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The comparative efficacy and safety of biologics and small molecules for treating patients with ulcerative colitis in Portugal: a systematic literature review and network meta-analysis

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Abstract. – OBJECTIVE: The use of biological drugs to treat ulcerative colitis (UC) represents a clear added value; nevertheless, many patients do not have a sustained response to these drugs. Small molecules were recently approved for the treatment of UC in Portugal. This network meta-analysis aimed to compare the efficacy and safety of the different therapies, including biological and small molecules, in patients prior exposed to biological treatment.

MATERIALS AND METHODS: A systematic review of the literature was performed on January 6, 2022, identifying all the relevant reports about the efficacy and safety of biologics (adalimumab, golimumab, infliximab, vedolizumab, ustekinumab) and small molecules (upadacitinib, filgotinib, tofacitinib) in the treatment of UC in Portugal. Network meta-analysis (NMA) was conducted using Bayesian Markov Chain Monte Carlo simulations. Results were presented in median Odds Ratio and Surface Under the Cumulative RAnking (SUCRA) score for each treatment.

RESULTS: Treatment of UC is divided into two phases: induction and maintenance. Upadacitinib 45 mg was the most efficacious therapy in achieving clinical remission and response and endoscopic improvement in the induction phase. Concerning the maintenance phase, upadacitinib 30 mg performed better than ustekinumab formulations in clinical remission and response, and endoscopic improvement. Regarding safety, there were no significant differences between all the drugs included in the analysis.

CONCLUSIONS: This network meta-analysis showed that upadacitinib reflects better efficacy compared to the available treatments for bio-exposed patients with moderate to severe UC. The safety profile is comparable to the other drugs.

Key Words:
Ulcerative colitis, Inflammatory bowel disease, Upadacitinib, Portugal.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) caused by inflammation in the inner lining of the large intestine which can lead to the development of ulcers[1]. Over time, many patients experience a worsening disease or an extent of the affected areas[2]. In Portugal, the average incidence of IBD between 2017 and 2019 was 20 new cases per 1,000 person-year[3]. During this period, patients aged between 20 and 39 years presented the highest incidence rates[3].

From a clinical point of view, periods of disease activity are the most important aspects that reduce the health-related quality of life (HRQoL), namely changes in bowel function, such as frequent diarrhea, rectal bleeding, and abdominal pain[4-6]. The goals of UC management have evolved, over time, from alleviating symptoms to mucosal healing and maintaining the quality of life[7]. Moderate to severe active UC can be medically managed with conventional therapy that includes 5-aminosalicylates, corticosteroids, immunosuppressants, and more recent drugs that include targeted small molecules and biologics[8,9]. The use of conventional therapy is out of the scope of this systematic review of the literature.

The medical management of UC is divided into two phases: induction to achieve remission, and maintenance to keep the patient in remission. In patients with inadequate response or intolerance to conventional therapy, biological therapy, and small molecules are used[9]. These are the drugs considered in this study: tumor necrosis factor inhibitors (TNFi), including infliximab, adalimumab, and golimumab, have been used for both induction and maintenance of remission[9,10];

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vedolizumab is an anti-integrin monoclonal antibody which is effective at inducing and maintaining remission with minimal side effects[9,11]; an anti-interleukin 12/23 (IL-12/23), ustekinumab, has been shown[9,12] to be effective in the induction and clinical/endoscopic remission with severe adverse effects similar to placebo. Recently approved treatments with small molecules include Janus kinase inhibitors (JAKi) such as tofacitinib and filgotinib[13-15]. Upadacitinib (UPA) is an oral JAKi that has demonstrated[16] efficacy in treating immune-mediated diseases such as UC. UPA's mechanism of action and favorable benefit-risk profile make it a potentially promising treatment in patients with moderate to severe active UC.

The main objective of this network meta-analysis (NMA) was to determine the comparative efficacy and safety of the different therapies either approved or in the process of being approved, in Portugal, as induction and maintenance therapies for adults with moderately to severely active UC, in patients with prior exposure to biologic therapy (bio-exposed). Since evidence available that allows the comparison of UC advanced treatments is scarce, this NMA supports the informed decision in choosing the most appropriate treatment for each patient, being the bio-exposed patients and the broader population of treated patients with inadequate response.

Materials and Methods

Systematic Literature Review

This systematic literature review (SLR) followed the Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA)[17]. A search was performed on January 6, 2022, to identify all relevant reports regarding the clinical efficacy and safety of UPA and other treatments for adult patients with moderate to severe active UC, in Portugal. The search was performed in English in two databases: the Medical Literature Analysis and Retrieval System Online [MEDLINE®] through Ovid MEDLINE® and Excerpta Medica Database [Embase®], in English and excluding animal studies.

