Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: https://www.tandfonline.com/loi/icmo20

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To cite this article: Nathalie C. Gemayel, Eugenio Rizzello, Petar Atanasov, Daniel Wirth & Andras Borsi (2019) Dose escalation and switching of biologics in ulcerative colitis: a systematic literature review in real-world evidence, Current Medical Research and Opinion, 35:11, 1911-1923, DOI: 10.1080/03007995.2019.1631058

To link to this article: https://doi.org/10.1080/03007995.2019.1631058

CURRENT MEDICAL RESEARCH AND OPINION
2019, VOL. 35, NO. 11, 1911–1923
https://doi.org/10.1080/03007995.2019.1631058
Article RT-0763/1631058

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REVIEW

Dose escalation and switching of biologics in ulcerative colitis: a systematic literature review in real-world evidence

Nathalie C. Gemayel[a], Eugenio Rizzello[b], Petar Atanasov[a], Daniel Wirth[c] and Andras Borsi[d]

[a]Health Economics & Market Access (HEMA), Amaris Consulting Ltd, Barcelona, Spain; [b]Health Economics & Market Access (HEMA), Amaris Consulting Ltd, London, UK; [c]Market Access, Janssen-Cilag GmbH, Neuss, Germany; [d]Market Access, Janssen EMEA, High Wycombe, UK

ABSTRACT

Background: Biologics used to treat ulcerative colitis (UC) may lose their effect over time, requiring patients to undergo dose escalation or treatment switching, and systematic literature reviews of real-world evidence on these topics are lacking.

Aim: To summarize the occurrence and outcomes of dose escalation and treatment switching in UC patients in real-world evidence.

Methods: Studies were searched through MEDLINE, MEDLINE IN PROCESS, Embase and Cochrane (2006–2017) as well as proceedings from three major scientific meetings.

Results: In total, 41 studies were included in the review among which 35 covered dose escalation and 12 covered treatment switching of biologics. Tumor necrosis factor antagonist (anti-TNF) escalation for all patients included at induction ranged from 5% (6 months) to 50% (median 0.67 years) and 15.2% to 70.8% (8 weeks) for anti-TNF induction responders. Mean/median time to dose escalation on anti-TNF ranged from 1.84 to 11 months. The most common switching pattern, infliximab → adalimumab, occurred in 3.8% (median 5.6 years) to 25.5% (mean 3.3 years) of patients.

Conclusions: Dose escalation and treatment switching of biologics may be considered as indicators of suboptimal therapy suggesting a lack of long-term remission and response under current therapies.

ARTICLE HISTORY
Received 17 August 2018
Revised 21 May 2019
Accepted 12 June 2019

KEYWORDS
Ulcerative colitis; infliximab; adalimumab; real-world evidence; dose escalation; systematic literature review

Introduction

Biologic therapies have significantly improved the management of patients affected by ulcerative colitis (UC), a chronic disease characterized by a diffuse inflammation of the rectal and colonic mucosa and delineated by periods of remissions and relapses. Due to the nature of the disease, patients are required to switch treatments, undergo dose escalation or ultimately undergo surgery which occurs at a rate of 3%–17% in adults[1].

The use of biologics such as tumor necrosis factor antagonists (anti-TNFs) or anti-integrins is recommended in moderate to severe UC patients who do not respond to conventional treatments including immunosuppressants by the European Crohn's and Colitis Organisation (ECCO) and the American Gastroenterological Association[2–4].

As a considerable proportion of patients do not respond to induction therapy (primary failure) or will lose response over time (secondary failure)[5], the third European consensus on the diagnosis and management of UC suggests maintaining a patient in remission via either a dose escalation of oral/rectal aminosalicylates, or an addition of thiopurine or biologic treatment (anti-TNF or vedolizumab) (ECCO statement 12 D)[3].

It is estimated that 5–50% of ulcerative colitis (UC) patients require dose escalation during the course of their treatment according to NICE and the UK Inflammatory Bowel Disease Audit[6–8]. A multinational chart review in Europe and Canada reported that 29.7% of anti-TNF initiators and 17.1% of anti-TNF switchers affected with UC required dose escalation[9], which underlines the loss of response in UC patients under induction or maintenance or intolerance to treatment. Treatment switching occurs in around a third of inflammatory bowel disease patients receiving anti-TNF who do not respond to therapy (primary failure) and a large portion of these patients will lose response (secondary failure) or be intolerant to the therapy, which is why research is needed to understand the extent to which it occurs and what the true effectiveness of biologics is in clinical practice[10].

Dose escalation is usually studied in clinical trials assessing the efficacy of biologics (ULTRA1, ULTRA2 and Suzuki et al. for adalimumab[11]; PURSUIT-SC and PURSUIT-Maintenance for golimumab; and ACT1, ACT2, Probert et al.[13] and UC-SUCCESS for infliximab[10]; all clinical study results were accessed via Clinicaltrials.gov), which may not be reflective of the true efficacy in routine clinical practice[11]. Therefore, the aim of this systematic literature review is to assess the evidence on dose escalation and treatment

CONTACT Nathalie C. Gemayel nathalie.gemayel@gmail.com Amaris Consulting & Innovation, Carrer de Guitard 45, 08014, Barcelona, Spain

switching in UC patients that occur in "real life" practice in primary and secondary non-responders or intolerant patients to have a better understanding of the real world patients live in[12–14].

The objectives of our research were the following:

1. Primary objective: to investigate the rates and outcomes of dose escalation and treatment switching in UC adult patients under biologic therapy in real life/clinical practice
2. Secondary objectives (related to dose escalation):
   - To quantify rates of response and remission, time to loss of response, rates of treatment de-escalation and adverse events after dose escalation
   - To identify the dosing regimens under dose escalation and time to dose escalation
   - To assess potential predictors that have been identified to play a role in dose escalation
3. Secondary objectives (related to treatment switching): to quantify the rates of response and remission and adverse events after treatment switching.

Methods

Dose escalation and treatment switching definitions

Dose escalation consists of a decrease in the interval between doses and/or an increase in the maintenance dose[15].

Treatment switching consists of switching from one therapy to a therapy of the same drug class or different drug class in order to treat a specific condition.

De-escalation is defined as an increase in the interval of administration or a decrease in the dosage strength of any treatment.

Literature search

The protocol for this review was not registered. The first phase of the literature search was conducted to establish the criteria to select relevant articles, including eligible study designs, patients, interventions and acceptable outcomes. Once the criteria were established and approved (see *Study selection*), a search strategy was developed to collect data on dose escalation and treatment switching in adult UC patients.

A systematic literature review was conducted on 22 May 2017 via Embase, MEDLINE (through Embase) and on 7 June 2017 via the Cochrane Library. The databases were searched for all studies reporting outcomes on dose escalation in daily clinical practice, time to dose escalation, clinical response/remission after dose escalation and predictors of dose escalation using the medical subject headings "ulcerative colitis"/exp OR "ulcerative colitis" OR "inflammatory bowel disease"/exp OR "inflammatory bowel disease" OR "ibd". Geographical limitations were not set.

A hand search was additionally performed in order to identify all studies of interest published by important European clinical societies, such as United European Gastroenterology Week (UEGW), European Crohn's and Colitis Organization (ECCO) and Digestive Disease Week (DDW). All studies obtained were then cross referenced.

The searches were restricted to capture literature published within the time frame of January 2006 until May and June 2017 to mark the uptake of anti-TNFs in the treatment regimen of ulcerative colitis (approval of infliximab in ulcerative colitis granted in September 2005 by the FDA and EMA in 2009).

Two authors independently examined titles and abstracts. All discrepancies were solved by discussion. If no agreement was found, a third reviewer was involved in the discussion.

