)	12.6 months (12–17.3)	1	6	q2w	100 mg–200 mg
Adalimumab	17	Retrospective (n = 14); Prospective (n = 3); Multicenter (n = 6); Single-Center (n = 3); *Other (n = 4)	Hospital (n = 4); Registry (n = 2); Clinic/Center (n = 3); Database (n = 4); Research Institute (n = 1); NR (n = 1)	73 (30–2968)	14.5 months (10.3–40.7)	7	4	EW–q10d	≥ 8.04 mg/day–40 mg
Infliximab	17	Retrospective (n = 13); Prospective (n = 3); Multicenter (n = 9); Single-Center (n = 4); *Other (n = 1)	Hospital (n = 11); Clinic/Center (n = 3); Database (n = 2); NR (n = 1)	79 (28–184)	15 months (12–56.4)	8	7	q3d– < q8w	< 5 mg/kg–10 mg/kg

Study designs and source/settings are not mutually exclusive

BID, every 12 h; *EHR*, electronic health records; *EOW*, every other week; *EW*, every week; *kg*, kilogram; *mg*, milligram; *N*, number within the overall population; *NR*, not reported; *q3d*, every 3 days; *q2w*, every 2 weeks; *q4w*, every 4 weeks; *q8w*, every 8 weeks; *SLR*, systematic literature review

*Other includes studies denoted exclusively as observational or open label

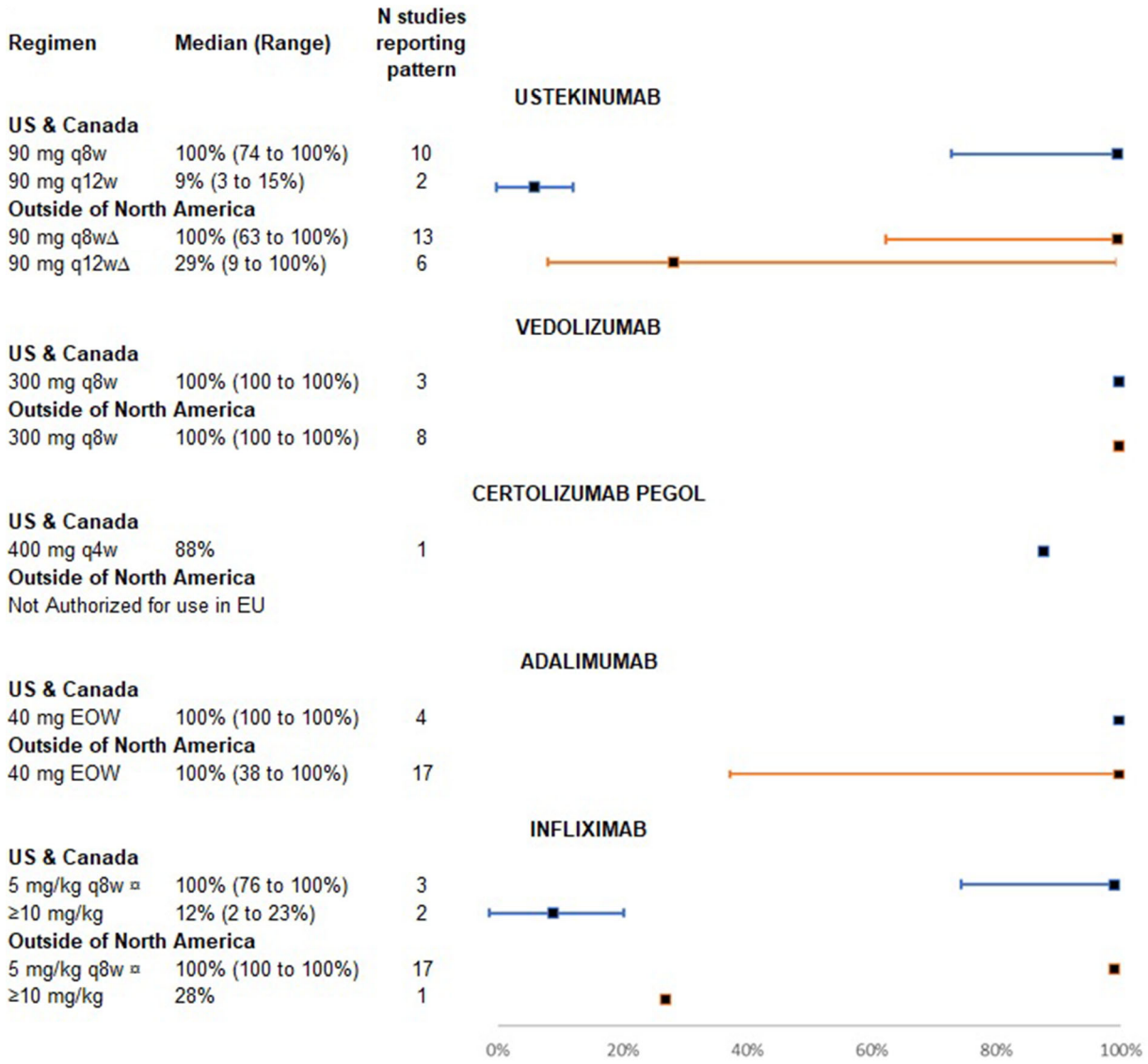


Fig. 2 Most reported initial maintenance dose patterns, Crohn's disease. *EOW*, every other week; *EU*, European Union; *kg*, kilogram; *mg*, milligram; *N*, number within the overall population; *q4w*, every 4 weeks; *q8w*, every 8 weeks; *q12w*, every 12 weeks. [Δ]Includes Biemans et al.'s 2020 [104] study where the maintenance pattern proportions were calculated based on the number of individuals at 12 weeks instead of baseline. [¤]Studies reporting 5 mg/kg were assumed to have dosing every 8 weeks. Source: [27–31, 33–37, 39–49, 51–56, 59–80, 82–104, 106–110, 112–133, 198–202]