Population, Intervention, Comparator, Outcomes, and Study design (PICOS) criteria are:

- Population: adults (≥16 years) with moderately to severely active UC [defined as a Full Mayo score (FMS) of 6 to 12 or an Adapted Mayo Score (AMS - i.e., FMS minus the Physician's Global Assessment – PGA – component) of 5 to 9, along with an Endoscopic Mayo Score (EMS) of 2 to 3] who have had an inadequate response, lost response, intolerance, or medical contraindication to either conventional therapy or a biologic agent. Exclusion criteria: Pediatric or adolescent (<16 years) populations.
- Interventions are described in **Appendix 1** [with placebo (PBO) used as a common comparator]. Exclusion criteria: conventional therapy only.
- Comparators: head-to-head comparisons (see **Appendix 1**) and/or placebo-controlled. Exclusion criteria: no comparator (i.e., single-arm RCTs).
- Outcomes: reported relevant efficacy [defined as a Full Mayo score (FMS) of 6 to 12 or an Adapted Mayo Score (AMS - i.e., FMS minus the PGA) of 5 to 9, along with an Endoscopic Mayo Score (EMS) of 2 to 3] and/or safety outcomes after 6 to 10 weeks of induction treatment OR after 40 to 54 weeks of maintenance treatment. Exclusion criteria: patient-reported outcomes; pharmacokinetics.
- Study design: phases 3+ randomized and double-blinded (only outcomes during randomized, double-blinded phases were assessed). Exclusion criteria: phase >3; non-randomized; open-label; observational.

Statistical Analysis

NMAs were conducted in a Generalized Linear Model (GLM) framework using Bayesian Markov Chain Monte Carlo (MCMC) simulations. All models were built using the Bayesian network meta-analysis (BNMA) package in the R statistical software (Auckland, New Zealand), designed to fit NMAs in a Bayesian framework using Just Another Gibbs Sampler (JAGS). Relative treatment effects were modeled as log odds for binary outcomes. From the log odds, median odds ratios (ORs) and their 95% Credible Interval (CrI) were derived. The statistical significance was considered as $p<0.05$. Then, given information on the absolute effects of a 'standard treatment' or Placebo (PBO) comparator, absolute treatment outcomes (i.e., probabilities of the binary outcome) were predicted. A Surface Under the Cumulative RAnking (SUCRA) score for each treatment was also computed, allowing to provide treatment ranking probabilities, i.e., from 0 (treatment is certain to be the worst) to 1 (treatment is certain to be the best). Finally, league

tables of the relative effect estimates (ORs) for all possible pairwise comparisons of the selected models were produced. Concerning efficacy, three outcomes were assessed in the NMA: clinical remission per FM Score, defined as FM score of ≤2 with no sub-score >1; clinical response per FM score, defined as a decrease from baseline in FM score ≥3 points and ≥30% accompanied by a decrease in Rectal Bleeding Sub-score (RBS) of ≥1 or an absolute RBS ≤1; endoscopic improvement (sometimes referred to as "mucosal healing" or "endoscopic response"), defined as Endoscopic Mayo sub-score (EMS) ≤1. The FM score consists of four items, each with a sub-score that ranges from 0 to 3 points: stool frequency sub-score (SFS), RBS, EMS, and physician's global assessment (PGA). Safety was analyzed in a combined sample of bio-exposed and bio-naïve populations (population not previously exposed to biologic therapy), and the following outcomes were included: all adverse events (AEs), discontinuation due to AEs, serious AEs (SAEs), and serious infections.

Finally, an intent-to-treat (ITT) analysis of efficacy outcomes was conducted to adjust maintenance outcomes by the likelihood of achieving clinical response at induction. This addresses a key limitation of previous maintenance NMAs based on induction responders only and does not capture the efficacy of treatments in the overall population.

Results

A total of 293 records were identified after the clinical SLR full-text review. After applying the NMA PICOS criteria, 22 original randomized controlled trials (RCTs), from 55 reports, were included in the NMA (Figure 1). An overview of these RCTs is presented in Table I.

Induction-Efficacy Outcomes: Clinical Remission

The evidence network available for clinical remission during the induction phase is shown in **Appendix 2**. Clinical remission NMA results during induction are described in Table II (sorted by descending SUCRA score). The corresponding league table for pairwise comparisons is shown in **Appendix 3**.

UPA45 was the most efficacious therapy in achieving clinical remission during induction, as demonstrated by a SUCRA score close to 97.3%, the highest compared to other interventions, followed by UST6, TOF10, FIL200, and VED300 (Table II). UPA45, UST6, TOF10, FIL200, and VED300 were all associated with greater odds of clinical remission than PBO during the induction phase, as shown by their statistically significant median ORs. Results from the pairwise comparisons in the league table show that UPA45 performed better than ADA160/80, FIL200, FIL100, and VED300 with regards to clinical remission during induction, as shown by statistically significant median ORs *vs.* these comparators (**Appendix 3**).