Study selection

For inclusion into the review, studies needed to fulfill the following criteria: (i) adult patients with a diagnosis of an active moderate to severe UC who were treated with (ii) biologic therapies including adalimumab, golimumab, infliximab and vedolizumab and enrolled in (iii) observational or real-world evidence studies.

i. **Population:** adult patients with ulcerative colitis, treated with biologic therapy who required a de-/escalation or required a switch in therapy.
ii. **Interventions:** adalimumab, golimumab, infliximab and vedolizumab in all available doses included in observational studies as a monotherapy or in combination with background therapy such as purine antimetabolites and in all possible administration routes.
iii. **Study type**: prospective and retrospective observational studies, cohort and database studies as well as case studies were included. Systematic literature reviews that included these types of studies were also included for cross-referencing.
Randomized controlled trials and clinical trials were excluded. Publications that were not written in English were also excluded.
iv. **Outcomes:** Rate of patients undergoing dose escalation or switching; time to dose escalation or switching; time spent on escalated dose or therapy to which patients were switched to; average dose to which patients were escalated to or therapy to which patients were switched to; rates of dose de-escalation after initial dose escalation; clinical outcomes of patients who underwent dose escalation or treatment switching; rate of adverse events as a result of dose escalation and switching; predictors of dose escalation.

Articles were excluded if they were based on a different intervention (i.e. surgery, pharmacotherapy other than biologics), different endpoint (i.e. clinical analysis, budget impact analysis, cost assessments), or a different indication (Crohn's disease, psoriasis, psoriatic arthritis, etc.).

The selected articles that met the inclusion criteria in accordance with the Population, Intervention, Comparison, Outcome, Study type (PICOS) scheme, were included in this review. The records were selected in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and can be seen in Figure 1.

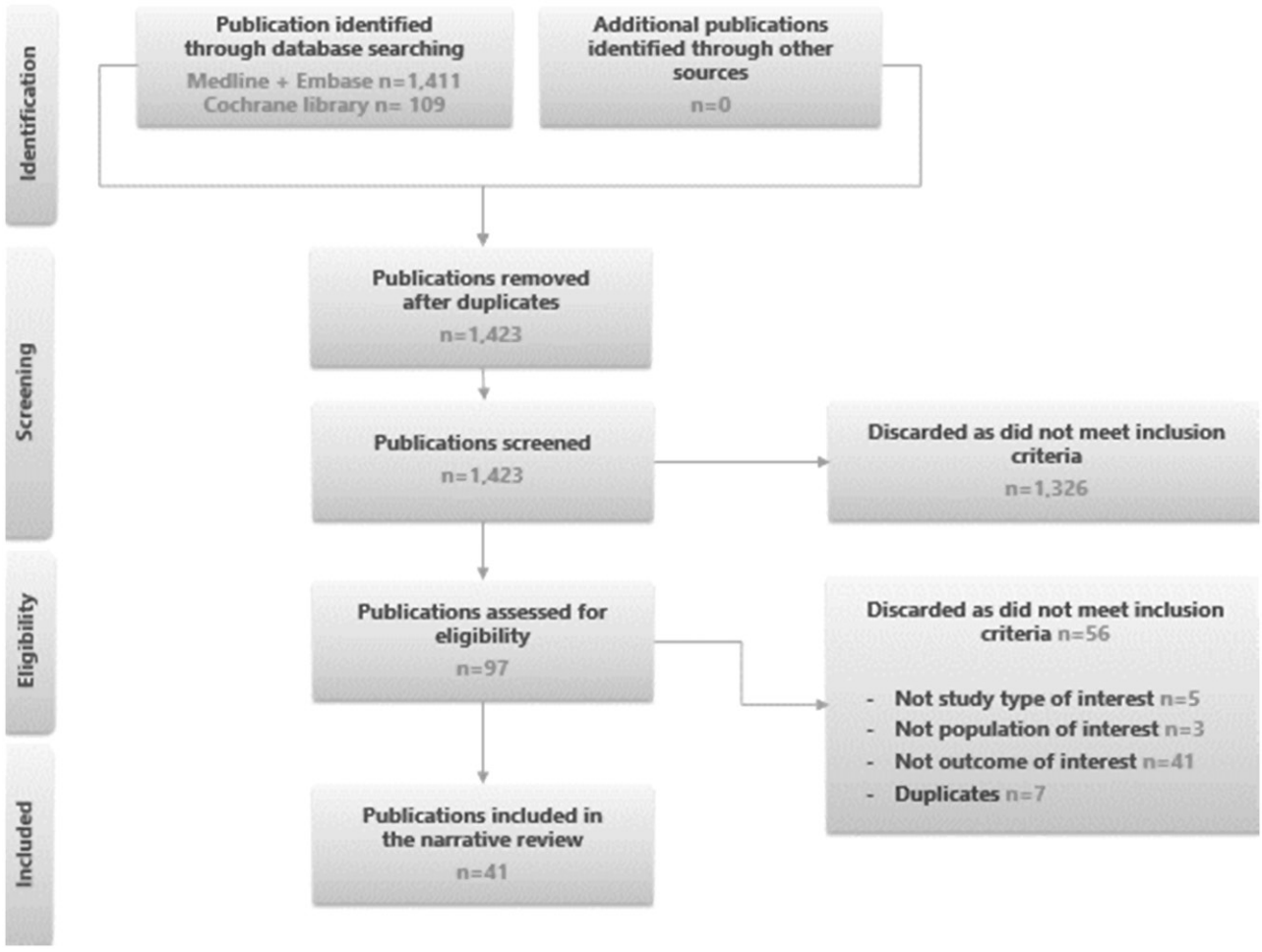

Figure 1. PRISMA chart for the review on dose escalation and treatment switching in UC.

Data extraction and analysis

Data from eligible studies were collected. Data extraction was carried out by three researchers and quality control has been done for at least 20% of extracted data, as defined in the study protocol.

Results were then tabulated and analyzed using descriptive statistics. All of the fields regarding the outcomes of interest (see PICOS in *Study selection*) were extracted if reported.

Statistical analysis

Descriptive statistics were reported for the study outcomes for all patients and for each of the dosing cohorts. Univariate, bivariate and multivariate analyses were not conducted to assess the association of baseline characteristics with cohorts or patient characteristics with dose escalation.

Results

Literature search results

After having applied a search strategy for dose escalation and treatment switching as described, 41 studies were identified amongst which 20 articles and 21 abstracts were identified, as shown in Figure 1. Regarding the geographical scope of these studies, 24 originated from Europe, 7 from the USA, 2 from Canada, 3 from Japan, 1 from Israel and 4 that did not report a specific country. Data largely emanated from retrospective data (80%) compared to prospective studies (20%), as shown in Table 1.

The time of patient follow-up across studies varied between 0.46 years and a median of 5.16 years across studies. Dose escalation and treatment switching were covered by respectively 35 and 12 studies.

Amongst the outcomes of interest in dose escalation, descriptive statistics were reported in all studies; however, effectiveness outcomes after dose escalation and/or treatment switching were reported only in respectively 11 and 2 studies. Predictors of dose escalation were only reported in 3 studies.

Dose escalation

Dose escalation in daily clinical practice

Dose escalation of moderate to severe UC patients was reported in 35 out of 41 studies identified through the predefined PICOS scheme and was reported for anti-TNF, IFX,

Table 1. Characteristics of identified studies.