82–85, 123–132]. Dose strength increases from 5 to 10 mg/kg were the most common dose escalation pattern observed [proportion: 8% in one NA study; 14% (range 3–67%) in 15 studies ONA] during follow-up (Fig. 3) [53, 54, 63, 64, 66, 68, 71, 72, 74–85, 123–126, 128–133]. Studies reporting only "10 mg/kg" without an interval were assumed to have dosing 10 mg/kg every 8 weeks.

Figure 4 presents the most common maintenance pattern for each selected therapy at the end of follow-up in CD, regardless of the initial dose.

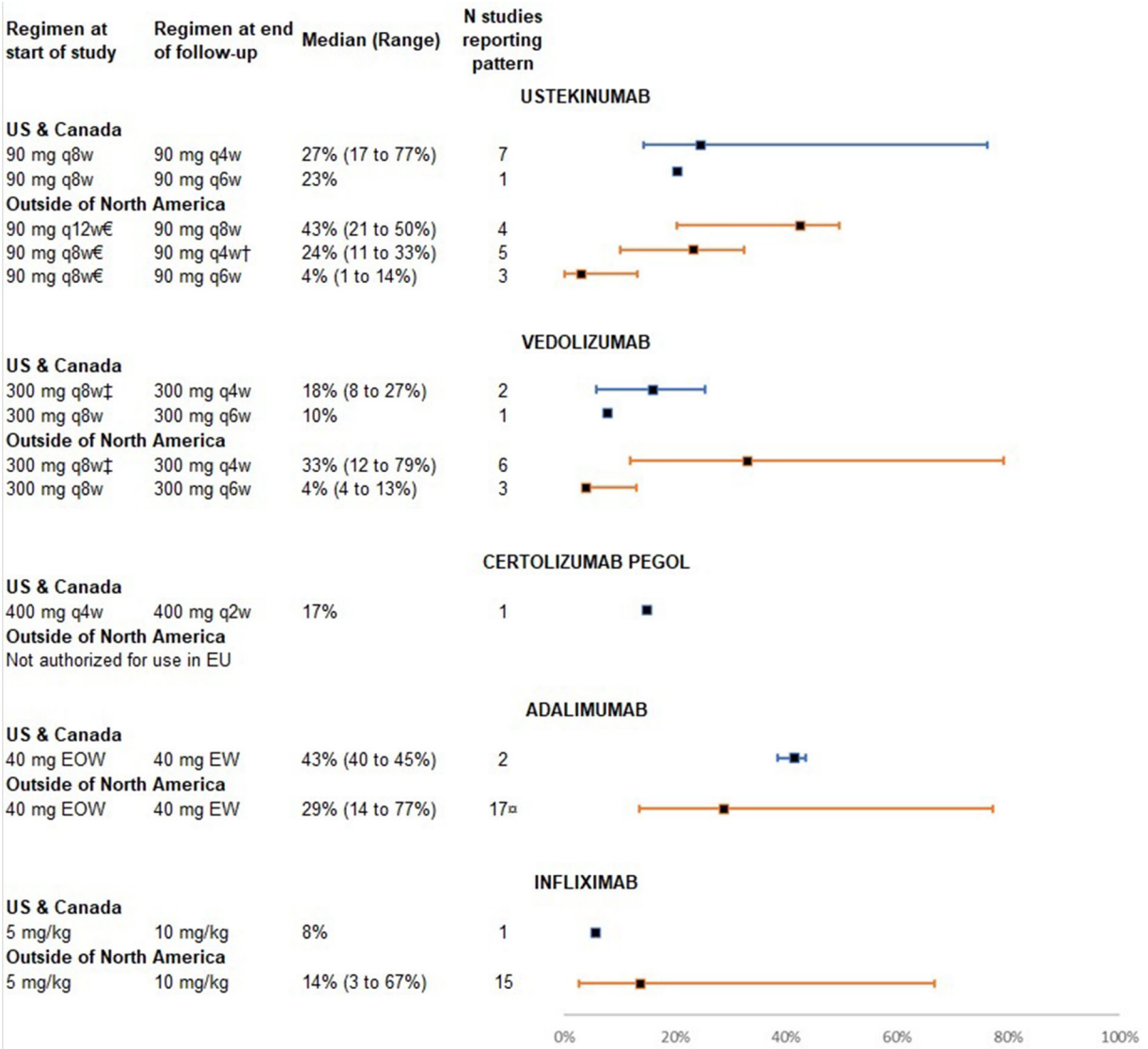


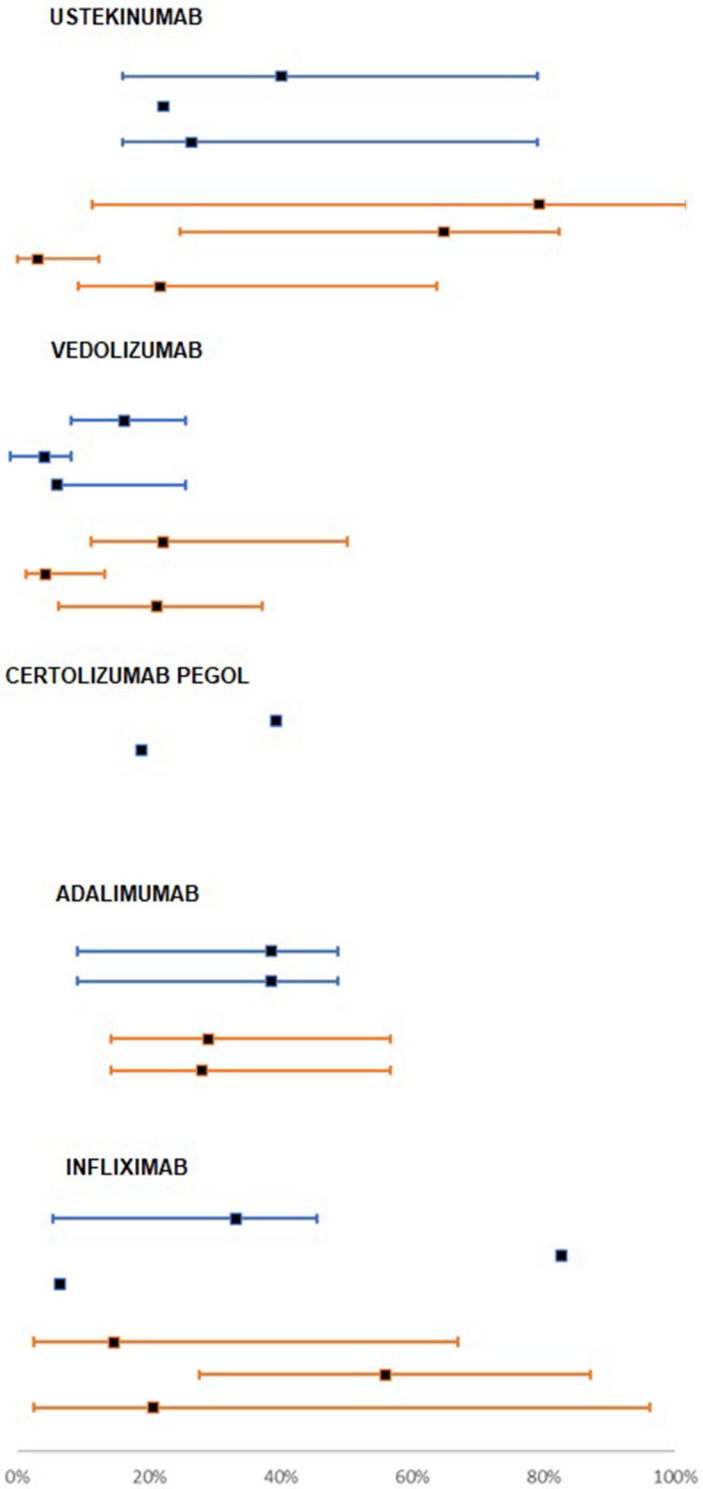
Fig. 3 Most reported dose escalation patterns, Crohn's disease. *EOW*, every other week; *EU*, European Union; *EW*, every week; *kg*, kilogram; *mg*, milligram; *N*, number within the overall population; *q2w*, every 2 weeks; *q4w*, every 4 weeks; *q6w*, every 6 weeks; *q8w*, every 8 weeks; *q12w*, every 12 weeks. €Includes Biemans et al.'s 2020 [104] study where the maintenance pattern proportions were calculated based on the number of individuals at 12 weeks instead of baseline. †Includes IV reinduction plus 90 mg q4w dosing. ‡Including maintenance patterns where only the interval (e.g., q8w) was reported. Source [29–31, 33, 35–37, 39, 40, 44–49, 51–54, 59–75, 77–83, 85–91, 95–97, 99, 101, 103–108, 110, 111, 114–118, 120–131, 133–139, 155, 209–211, 214]

Results in UC

Overview