Induction-Efficacy Outcomes: Clinical Response

The evidence networks available for clinical response during the induction phase are shown in **Appendix 2**. Clinical response NMA results during induction are described in **Appendix 4**, and the corresponding league table for pairwise comparisons is shown in **Appendix 5**.

UPA45 ranked 1st with the greatest certainty of being the best intervention to clinical response (SUCRA score of 99.3%), with the nearest intervention being FIL200 with a SUCRA score of 79.1%. UPA45, FIL200, TOF10, UST6, and FIL100 all had greater efficacy than PBO regarding clinical response, as shown by their statistically significant median ORs (**Appendix 4**). Results from the pairwise comparisons in the league table show greater efficacy of UPA45 compared to all other interventions except one (FIL200) with a statistically significant median OR of clinical response (**Appendix 5**).

Induction-Efficacy Outcomes: Endoscopic Improvement

The evidence networks available for endoscopic improvement during the induction phase are shown in **Appendix 2**.

Endoscopic improvement NMA results during induction are described in **Appendix 4**, and the corresponding league table for pairwise comparisons is shown in **Appendix 6**. UPA45 ranked 1st with the greatest probability of achieving endoscopic improvement during induction in bio-exposed populations, as demonstrated by a SUCRA score of 99.3%, with the nearest intervention being TOF10 with a SUCRA score of 78.0% (**Appendix 4**). Results from the pairwise comparisons in the league table show greater efficacy in UPA45 compared to all other interventions except one (TOF10) with statistically significant me-