Authors, year	Country	Full text or abstract	Study design	Study period	Methods of data collection	UC sample size (*n*)	Females/ males (*n*)	Age (mean or median y)
Afif et al. 2009[16]	USA	Full text	Uncontrolled trial	8 November 2006–17 September 2007	Medical records	20	8/12	38
Alzafiri et al. 2011[17]	Canada	Full text	Retrospective study	2000–2008	Database	26	14/12	38.4
Amiot et al. 2016[18]	France	Full text	Multicenter, prospective study	June–December 2014	41 French centers	121	54/67	42.8
Angelison et al. 2014[19]	Sweden	Abstract	Retrospective study	November 2004–December 2011	Local registries at 9 Swedish IBD centers	243	98/145	26.3
Armuzzi et al. 2013[20]	Italy	Full text	Open-label retrospective study	April 2006–July 2011	22 Italian referral centers	88	53/35	27.7
Armuzzi et al. 2013[21]	Italy	Abstract	Prospective study	NR	NR	40	24/16	37
Baert et al. 2014[22]	Belgium	Full text	Retrospective study	July 2005–December 2012	Electronic charts of the patients	73	31/42	28.1
Baki et al. 2015[23]	Germany	Full text	Uncontrolled, open-label retrospective	January 2011–February 2014	Electronic patient charts and medical records	72	39/33	33
Black et al. 2016[24]	England	Full text	Retrospective study	1 January 2010–31 March 2014	Hospital Treatment Insights database/ NHS Hospital Episode Statistics data	191	109/82	41
Bressler et al. 2016[25]	Canada	Abstract	Retrospective study	August 2012–August 2015	Patient support program (PSP), BioAdvance	136	67/69	44.4
Cappello et al. 2013[26]	Italy	Abstract	Retrospective multicenter study	January 2008–June 2012	Clinical records in 9 referral centers from Southern Italy	257	107/150	35.7
Cappello et al. 2014[27]	Italy	Abstract	Retrospective multicenter study	January 2008–June 2012	11 centers from Southern Italy	160	61/99	35.5
Cesarini et al. 2014[28]	Europe	Full text	Retrospective multicenter study	2009–2012	Database from participating institutions	41	11/30	46.6
Christensen et al. 2015[29]	Denmark	Full text	Retrospective, observational study	Patients on ADL until February 2014	Danish inflammatory bowel disease center (Department of Gastroenterology, Herlev Hospital)	33	21/12	37
Daperno et al. 2016[30]	Italy	Abstract	Prospective observational study	NR	Three institutions in Italy	54	NR	38.7
Dumitrescu et al. 2015[31]	France	Full text	Retrospective study	January 2006–May 2013	Personal database and/or a standardized hospital in-patient diagnostic data set	157	73/84	37.6
Echarri et al. 2015[32]	Spain	Abstract	Retrospective observational study	January 2011–April 2014	NR	21	NR	NR
Fernández-Salazar et al. 2015[33]	Spain	Abstract	Observational study, retrospective	2003–2014	NR	144	NR	NR
Fernández-Salazar et al. 2014[34]	Spain	Abstract	Multicentric and retrospective study	June 2003–September 2013	Four Spanish hospitals	88	37/51	35
Hatoum et al. 2014[35]	US	Abstract	Retrospective cohort study	2005–2012	US Clinformatics administrative health claims database	587	283/304	42.8
Hudis et al. 2009[36]	NR	Abstract	Retrospective study	NR	Tertiary referral center and an affiliated VA hospital	9	5/9	NR
Hussey et al. 2016[37]	Ireland	Full text	Retrospective cross-sectional study	2007	IBD databases from two Trinity College Dublin affiliated hospitals centers	52	18/34	45
Iborra et al. 2016[38]	Spain	Full text	Retrospective cohort study	1 year	The Spanish National Inflammatory Bowel Disease Study of Genetic and Environmental Factors database ENEIDA	263	Cohort 1 (TNF naive): 29/87 Cohort 2 (non TNF naive): 75/176	Cohort 1 (TNF naïve): 5/7 Cohort 2 (non-TNF naïve): 7/2
Lindsay et al. 2016[39]	Europe	Abstract	Retrospective, multicenter study	June 2009–June 2013	NR	538	253/285	42
Ladd et al. 2016[40]	Liechtenstein	Abstract	Retrospective study	June 2014–August 2015	Medical records	15	Cohort 1 (VDZ 300 mg q4w): 5/7	Cohort 1 (VDZ 300 mg q4w): 38

(*continued*)

Table 1. Continued.

Authors, year	Country	Full text or abstract	Study design	Study period	Methods of data collection	UC sample size (*n*)	Females/ males (*n*)	Age (mean or median y)
							Cohort 2 (VDZ 300 mg q6w): 7/2	Cohort 2 (VDZ 300 mg q6w): 36
Naymagon et al. 2013[41]	NR	Abstract	NR	1 January 2010–31 March 2013	Institutional database	58	NR	NR
Null et al. 2017[42]	USA	Full text	Retrospective study	1 January 2007–31 December 2014	Humana Research Database (Louisville, KY)	295	149/146	50.9
Oussalah et al. 2010[43]	NR	Abstract	Retrospective, multicenter study	January 2000–August 2009	NR	191	NR	NR
Patel et al. 2017[44]	USA	Full text	Retrospective study	1 January 2005–31 December 2013	US commercial claims database	1699	866/833	47.5
Rostholder et al. 2012[45]	USA	Full text	Retrospective study	2000–2009	EMR	56	26/30	41
Rubin et al. 2012[46]	USA	Abstract	Retrospective study	2006–2010	US commercial claims database	21,371	NR	40–46
Salomonsson et al. 2015[47]	Sweden	Abstract	Longitudinal, retrospective study	January 2010–April 2014	National Drug Registry and the National Patient Registry	587	NR	NR
Sandborn et al. 2015[48]	USA	Full text	Retrospective study	October 2012–April 2014	Patient chart reviews	804	Cohort 1 (ADA): 162/218 Cohort 2 (IFX): 183/241	Cohort 1 (ADA): 39 Cohort 2 (IFX): 39.3
Takada et al. 2016[49]	Japan	Abstract	NR	June 2010–July 2015	NR	72	34/38	NR
Taxonera et al. 2017[50]	Spain	Full text	Retrospective multicenter study	January 2013–September 2015	Data generated in routine clinical practice	142	70/72	46
Taxonera et al. 2014[51]	Spain	Full text	Prospective, observational study	July 2008–January 2010	Data from the bowel disease unit	38	22/16	41.9
Taxonera et al. 2015[52]	NR	Full text	Multicenter, retrospective study	October 2008–January 2012	14 IBD referral centers	79	38/41	46
Taxonera et al. 2017[53]	Spain	Full text	Retrospective multicenter study	October 2011–January 2014	15 inflammatory bowel diseases (IBD) referral centers	184	NR	NR
Weil et al. 2016[54]	Israel	Abstract	Retrospective cohort study	January 2010–December 2014	Maccabi Healthcare Services (MHS) database	204	110/94	36.1
Yamada et al. 2014[55]	Japan	Full text	Retrospective study	January 2003–June 2013	Kyoto University Hospital medical records	33	13/20	43.2
Yoshimura et al. 2016[56]	Japan	Abstract	Retrospective study	NR	NR	111	NR	NR

Abbreviations. NR, Not reported; *n*, Sample size; y, Years.

adalimumab (ADA), golimumab (GOL) and vedolizumab (VDZ) for different types of patient populations (all patients included at induction, induction responders only, primary or secondary non-responders).

The rate of escalation in all anti-TNF patients included at induction ranged from 5% in 380 patients at 6 months[48] to 50% in 54 patients at a median of 0.67 years[30], while escalation in anti-TNF induction responders ranged from 15.2% in 257 patients[26] to 70.8% in 24 patients at 8 weeks[55]. Patel et al. conducted a study in the USA on 1669 anti-TNF naïve UC patients and reported an increased rate of dose escalation over time, 16% at 6 months, 28% at 12 months, 40% at 24 months and 44% at 36 months[44].