Nineteen UC studies reported reasons for dose escalation. The most commonly reported reasons (79%) for dose escalation were partial response, no response, or loss of response; few were related to evidence of inflammation assessed by endoscopy or biomarkers (Supplementary Material) [44–47, 51, 52, 110, 123, 132, 134–148]. The most common initial maintenance dose (Fig. 5), dose escalation

Regimen	Median (Range)	N studies reporting pattern
USTEKINUMAB		
US & Canada		
90 mg <q8w	40% (17 to 77%)	7
90 mg q6w	23%	1
90 mg q4w	27% (17 to 77%)	7
Outside of North America		
90 mg <q12w ¤	78% (12 to 100%)	20Δ
90 mg q8w	64% (25 to 81%)	14Δ
90 mg q6w	4% (1 to 13%)	4
90 mg q4w	22% (10 to 63%)	12
VEDOLIZUMAB		
US & Canada		
<q8w	18% (10 to 27%)	4*
300 mg q6w	6% (1 to 10%)	2
300 mg q4w	8% (8 to 27%)	4*
Outside of North America		
<q8w	22% (11 to 50%)	7
300 mg q6w	4% (1 to 13%)	3
300 mg q4w	21% (6 to 37%)	6
CERTOLIZUMAB PEGOL		
US & Canada		
200 mg q2w	40%	1
400 mg q2w	20%	1
Outside of North America		
Not Authorized for use in EU		
Not Authorized for use in EU		
ADALIMUMAB		
US & Canada		
<EOW	40% (11 to 50%)	3
40 mg EW	40% (11 to 50%)	3
Outside of North America		
<EOW	29% (14 to 57%)	20
40 mg EW	28% (14 to 57%)	19
INFLIXIMAB		
US & Canada		
10 mg/kg q8w€	35% (8 to 47%)	3
5 mg/kg q8w	83%	1
>10 mg/kg q4-8w	9%	1
Outside of North America		
10 mg/kg q8w€	15% (3 to 67%)	14
5 mg/kg q8w	56% (28 to 87%)	15
5 mg/kg q4-7w	21% (3 to 96%)	9