The rate of dose escalation of IFX in all anti-TNF naive patients included at induction was reported in seven studies and ranged from 6% in 434 patients at 6 months[48] to 48.1% in 54 patients at a median of 4 months[23].

For induction responders of IFX, dose escalation was reported in seven studies and ranged from 15.2% in 257 patients[26] (time to dose escalation was not reported by Cappello et al.[26]) to 70.8% in 24 patients at 8 weeks[55]. For IFX patients in mucosal healing at maintenance and in response or remission at induction, dose escalation occurred in respectively 15% of 40 patients within the second year[21] and 36.8% of 144 at 9 months[33].

Dose escalation of IFX occurred at baseline in 157 patients with primary or secondary loss of response at a median of 6 months[31] and in 79 patients with a secondary loss of response at a median of 9.2 months[52].

Dose escalation of ADA was reported in 14 studies for either anti-TNF naïve and/or anti-TNF experienced patients.

Dose escalation of ADA in anti-TNF naïve patients included at induction was reported in four studies and ranged from 5% in 380 patients at 6 months[48] to 45.9% in 37 patients at a median of 5 months[23]. Whereas, dose escalation of induction responders of anti-TNF naïve patients under ADA was reported in three studies and occurred in 17.6% of 68 patients at a median of 6 months[53] and 46.6% in 58 patients at 2.75 years[35].

Dose escalation of ADA among anti-TNF experienced patients who responded to induction occurred in 55.2% of 116 patients at a median of 5 months[53].

Dose escalation of ADA in both anti-TNF naïve and anti-TNF experienced patients included at induction was reported in five studies and ranged from 25% in 52 patients at 12 months[37] to 50% in 54 patients at a median of 0.67 years[30]. ADA escalation of induction responders in both anti-TNF naïve and anti-TNF experienced occurred in 43.5% of 191 patients at a median of 4.57 months[24].

For induction responders of ADA who were either anti-TNF naïve or anti-TNF experienced, dose escalation occurred for 43.5% of 191 patients at a median time of 4.57 months.

Dose escalation under GOL for everyone included at induction occurred in 22% of 142 patients at a median of 5 months[50] and in 3.6% of 136 induction responders after 3 years[25].

Dose escalation under VDZ after failure (defined as inadequate response to the drug) of anti-TNF occurred in 20% of 15 patients (time to dose escalation was not reported by Ladd et al.[40]) in response or remission at maintenance[40] and in 47.1% of 121 induction responders at 1 year[18]. Dose escalation under VDZ increased over time in 121 induction responders as such: 9.9%, 29.8%, 43% and 47.1% at respectively 1.4 months, 3.2 months, 5 months and 1 year[18].

The dose escalation regimen was only reported in 14 studies out of which seven were appointed to a dose escalation under IFX, five to a dose escalation under ADA, one to a dose escalation under GOL and two to a dose escalation under VDZ.

IFX initial and escalated regimen was commonly reported as 5 mg/kg q8w and 10 mg/kg q8w or 5 mg/kg q4–6w respectively in seven studies[28,30,33,34,45,52,55]. The most frequent initial and escalated regimen for ADA was 40 mg or 80 mg q2w and 40 mg q1w respectively[16,20,29,36,37]. Only one study reported the initial and escalated regimen of GOL which was 50 or 100 mg q4wk and 100 or 200 mg q4wk respectively[50]. VDZ initial and escalated regimen in two studies was 300mq q8w and 300mq q4w respectively[18,40].

Detailed information concerning the rate of dose escalation, sample size and regimen for each study are shown in Table 2.

Response and remission after dose escalation

Results reporting clinical response and clinical remission after dose escalation found for ADA, GOL, IFX and VDZ are shown in Figures 2 and 3. In a study in which less than 30 anti-TNF naïve patients underwent IFX dose escalation, clinical response was achieved in 92.30% of 26 patients at week 6[28] and 86.70% of 15 patients at week 8[28]. In two studies in which more than 70 anti-TNF naïve patients underwent IFX dose escalation, clinical response was achieved in 55% of 157 patients at week 8[31], 68.40% of 79 patients at week 12[52] and 43% of 157 patients at week 24[31] (Figure 2).

In two studies in which less than 30 patients dose escalated, clinical remission was achieved in 34.6% of 26 patients at week 6[28] and 77% of 26 patients at week 52[28] after a shortened dose interval. After a doubled dose IFX, clinical remission was achieved in 66.70% of 15 patients at week 8[28] and in 19% of 27 patients[45] and 53% of 15 patients at week 52[28]. In two studies in which more than 70 patients dose escalated, clinical remission was achieved in 18% of 157 patients at week 8 after a doubled dose of IFX[31], in 51.90% of 79 patients at week 12[52], and in 24% of 157 patients at week 52 after a doubled dose of IFX[31] (Figure 3).

Taxonera et al.[53] is the only publication reporting the achieved clinical response and remission after dose escalation for ADA. Clinical response after ADA escalation at week 8 was achieved in 58.30% of 12 anti-TNF naïve patients compared to 40.6% of 64 anti-TNF experienced patients. Clinical remission at week 8 after ADA dose escalation was achieved by 26.30% of 12 anti-TNF patients compared to 16.66% of 64 the anti-TNF experienced patients.

Time to dose escalation

Mean/median time to dose escalation was reported in 13 out of 41 publications for IFX and ADA, and respectively ranged

Table 2. Dose escalation outcomes in daily practice.