◀**Fig. 4** Most reported dose patterns at the end of follow-up in Crohn's disease. *EOW*, every other week; *EU*, European Union; *EW*, every week; *kg*, kilogram; *mg*, milligram; *N*, number within the overall population; *q2w*, every 2 weeks; *q4w*, every 4 weeks; *q4-7w*, every 4–7 weeks; *q6w*, every 6 weeks; *q8w*, every 8 weeks; *q12w*, every 12 weeks. ¤Studies reporting 90 mg q2-8w include interval shortenings and re-inductions if they occurred together. ΔIncludes one study with 'NR' reported as the patient proportion for 90 mg q8w [36, 37]. *Including Reinglas et al. [107] who did not report the number of individuals on 300 mg q8w or 300 mg q4w at the end of follow-up. €Studies reporting 10 mg/kg were assumed to have dosing every 8 weeks. Source: [21, 28–33, 35–54, 58–76, 79, 80, 82–89, 92–104, 106, 107, 109–113, 115–126, 128–132, 198–215]

patterns (Fig. 6), and last dose at the end of follow-up (Fig. 7) are described by region below, with full details in the Supplementary Material.

Tofacitinib

One tofacitinib study, conducted in Spain, did not report initial maintenance dosages, yet EMA label indications are 5 mg two times a day (BID) for the treatment of UC [149, 150]. Though patterns of dose escalation could not be ascertained, it was reported that 8% of patients were on 10 mg of tofacitinib BID at the end of follow-up (Fig. 7) [150].

Ustekinumab

Two studies conducted in NA reported initial maintenance dosing of 90 mg every 8 weeks in all patients (100%; range 100–100%), per FDA recommendations (Fig. 5) [151–153]. Initial dosing of 90 mg every 12 weeks was reported in only one of the two studies conducted ONA (7% of patients) [154]. When initially started on 90 mg every 8 weeks, the most common dose escalation pattern in NA studies was an interval shortening to 90 mg every 4 weeks (47% of patients) or 90 mg every 6 weeks (12% of patients) (Fig. 6) [151–153]. In studies ONA, interval shortening to every 6 weeks or every 4 weeks was reported in 27% of patients who were started on an initial interval of every 12 weeks or every 8 weeks (Supplementary Material) [154, 155].

Vedolizumab

Studies in NA ($N = 6$) and ONA ($N = 5$) reported an initial starting maintenance dose of vedolizumab per local regulatory recommendations (e.g., 300 mg every 8 weeks) in a median of 100% of patients (Fig. 5) [7, 42–46, 48, 49, 51, 52, 107, 110, 134–136, 147, 148, 156, 157]. The most common dose escalation pattern for UC patients on vedolizumab was an interval shortening from 300 mg every 8 weeks to 300 mg every 4 weeks (Fig. 6) [44–49, 51, 52, 89, 107, 110, 134–136, 147, 148, 156]. Studies that reported dosing "every 8 weeks" without strength were assumed to have 300 mg/kg every 8 weeks.

Golimumab

All included studies ($n = 6$) were from ONA where local regulatory guidelines recommend initial dosing based upon patient weight (50 mg every 4 weeks if < 80 kg; 100 mg every 4 weeks if > 80 kg) [144–146, 157–162]. The most common initial maintenance pattern was 100 mg every 4 weeks in a median of 47% of patients (range 43–100%) (Fig. 5) [7, 144–146, 157, 159–161]. A dose strength increase from 50 to 100 mg was observed in a median of 76% of patients in four studies conducted ONA (Fig. 6) [144–146, 160–162].

Adalimumab

The studies ($N = 10$) conducted ONA reported initial maintenance dosing according to the EMA label recommendation (e.g., 40 mg EOW) in a median of 100% (range 94–100%) of patients (Fig. 5) [7, 61, 123, 137, 138, 157, 163–172]. Dose escalation patterns were not reported in NA studies, yet were most commonly interval shortenings to 40 mg EW (median proportion 39%; range 30–56%) in studies ONA (Fig. 6) [61, 123, 137, 138, 163–167, 169–172]. A dose strength increase to either 80 mg EOW from baseline (2%) or to an average biweekly dose ≥ 50 mg (median proportion 22%; range 2–74%) was also reported