Authors, year	Drug	Sample (*N*)	DE patients (% or Indexed at DE)	Population included in the proportion of DE	Initial regime	Escalated regime	Follow-up period (y)	Time to escalation (mo or y)
Afif et al. 2009[16]	ADA	20	35%	Everyone included at induction	40 mg q2w	40 mg q1w	tot time 0.46y	TDE 1.84 mo–3.68 mo
Amiot et al. 2016[18,57,a]	VDZ	121	9.9%	Induction responders	300 mg q8w	300 mg q4w	tot time 1 y	TOA 1.4 mo
Amiot et al. 2016[18]	VDZ	121	29.8%	Induction responders	300 mg q8w	300 mg q4w	tot time 1 y	TOA 3.2 mo
Amiot et al. 2016[18]	VDZ	121	43%	Induction responders	300 mg q8w	300 mg q4w	tot time 1 y	TOA 5 mo
Amiot et al. 2016[18]	VDZ	121	47.1%	Induction responders	300 mg q8w	300 mg q4w	tot time 1 y	TOA 6.9 mo
Amiot et al. 2016[18]	VDZ	121	47.1%	Induction responders	300 mg q8w	300 mg q4w	tot time 1 y	TOA 1 y
Armuzzi et al. 2013[20]	ADA	88	35.2%	Everyone included at induction	80 or 40 mg at wk2	80/40 mg q1w	Median 1.29 y	TOA Median 1.29 y
Armuzzi et al. 2013[21]	IFX	40	15%	Patients in mucosal healing at maintenance	NR	NR	NR	TOA within y2
Baert et al. 2014[22]	ADA	73	30.1%	Everyone included at induction	40 mg q1w	NR	Median 1.69 y	TDE Median 2.7 mo
Baki et al. 2015[23,b]	IFX	54	48.1%	Everyone included at induction	NR	NR	Median 2.25 y	TDE Median 4 mo
Baki et al. 2015[23]	ADA	37	45.9%	Everyone included at induction	NR	NR	Median 2.25 y	TDE Median 5 mo
Black et al. 2016[24]	ADA	191	43.5%	Induction responders	NR	NR	NR	TDE Median 4.57 mo
Bressler et al. 2016[25]	GOL	136	3.6%	Induction responders	100 mg q4w	NR	3 y	TOA 3 y
Cappello et al. 2013[26]	IFX	257	15.2%	Induction responders	5 mg/kg	NR	Median 2.17 y	NR
Cappello et al. 2014[27]	IFX	160	21.0%	Induction responders	5 mg/kg	NR	Median 2.33 y	NR
Cesarini et al. 2014[28]	IFX	15	Indexed at DE	Patients with 2nd LoR	5 mg/kg q8w	10 mg/kg q8w	tot time 1 y	NR
Cesarini et al. 2014[28]	IFX	26	Indexed at DE	Patients with 2nd LoR	5 mg/kg q8w	5 mg/kg q4–q6w	tot time 1 y	NR
Christensen et al. 2015[29]	ADA	33	21.2%	Everyone included at induction	160–80–40 mg, or 80–40 mg q1w	40 mg q1w–q10 d or 80 mg q1w	Median 0.62 y	TOA Median 0.62 y
Daperno et al. 2016[30]	ADA	54	50%	Everyone included at induction	5 mg/kg q8w	NR	Median 0.67 y	TOA Median 0.67 y
Dumitrescu et al. 2015[31]	IFX	157	Indexed at DE	Patients with a 1st or 2nd LoR	5 mg/kg q6-7w	10 mg/kg q6–7w	Median 1.8 y (1.0–3.1)	TDE Median 6 mo
Echarri et al. 2015[32]	IFX	21	71.4%	NR	NR	NR	NR	TOA 1 y
Fernández-Salazar et al. 2015[33]	IFX	144	36.8%	Patients in response or remission at induction	NR	5 mg/kg q6w or 10mg/kg q8w	Median 3.17 y	TDE Mean 9 mo
Fernández-Salazar et al. 2015[33]	IFX	144	25%	Patients in response or remission at induction	NR	5 mg/kg q6w	Median 3.17 y	TDE Mean 9.5 mo
Fernández-Salazar et al. 2015[33]	IFX	144	5%	Patients in response or remission at induction	NR	10 mg/kg q8w	Median 3.17 y	TDE Mean 9mo
Fernández-Salazar et al. 2015[33]	IFX	144	7%	Patients in response or remission at induction	NR	10 mg/kg q6w	Median 3.17 y	TDE Mean 6 mo
Fernández-Salazar et al. 2014[34]	IFX	88	39.8%	Everyone included at induction	5 mg/kg q8w	10 mg/kg q8w and/or 5 mg/kg q4w	tot time 3.5 y	TOA 2.08 y
Hatoum et al. 2014[35]	ADA	58	46.6%	Induction responders	NR	NR	Mean 2.75 y	TOA Mean 2.75 y
Hatoum et al. 2014[35]	IFX	280	51.4%	Induction responders	NR	NR	Mean 2.75 y	TOA Mean 2.75 y
Hudis et al. 2009[36]	ADA	7	42.9%	Everyone included at induction	NR	ADA 40mg q1w	NR	NR
Hussey et al. 2016[37]	ADA	52	25%	Everyone included at induction	40 mg q2w	NR	tot time 1 y	TOA 12 mo
Iborra et al. 2016[38]	ADA	263	35.4%	Everyone included at induction	NR	NR	tot time >1 y	TDE Mean 4.73 mo
Iborra et al. 2016[38]	ADA	87	24%	Everyone included at induction	NR	NR	tot time >1 y	TDE Mean 4.73 mo
Iborra et al. 2016[38]	ADA	176	41%	Everyone included at induction	NR	NR	tot time >1 y	TDE Mean 4.73 mo
Lindsay et al. 2016[39]	anti-TNF	538	26%	Everyone included at induction	NR	NR	tot time 2 y	TOA 2 y
Ladd et al. 2016[40]	VDZ	15	20%[c]	Patients in response or remission at maintenance	300 mg q8w	300 mg q4w	NR	NR
Naymagon et al. 2013[41]	IFX	58	13.8%	Everyone included at induction	NR	NR	tot time 3.25 y	TOA 0.46 mo
Oussalah et al. 2010[43]	IFX	191	45%	Induction responders	NR	NR	NR	NR
Patel et al. 2017[44,d]	anti-TNF	1699	1) 16%	Everyone included at induction	NR	NR	tot time 3 y	TOA 6 mo
Patel et al. 2017[44]	anti-TNF	1699	2) 28%	Everyone included at induction	NR	NR	tot time 3 y	TOA 12 mo
Patel et al. 2017[44]	anti-TNF	1699	3) 40%	Everyone included at induction	NR	NR	tot time 3 y	TOA 24 mo
Patel et al. 2017[44]	anti-TNF	1699	4) 44%	Everyone included at induction	NR	NR	tot time 3 y	TOA 36 mo
Rostholder et al. 2012[45]	IFX	50	54%	Induction responders	5 mg/kg q8w	10 mg/kg q8 w or 5 mg/kg q4–6 w	Mean 3.17 y	TDE Mean 0.92 y
Rubin et al. 2012[46]	IFX	128	11.2%	Everyone included at induction	NR	NR	tot time 1 y	TOA 12 mo
Salomonsson et al. 2015[47]	ADA	587	46.5%	Induction responders	NR	ADA 40qw	tot time 1 y	TDE Median 2.76 mo
Salomonsson et al. 2015[47]	ADA	587	32.5%	Everyone included at induction	NR	≥50 mg	tot time 1 y	NR
Sandborn et al. 2015[48,e]	ADA	380	5%	Everyone included at induction	NR	NR	tot time 1.5 y	TOA 6 mo
Sandborn et al. 2015[48]	ADA	380	8%	Everyone included at induction	NR	NR	tot time 1.5 y	TOA 12 mo
Sandborn et al. 2015[48]	ADA	380	13%	Everyone included at induction	NR	NR	tot time 1.5 y	TOA 18 mo
Sandborn et al. 2015[48]	IFX	424	6%	Everyone included at induction	NR	NR	tot time 1.5 y	TOA 6 mo
Sandborn et al. 2015[48]	IFX	424	11%	Everyone included at induction	NR	NR	tot time 1.5 y	TOA 12 mo
Sandborn et al. 2015[48]	IFX	424	11%	Everyone included at induction	NR	NR	tot time 1.5 y	TOA 18 mo
Taxonera et al. 2014[51]	IFX	38	42.1%	Induction responders	NR	NR	NR	TDE Median 6.6 mo
Taxonera et al. 2015[52]	IFX	79	Indexed at DE	Patients with 2nd LoR	NR	NR	Median 1.25 y	TDE Median 9.2 mo
Taxonera et al. 2015[52]	IFX	30	Indexed at DE	Patients with 2nd LoR	NR	10 mg/kg/q8w	Median 1.25 y	TDE Median 9.2 mo
Taxonera et al. 2015[52]	IFX	21	Indexed at DE	Patients with 2nd LoR	NR	5 mg/kg/q4w	Median 1.25 y	TDE Median 9.2 mo
Taxonera et al. 2015[52]	IFX	28	Indexed at DE	Patients with 2nd LoR	NR	5 mg/kg/q6w	Median 1.25 y	TDE Median 9.2 mo
Taxonera et al. 2017[53]	ADA	184	41%	Induction responders	NR	NR	Median 1.91 y	TDE Median 4 mo
Taxonera et al. 2017[53]	ADA	116	55.2%	Induction responders	ADA	NR	Median 1.91 y	TDE Median 5 mo

(*continued*)

Table 2. Continued.