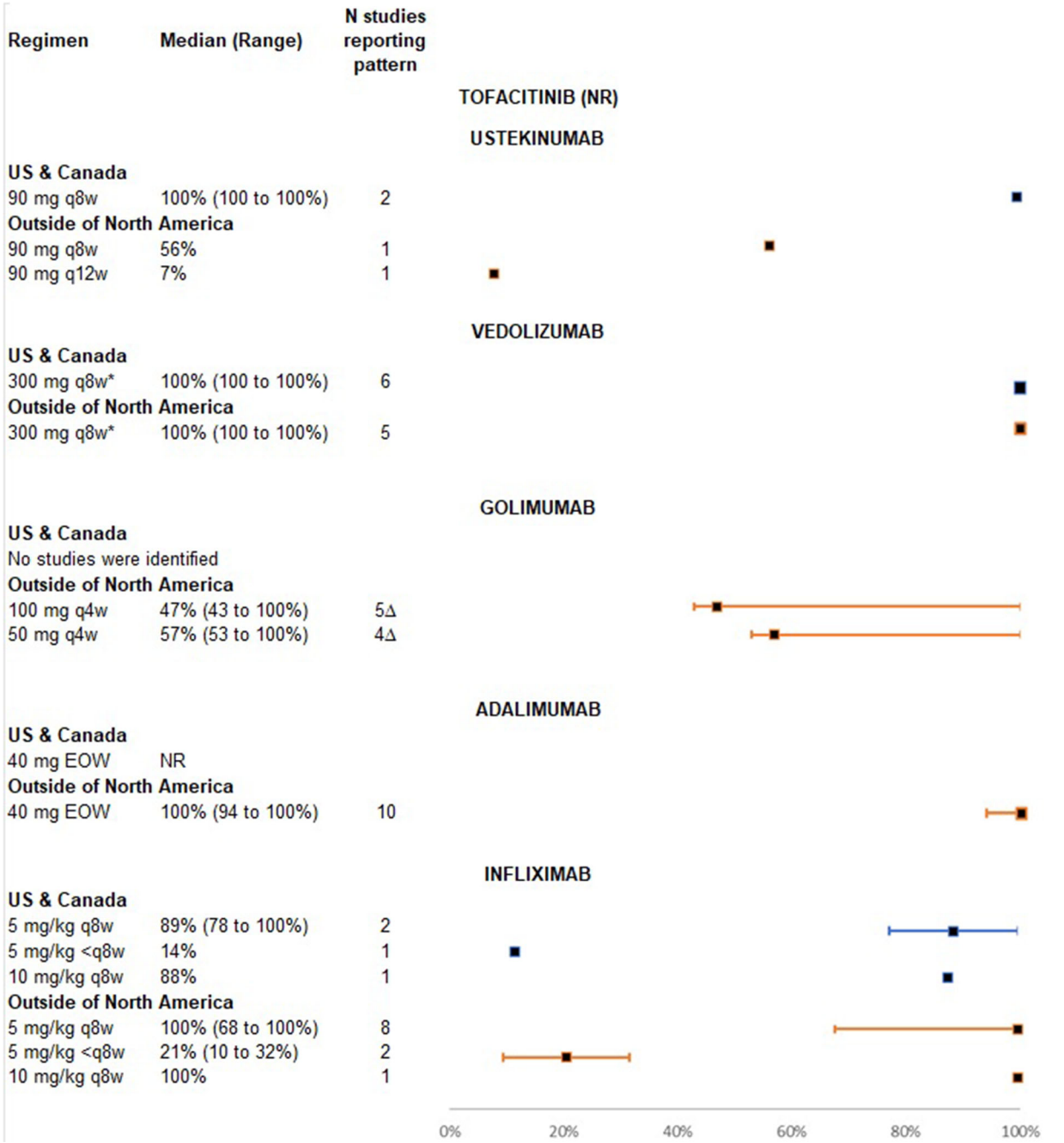


Fig. 5 Most reported initial maintenance dose patterns, ulcerative colitis. *EOW*, every other week; *kg*, kilogram; *mg*, milligram; *N*, number within the overall population; *NR*, not reported; *q4w*, every 4 weeks; *q8w*, every 8 weeks; *q12w*, every 12 weeks. *Includes studies that reported 300 mg dosing and every-8-week dosing. ΔIncludes two studies that did not report on the number of individuals on the recorded maintenance dose [144–146, 159–161]. Source: [7, 42–46, 48, 49, 51, 52, 61, 107, 110, 123–125, 127, 132, 134–148, 151–154, 156, 157, 159–161, 163–179, 216]