Authors, year	Drug	Sample (*N*)	DE patients (% or Indexed at DE)	Population included in the proportion of DE	Initial regime	Escalated regime	Follow-up period (y)	Time to escalation (mo or y)
Taxonera et al. 2017[53]	ADA	68	17.2%	Induction responders	ADA	NR	Median 1.91 y	TDE Median 6 mo
Taxonera et al. 2017[50]	GOL	142	22%	Everyone included at induction	50/100 mg q4wk	100/200 mg q4wk	Median 1 y	TDE Median 5 mo
Weil et al. 2016[54]	anti-TNF	204	8%	Everyone included at induction	NR	NR	tot time 1 y	NR
Yamada et al. 2014[55]	IFX	24	70.8%	Induction responders	5 mg/kg q8w	10 mg/kg q8w or 5 mg/kg q4–6w	Median 3 y	TOA 8w

Abbreviations. Anti-TNF, Tumor necrosis factor antagonist; DE, Dose escalation; mo, Months; *n*, Sample size; LoR, Loss of response; NR, Not reported; qw, Every week; TDE, Time to dose escalation; TOA, Time of assessment; w, Week; y, Year; ADA, Adalimumab; GOL, Golimumab; IFX, Infliximab; VDZ, Vedolizumab; tot, Total time.
Studies by the same author mentioned more than once refer to different cohorts or subgroup analysis of patients who escalated at different times.
[a]Rates of dose escalation were obtained from the updated study by Amiot et al. published in 2017[57].
[b]Number of enrolled patients was 72: 35 patients received IFX, 17 underwent treatment with ADA, and 20 patients were on both medications consecutively (15 IFX first, 5 ADA first). Among patients receiving IFX therapy, information on dose escalation was missing for one patient.
[c]Five out of 15 patients who responded to VDZ 300 mg q8w at week 14 had lost response and dose escalated which would explain the low rate of dose escalation.
[d]The majority of patients were under anti-TNF with infliximab (68.4%), adalimumab (29.3%), golimumab (0.4%) and certolizumab (1.5%). The remaining non-anti-TNF agent used was natalizumab (0.4%).
[e]The probabilities of dose escalation for ADA and IFX patients over time were obtained from unadjusted time-to-event analyses of dose escalation; however, a significant number of patients over 1 year discontinued treatment or were lost to follow up.

from 4 months[23] to 11 months[45] and from 1.84 months[16] to 6 months[53] as shown in Table 2. Time to dose escalation for patients treated with GOL was reported by Taxonera et al.[50] as a median of 5 months.

Time to dose escalation for VDZ was not provided.

Time to loss of response after dose escalation

Taxonera et al.[52,53] are the only two publications that define the percentage of patients that lose response after dose escalation.

Median time to loss of response after dose escalation was assessed for IFX and ADA at 15 (IQR 8–26)[52] and 17 (IQR 9–43)[53] months, respectively. Taxonera et al. reported that among IFX and ADA dose escalators, 33% of IFX patients experienced loss of response at 1.25 years and 23.37% of ADA dose escalators experienced loss of response at 1.91 years.

Treatment de-escalation

Although de-escalation is not referred to as being effective in treating patients in order to achieve or maintain clinical response and remission, it was reported in eight out of 35 dose escalation studies.

Four studies reported the proportion of dose de-escalation under IFX treated patients[28,31,33,52], which ranged from 15% of 79 dose escalated patients at a median time to dose de-escalation of 6 months[52] to 51% of 41 dose escalated patients at a mean time to dose de-escalation of 13.6 months[28]. In the totality of cases, patients were de-escalated to a regimen of 5 mg/kg every 8 weeks.

Dose de-escalation under ADA was reported by four studies. In anti-TNF naïve patients only, median time to dose de-escalation was 162 days in 191 dose escalated patients[47]. In anti-TNF naïve and experienced patients combined, median time to dose de-escalation was between 21 days in 83 dose escalated patients[24] and 5 months in 31 dose escalated patients[20].

Adverse events after dose escalation

Adverse events after dose escalation are not extensively monitored and only five studies reported adverse events data following an anti-TNF dose escalation.

Iborra et al. reported adverse events in 6.5% of 93 patients who dose escalated under ADA[38], whilst four studies reported adverse events which ranged from 8% to 14.30% of respectively 157 and 53 patients who dose escalated under IFX[31,34,51,52].

Detailed information on the type of adverse event after dose escalation was only reported in one study by Dumitrescu et al.[31]. The highest rate of adverse event was attributed to acute or delayed infusion reactions which affected 6% of IFX dose escalated patients.

Predictors of dose escalation

Predictors of dose escalation are not well documented and were only reported in three papers out of 35 studies on

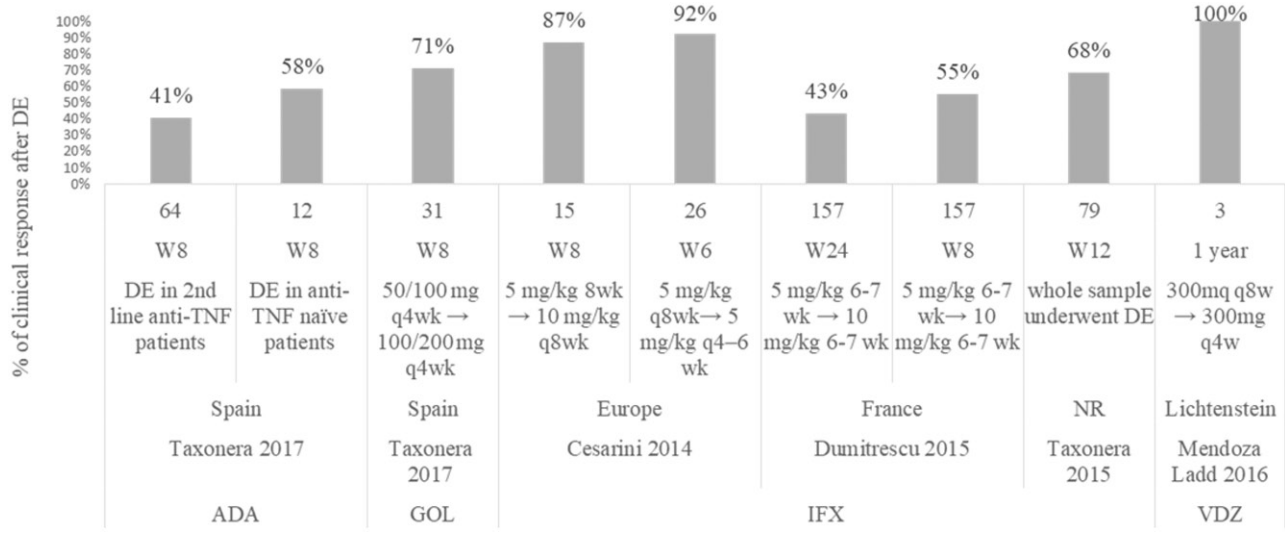

Figure 2. Percentage of patients with clinical response after dose escalation. Taxonera 2017 (ADA)[53], Taxonera 2017 (GOL)[50] , Cesarini 2014 (IFX)[28], Dumitrescu 2015 (IFX)[31], Taxonera 2015 (IFX)[52], Ladd 2016 (VDZ)[40].

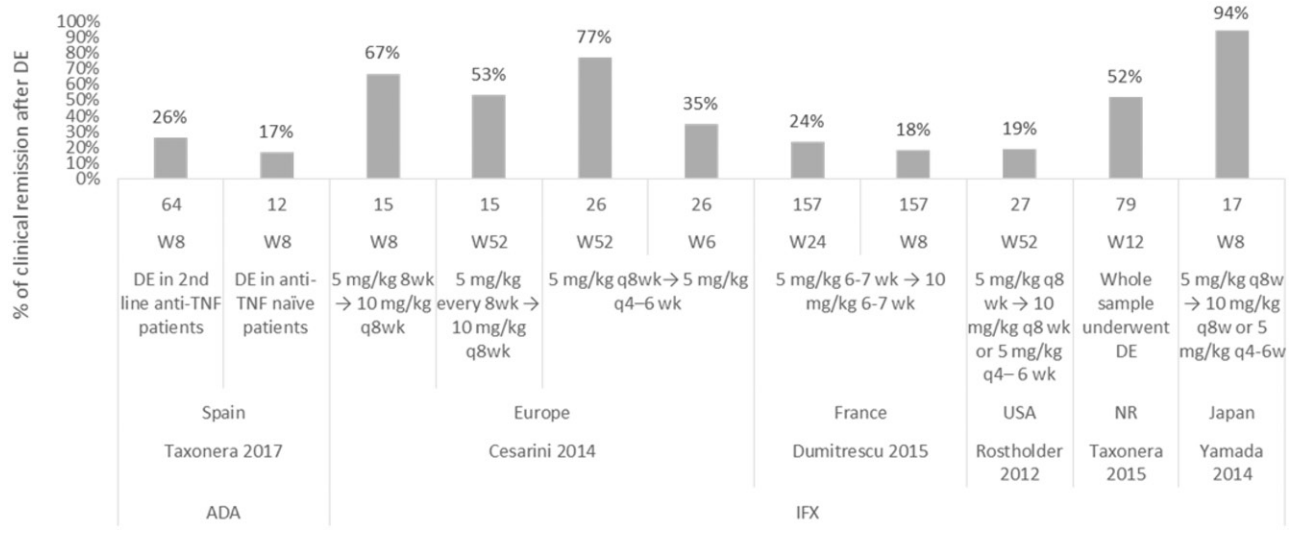

Figure 3. Percentage of patients in clinical remission after dose escalation. Taxonera 2017 (ADA)[53], Cesarini 2014 (IFX)[28], Dumitrescu 2015 (IFX)[31], Taxonera 2015 (IFX)[52], Rostholder 2012 (IFX)[45], Yamada 2014 (IFX)[55].

dose escalation (Fernández-Salazar et al.[33], Oussalah et al.[43], Taxonera et al.[51]).

Three factors were found to significantly predict and enhance the likeliness of a dose escalation: initiating IFX in acute severe colitis patients (HR = 2.75, $p = .01$)[43], having ulcerative colitis compared with Crohn's disease (HR = 2.73, $p = .007$)[51] and using immunomodulator therapy before a treatment with IFX (HR = 3.999, $p = .008$)[33].

None of the studies identified above reported disease duration and metabolic concentrations (i.e. iron binding capacity) as predictors of dose escalation.

Treatment switching

Treatment switching in daily clinical practice

Switching patterns ranged between 1% in 380 patients at 6 months[48] to 26% in 538 patients at 2 years[39] in six studies comprising more than 200 patients (Table 3).

The switching pattern IFX → ADA[17,19,23,29,49] was reported in five studies and ranged between 3.8% at a median time of 5.16 years to 25.5% at a mean of 3.3 years in respectively 26 and 98 patients (Table 3).

Another study by Baki et al.[23] with a median follow-up period of 2.5 years reported a switch from ADA → IFX in 6.94% of 72 UC patients, indicating its very low use in treatment of UC in contrast to the switching scheme reported above.

Six switching patterns in UC were tied to a switch from or to an anti-TNF in seven studies: 1 anti-TNF → ADA[56], 1 anti-TNF → IFX[56], 3 IFX → anti-TNF[35,42,48], 2 ADA → anti-TNF[35,48], 2 anti-TNF→ anti-TNF[39,44] and 1 anti-TNF→ anti-TNF or VDZ[54]. As these switching patterns were reported in studies comprising different sample sizes and time of assessments or switching, no sub-analysis could be performed.

Two studies by Patel et al.[44] and Sandborn et al.[48] reported the proportion of switching over time. In a sample size of 1699 patients, switching from an anti-TNF→ anti-TNF

Table 3. Treatment switching in daily clinical practice.

Authors, year	Sample (*N*)	Treatment sequence	Treatment switching (%)	Time at switch (y)
Alzafiri et al. 2011[17]	26	IFX → ADA	3.8%	Median 5.16 y
Angelison et al. 2014[19]	98	IFX → ADA	25.5%	Mean 3.3 y
Baki et al. 2015[23]	72	IFX → ADA	21%	Median 2.25 y
Baki et al. 2015[23]	21	ADA → IFX	7%	Median 2.25 y
Christensen et al. 2015[29]	33	IFX → ADA	100%	At baseline
Hatoum et al. 2014[35]	280	IFX → anti-TNF	15%	Mean 2.75 y
Hatoum et al. 2014[35]	58	ADA → anti-TNF	7%	Mean 2.75 y
Lindsay et al. 2016[39]	538	anti-TNF → anti-TNF	26%	2 y
Null et al. 2017[42]	245	IFX → anti-TNF	4.5%	1 y
Patel et al. 2017[44]	1699	anti-TNF → anti-TNF	2%	0.5 y
			6%	1 y
			10%	2 y
			11%	3 y
Sandborn et al. 2015[48]	424	IFX → anti-TNF	3.3%, 58.2%, 100%	0.5 y, 1 y, 1.5 y
Sandborn et al. 2015[48]	380	ADA → anti-TNF	3.6%	0.5 y
			63%	1 y
			100%	1.5 y
Takada et al. 2016[49]	72	IFX → ADA	8.3%	0.17 y
Weil et al. 2016[54]	204	anti-TNF → anti-TNF or VDZ	14%	1 y
Yoshimura et al. 2016[56]	35	anti-TNF → ADA	40%	1 y
Yoshimura et al. 2016[56]	76	anti-TNF → IFX	16%	1 y

Abbreviations. Anti-TNF, Tumor necrosis factor antagonist; *n*, Sample size; y, Year, ADA, Adlimumab; IFX, Infliximab; VDZ, Vedolizumab.

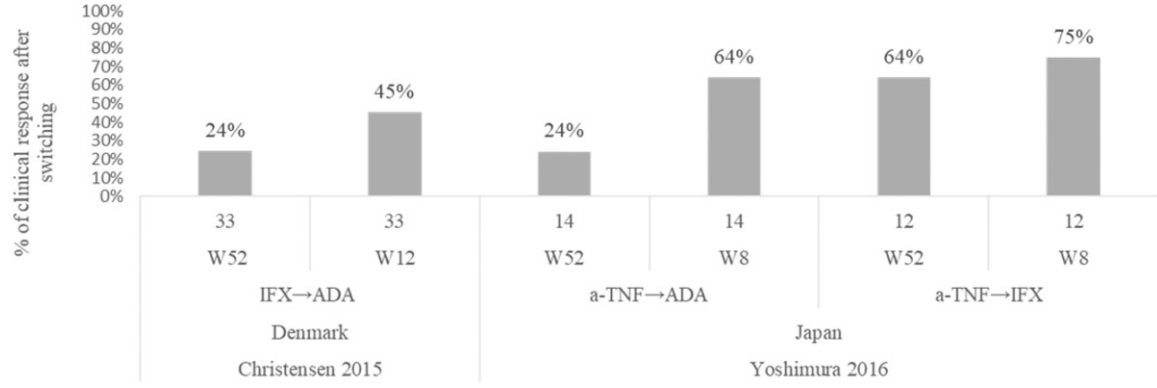

Figure 4. Percentage of patients with clinical response after switching Christensen 2015[29], Yoshimura 2016[56].

or VDZ occurred in 6% of UC patients at 6 months and 11% of UC patients at 36 months[44]. Switching from ADA → anti-TNF occurred in 1% of UC patients at 6 months, to 4% of patients at 12 months and 4% of patients at 18 months. Switching from IFX→anti-TNF occurred in 1.5% of patients at 6 months, to 2% patients at 12 months and 3% patients at 18 months[48].