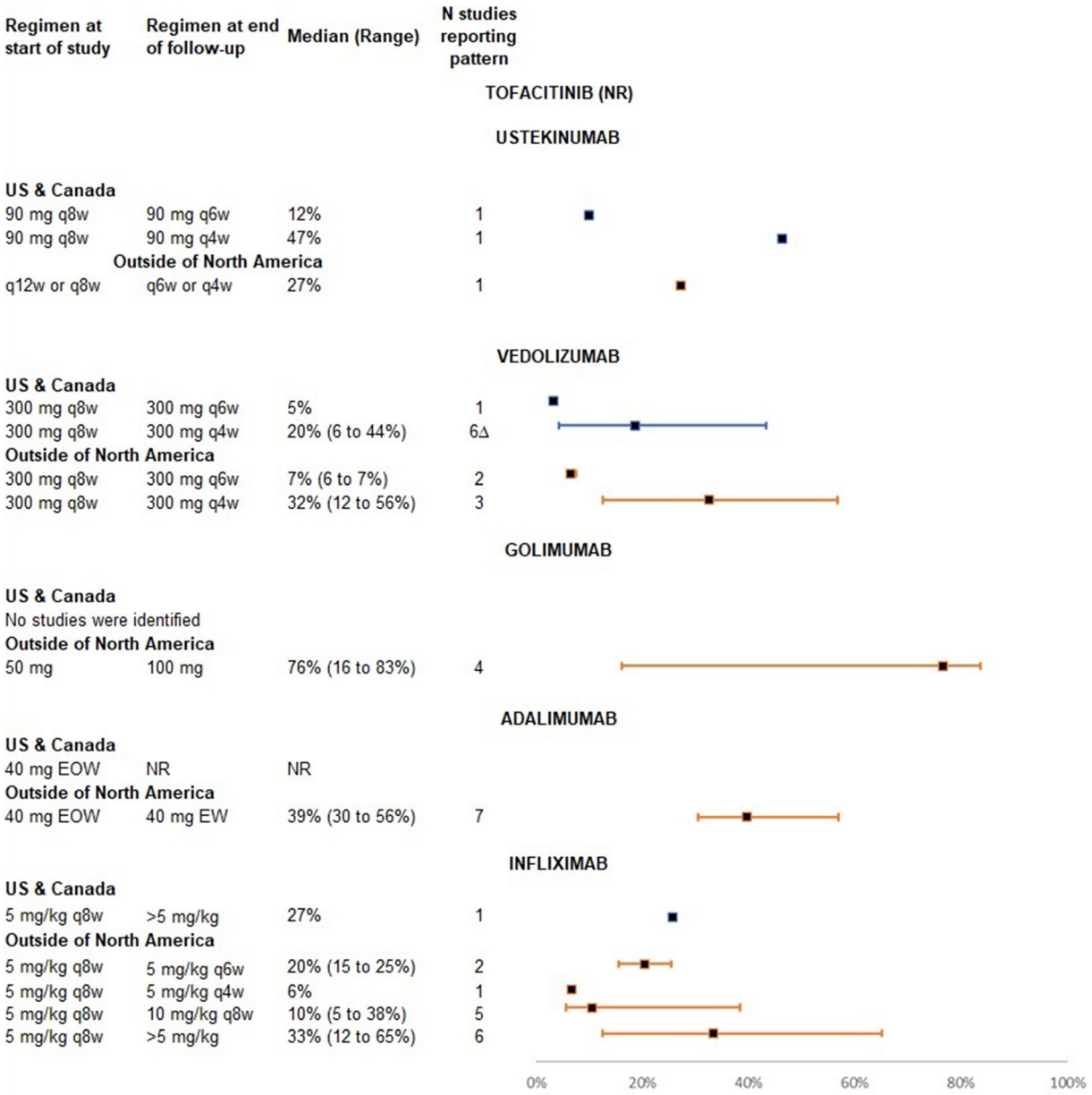
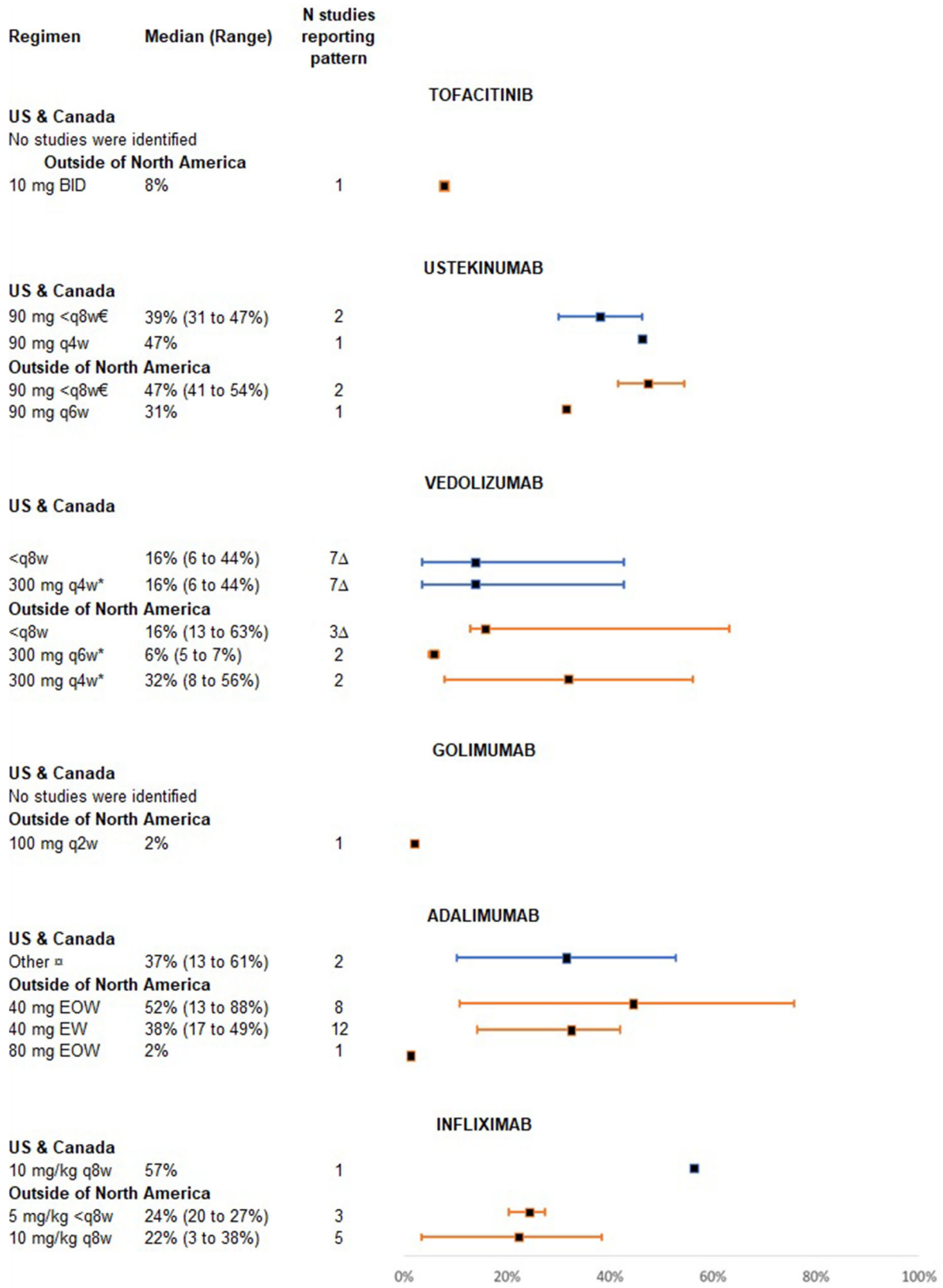


Fig. 6 Most reported dose escalation patterns, ulcerative colitis. *EOW*, every other week; *EW*, every week; *kg*, kilogram; *mg*, milligram; *N*, number within the overall population; *NR*, not reported; *q4w*, every 4 weeks; *q6w*, every 6 weeks; *q8w*, every 8 weeks. Source: [7, 44–49, 51, 52, 61, 89, 107, 110, 123–125, 127, 132, 134–148, 151–157, 160–167, 169–172, 175–179, 217, 218]

in patients ONA (Supplementary Material) [7, 137, 138, 157, 168, 169].

Infliximab

Two studies conducted in NA reported an initial maintenance pattern in alignment with FDA label recommendations (5 mg/kg every 8 weeks) in a median of 89% of patients (range 78–100%) [124, 125, 127, 173, 174]. Outside of NA, most studies ($N = 8$) reported an initial maintenance dose of 5 mg/kg every 8 weeks in a median of


Regimen
Median (Range)
N studies reporting pattern
TOFACITINIB
US & Canada
No studies were identified
Outside of North America
10 mg BID 8% 1
USTEKINUMAB
US & Canada
90 mg <q8w€ 39% (31 to 47%) 2
90 mg q4w 47% 1
Outside of North America
90 mg <q8w€ 47% (41 to 54%) 2
90 mg q6w 31% 1
VEDOLIZUMAB
US & Canada
<q8w 16% (6 to 44%) 7Δ
300 mg q4w* 16% (6 to 44%) 7Δ
Outside of North America
<q8w 16% (13 to 63%) 3Δ
300 mg q6w* 6% (5 to 7%) 2
300 mg q4w* 32% (8 to 56%) 2
GOLIMUMAB
US & Canada
No studies were identified
Outside of North America
100 mg q2w 2% 1
ADALIMUMAB
US & Canada
Other ¤ 37% (13 to 61%) 2
Outside of North America
40 mg EOW 52% (13 to 88%) 8
40 mg EW 38% (17 to 49%) 12
80 mg EOW 2% 1
INFLIXIMAB
US & Canada
10 mg/kg q8w 57% 1
Outside of North America
5 mg/kg <q8w 24% (20 to 27%) 3
10 mg/kg q8w 22% (3 to 38%) 5
0%
20%
40%
60%
80%
100%

◀**Fig. 7** Most reported dose patterns at the end of follow-up, ulcerative colitis. *BID*, every 12 h; *EOW*, every other week; *EW*, every week; *kg*, kilogram; *mg*, milligram; *N*, number within the overall population; *q2w*, every 2 weeks; *q4w*, every 4 weeks; *q6w*, every 6 weeks; *q8w*, every 8 weeks. [€]Includes reported dosing of every 4–6 weeks; *Includes studies that only reported q6w and q4w dosing, respectively. [Δ]Includes two studies that did not report the number of individuals dose escalated [111, 164]. [¤]Reported dosages include 40 mg q7-10d, biweekly dose ≥ 50 mg, 40 mg q10d, ≥ 4 mg q1d, an increase of ≥ 50% compared to label-recommended daily dose, and a doubling of the average daily dose. Source: [21, 42–49, 51, 52, 62, 92, 110–112, 115, 128, 141–145, 152–154, 157–160, 164, 171, 173–183, 196]

100% of patients (range 68–100%) [7, 123, 132, 139–143, 157, 175–179].

Infliximab studies conducted ONA reported an interval shortening to either 5 mg/kg every 6 weeks (median proportion 20%; range 15–25%) or 5 mg/kg every 4 weeks (proportion 6%) from a starting dose of 5 mg/kg every 8 weeks (Fig. 6) [123, 140, 141, 143, 177, 178]. A dose strength increase from 5 to 10 mg/kg was reported in a median 10% of patients (range 5–38%) in five studies conducted ONA [132, 139–143, 175, 176, 178, 179]. Six studies ONA also reported a dose strength increase to > 5 mg/kg in a median of 33% of patients (Supplementary Material) [7, 127, 132, 140–143, 157, 175, 176, 178, 179]. One NA study reported a dose strength increase from 5 to > 5 mg/kg in 27% of patients [124, 125, 127].

Figure 7 presents the most common maintenance pattern for each selected therapy at the end of follow-up in UC, regardless of the initial dose.

DISCUSSION

Two SLRs were conducted to evaluate the magnitude of dose escalations in non-interventional studies of patients receiving maintenance therapies for CD and UC. Data were extracted to identify any interval shortening or dose-strength increase among individuals treated with ustekinumab (CD/UC), vedolizumab (CD/UC), adalimumab (CD/UC), infliximab (CD/UC), certolizumab pegol (CD), golimumab (UC), and tofacitinib (UC). Overall, 100 CD and 54 UC publications were fully extracted for inclusion in this study.