Data on the time from loss of response after switching was not reported, as well as the time spent on therapy before switching.

The cause of switching was not reported or specified in the majority of the studies; however, three studies reported a switching due to loss of response[23,47,49], and two studies reported a switching due to adverse events with IFX[23,29] or ADA[23].

Response and remission after treatment switching

Clinical response and remission achieved after switching were reported in respectively one study by Christensen et al.[29] and two studies Christensen et al.[29] and Yoshimura et al.[56], indicating weak evidence on this topic.

Following a whole sample size switch of 33 patients from IFX → ADA in Christensen et al.[29] during a median of 0.62 years, the proportion of patients in clinical response remarkably decreased from 45% at 12 weeks to 24% after 1 year, showing a consecutive loss of response to ADA (Figure 4).

Yoshimura et al.[56] found that the long term response at week 52 after switching was significantly lower in the ADA sub-group with prior exposure to anti-TNF compared with the IFX group (24% vs. 64%) (Figure 4).

Rates of patients in clinical remission a year after switching were reported in two studies[29,56]. Yoshimura et al. reported that 85.7% of 44 patients who switched from anti-TNF to IFX and 37.5% (9/14) of 14 patients who switched from anti-TNF to ADA had maintained remission[56]. Christensen et al. reported that 18% of 33 patients who switched from IFX to ADA were in clinical remission[29].

Adverse events after treatment switching

Only one study by Christensen et al. with a median follow-up duration of 0.62 years reported the occurrence of adverse

events following switching. Two patients amongst 33 patients who switched from IFX → ADA experienced an allergic reaction to ADA after a year[29].

Discussion

The objective of this systematic literature review is to understand the evidence on dose escalation in a real-world setting and its impact on patients' outcomes. However, as the overall incidence of UC is reported as 1.2–20.3 cases per 100,000 persons per year, real-world evidence literature on dose escalation and treatment switching in ulcerative colitis is scarce, with a total number of articles amounting to respectively 34 and 12.

The average rate of dose escalation within 1 year across anti-TNF and anti-integrin therapy, irrespective of disease duration, sample size and follow-up study duration, is equivalent to 36%. This finding is consistent with a recent systematic literature review on dose escalation in Crohn's disease by Einarson et al.[15] which reported that approximately 30% of patients required dose escalation during the first year of treatment.

Similarly, time to dose escalation of IFX in UC patients was approximately 7.6 months, which is consistent with the time to dose escalation of IFX patients in Crohn's disease according to the findings of Einarson et al. There is very limited evidence on time to loss of response after dose escalation in UC patients, which was only reported by two studies[52,53] and indicates the failure (defined as complete loss of response, as judged by the treating physician) of ADA and IFX at 17 and 15 months respectively.

Solid comparison on the superiority of IFX, VDZ or ADA on clinical response and remission in a real-world setting is not possible, as the heterogeneity in sample size, patient population and time points at which clinical response and remission were reported differ and the number of publications that report these outcomes is low. The long-term outcome of dose escalation is not widely understood and needs to be further investigated.

Adverse events after dose escalation are poorly monitored, but anti-TNFs are not without risk, the rate of adverse events ranged between 6% and 14.3% in an average sample size comprising more than 50 patients. This is consistent with the literature as a recent multinational chart review reported that, in general terms, one in five UC patients experienced adverse events with their anti-TNF treatment[9].

Although anti-TNF failure has been identified as a predictor of dose escalation in patients treated with a second biologic, solid evidence on predictors of dose escalation in ulcerative colitis patients is lacking. Taxonera et al. have shown that anti-TNF failure in UC is a predictor of dose escalation and colectomy. Anti-TNF-naïve patients had significantly lower adjusted rates of ADA dose escalation and need for colectomy compared to anti-TNF failure patients (HR 0.26; $p < .004$)[53].

There are several potential limitations that arise from our review, therefore this review should be considered as a qualitative synthesis of the findings.

The variety of the patient selection across the 41 studies selected (e.g. induction responders versus secondary loss of response patients) as well as the lack of information on baseline characteristics stratified by population subgroup (only provided in four studies) and disease activity index (only reported in 12 studies) prevents the conducting of a robust and conclusive statistical analysis. Moreover, there is a lack of a harmonized definition on clinical remission in ulcerative colitis patients, with definitions varying across 10 studies. According to the ECCO, there is no fully validated definition of disease activity and clinical remission in ulcerative colitis, but a consensus on defining remission according to a stool frequency of $\leq$3/day with no bleeding and no mucosal lesions at endoscopy[58].

The variety of patient follow-up time, sample size and time of assessment makes it also difficult to compare and interpret the proportion of dose escalation and treatment switching across different therapies and lines of treatments as well as to make any correlations between the use of prior anti-TNF medication and the time to dose escalation or treatment switching.

Data reporting, particularly in abstracts, was often incomplete and therefore patient characteristics, time to escalation and treatment switching outcomes were very scarcely documented.

Dose escalation in ulcerative colitis patients is usually reflective of the clinical unmet need of available treatments; however, data are still insufficient to understand the outcomes of dose escalation. Our findings strongly suggest a lack of long term remission and response with current biologic therapies in ulcerative colitis and the need for new and more effective products for patients, as the occurrence of switching and dose escalation particularly may be considered indicators of suboptimal therapy[44].

Discrepancy in the findings and lack of data reported on biologics used before or after switching may reflect an absence of good standardized clinical practice regarding biologic switching.

Conclusion

A sample of around 29,000 ulcerative colitis patients across 41 publications have been included in the real-world data analysis on the proportion of and outcomes of dose escalation, as well as treatment switching, of biologics.

Studies indicate that a significant number of ulcerative colitis patients dose escalate and switch treatments, with the most recurring switching pattern being from IFX → ADA reflecting current clinical practice.

Additional studies are needed to understand the time to which patients dose escalate or switch treatments, as well as the clinical outcomes resulting from dose escalation and treatment switching. These outcomes could ideally be used as a proxy indicator to measure the effectiveness of dose escalation and treatment switching in each biologic if strong evidence existed on the matter.

A greater amount of research would also be required in order to understand the gradient for escalation rates

according to the different lines of treatment, as well as the occurrence of treatment switching, which would help in managing patients who lose response to biologic therapies.

Transparency

Declaration of funding

Janssen Pharmaceutical NV, Beerse, Belgium funded the study.

Author contributions: The specific contribution of each author to this review is as follows. P.A. and D.W. designed the study. N.C.G., E.R. and P.A. conducted the literature search, data extraction and data analysis. N.C.G. and E.R. wrote the manuscript. A.B., D.W. and P.A. participated in the data analysis and manuscript revisions. All authors critically revised the manuscript for important intellectual content and final manuscript edits.

Declaration of financial/other relationships

N.C.G., E.R. and P.A. have disclosed that they are employees of an independent company, Amaris Consulting Ltd, that received funding for the contribution to the study design and data analyses. D.W. and A.B. have disclosed that they are employees of Janssen. *CMRO* peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgements

The authors would like to express thanks to Dominik Naessens, Janssen Cilag NV, Beerse, Belgium, for critical review of the final manuscript.

ORCID

Nathalie C. Gemayel http://orcid.org/0000-0001-6252-6276
Daniel Wirth http://orcid.org/0000-0002-3302-3001
Andras Borsi http://orcid.org/0000-0003-4612-9830

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