All included studies, except those reporting on ustekinumab, reported patients starting maintenance dosing per label indications. In studies of ustekinumab conducted ONA, a median of 100% of patients with CD and 56% of patients with UC started on maintenance at 90 mg every 8 weeks. During the follow-up, there was a significant dose creep (e.g., increased doses or shortened intervals) for each selected advanced therapy, yet the escalations were generally aligned with the EMA escalation allowances. However, some dose patterns outside of label recommendations were observed, such as ustekinumab from 90 mg every 8 weeks to every 4 weeks; vedolizumab from every 8 weeks to every 6 weeks. Dose strength increases were commonly reported for infliximab in CD and UC studies, and evidence regarding dose escalation patterns for certolizumab pegol, golimumab, and tofacitinib was limited.

Despite more frequent reliance on dose escalation to regain clinical response and induce remission, studies evaluating the effectiveness of standard vs. escalated doses are scarce and outcomes were assessed differently. As such, an assessment of clinical outcomes was outside of the initial scope of the SLR and synthesis of outcome data was not feasible. In a critical appraisal of advanced therapy dose escalation in IBD treatment, the Canadian Agency for Drugs and Technologies in Health (CADTH) found limited evidence to demonstrate the incremental efficacy of escalated vs. standard dosing [180]. Report findings showed that clinical effectiveness and safety between populations on standard and escalated doses were similar [180]. However, patients who dose escalated due to loss of response might have different disease characteristics than those without dose escalation, which could potentially confound the comparison of efficacy between the two groups. In addition, the use of escalated doses of advanced therapeutics often results in increased costs [7, 16, 17]. In general, compared to standard of care, the cost of

advanced therapies is thought to be offset in the long term by reductions in healthcare resource utilization as well as improved quality of life, leading to reductions in indirect costs [7, 16, 21, 181]. However, the cost-effectiveness of escalated vs. standard dosing remains unclear and could not be assessed robustly without proper quantification of the incremental efficacy associated with escalated dosing. More studies are needed to evaluate effectiveness, particularly in terms of clinical outcomes, safety, and health care resource utilization, associated with dose escalation to enable a more robust cost-effectiveness evaluation on dose escalation as well as to inform therapeutic decision making.

Even though improved treatment strategies and the use of more effective therapeutics have greatly enhanced the management of CD and UC, there are still many unmet needs in IBD. Recent research has shown that a substantial number of patients experience treatment failure and/or loss of response with first- or second-line advanced therapies [182–186]. Loss of response, though a common occurrence in IBD treatment, is multifactorial and can be caused by inadequate drug concentrations, antidrug antibody formation, sub-optimal adherence to treatment, or uncontrolled inflammation [24, 26, 184, 187–191]. Loss of response presents a major challenge in clinical practice due to the limited availability of effective treatment alternatives and adverse impacts on patient quality of life [23, 182, 184, 186, 188, 192]. Clinicians thus have a pressing need to use treatment strategies such as dose escalation to reclaim or maintain clinical response [25, 84, 182, 183, 186]. The frequent occurrence of dose escalations, therefore, underscores the need for effective treatment with long-term durability [182, 186].

Although reported less frequently, other reasons for dose escalation include continued endoscopic inflammation, elevated levels of biomarkers (C-reactive protein, fecal calprotectin), and lower level of drug serum. This might indicate that dose escalation is used in a tight control or treat-to-target management approach. As recommended by the updated STRIDE II consensus recommendation, long-term treatment goals including lower inflammatory biomarker levels or achievement of endoscopic healing could lead to long-term remission [25, 182, 186, 193–195]. The CALM study has demonstrated timely escalation with adalimumab dose in a tight control approach is associated with greater clinical and endoscopic improvements as well as reduced hospitalization events than conventional management in CD [196, 197]. Therefore, reason for dose escalation might also play a role in understanding the associated clinical benefit of dose escalation.

Limitations

There are several limitations of the SLRs and included studies. First, the inclusion of non-interventional observation studies may contribute to heterogeneity due to the wide variability in observed study methods, outcome measures, and patient characteristics. Second, study design of included articles may have also contributed to the increased frequency of dose escalation reporting. For example, some publications reported on dose escalation in patient populations where a therapeutic drug monitoring (TDM) algorithm was used to optimize treatment. The use of TDM algorithms to guide dosing often results in dose adjustments to levels much higher than those in routine practice. In addition, some included studies focused on populations that were likely to experience dose escalation or specifically aimed to report on the efficacy of dose escalation, thereby increasing the likelihood of dose escalation overestimation. To mitigate this, studies that included patients who were on an escalated dose at study onset were excluded. Finally, the search strategy was limited to the availability of indexed terms involving dose escalation, which may have introduced selection bias. Bibliographic and hand searches were employed to capture any previously unidentified studies.

CONCLUSION

Dose escalation in CD and UC is common. The reported dose escalation patterns and escalation rates vary by region and by CD and UC. Most

escalation patterns reported were aligned with regulatory recommendations while some reported more diverse or aggressive dose escalation. Future studies are needed to evaluate optimal approaches for maintaining treatment effectiveness and durability in CD and UC patients.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data availability. All data generated or analysed during this study are included in this published article (and its supplementary information files).

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