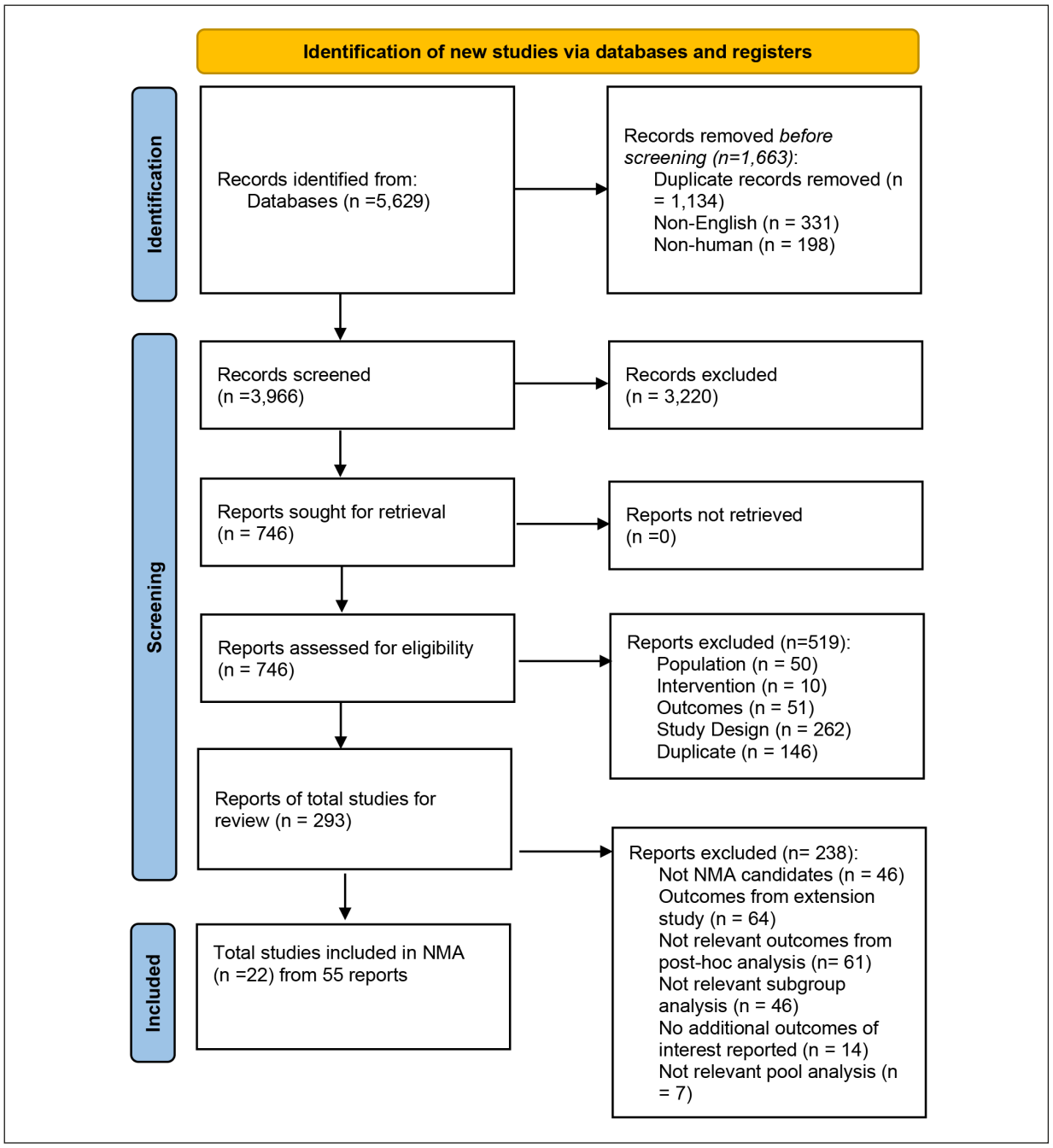

Figure 1. PRISMA flow diagram. Adapted from Page et al[18].

dian OR of endoscopic improvement *vs.* UST6, ADA160/80, both FIL formulations and VED300 (**Appendix 6**).

Induction-Safety Outcomes: All AEs

Safety outcomes were analyzed in an overall safety population, regardless of patients' prior exposure to biologics.

The evidence network available for all AEs during the induction phase is shown in **Appendix 2**.

All AEs NMA results during induction are described in **Appendix 4**, and the corresponding league table for pairwise comparisons is shown in **Appendix 7**. UPA45 ranked 10th with a SUCRA score of 24.4% in terms of being the safest

Table I. Overview of the 22 RCTs included in the NMA.

Study	Phase	UC severity	Bio-experienced	Asian study population	Induction Phase			Maintenance Phase						Primary (bold) and secondary publication(s)
					Duration (weeks)	Total N	Included regimen(s) (+PBO)	RCT design	Induction treatment	Induction status	Duration (weeks)	Total N	Included regimen(s) (+PBO)	
ACT-1 (NCT00036439)	3	FM6/12; EMS2	Naïve		8	364	INF10 INF5	TT	INF10 INF5 PBO	All	46	364	INF10 INF5	Rutgeerts et al [18]
ACT-2 (NCT00096655)	3	FM6/12; EMS2	Naïve		8	364	INF10 INF5	Excluded: Duration <40 weeks						
GEMINI 1 (NCT00783718)	3	FM6/12; EMS2	Mixed		6	374	VED300	RR	VED300	FM response	46	373	VED300Q8W VED300Q4W	Feagan et al [19]; Sandborn et at[20]; Feagan et al[21]
Japic CTI-060298	3	F M 6 / 1 2 ; EMS2	Naïve	X	8	208	INF5	Excluded: Duration <40 weeks						Kobayashi et al[22]
Jiang 2015	NR	FM6/12; EMS2	Naïve	X	8	123	INF5 (INF3.5 excluded)	Excluded: Duration <40 weeks						Jiang et al [23]
M10-447 (NCT00853099)	2/3	FM6/12; EMS2	Naïve	X	8	274	ADA160/80 (ADA80/40 excluded)	TT	ADA160/80 ADA80/40 PBO	All	44	274	A D A 4 0 Q 2 W (ADA160/80 and ADA80/40 combined)	Suzuki et al[24]
NCT01551290	3	FM6/12; EMS2	Naïve	X	8	99	INF5	Excluded: Duration <40 weeks						REMICADEUCO3001[25]
NCT02039505	3	F M 6 / 1 2 ; EMS2	Mixed	X	10	246	VED300	RR	VED300	FM response	50	83	VED300Q8W	Motoya et al [26]; Nagahori et al [27]
OCTAVE 1 (NCT01465763)	3	FM6/12; EMS2; RBS1	Mixed		8	598	TOF10	Maintenance in OCTAVE Sustain						Sandborn et al[28]; Lichtenstein et al[29]; Dubinsky et al[30]; Sandborn et al[31]; Sandborn et al [32]; D'Haens et al[33]; Hanauer et al [34]; Chiorean et al [35]; Danese et al[36]; Sands et al[37]; Vavricka et al[38]; Reinisch et al[39]; Feagan et al [40]; Gary et al[41]; Hudesman et al[42]
OCTAVE 2 (NCT01458951)	3	FM6/12; EMS2; RBS1	Mixed		8	541	TOF10	Maintenance in OCTAVE Sustain						
OCTAVE Sustain (NCT01458574)	3	FM6/12; EMS2; RBS1	Mixed		Induction in OCTAVE 1 and OCTAVE 2			RR	TOF10 TOF15 PBO	FM response	52	593	TOF10 TOF5	
PURSUIT-J (NCT01863771)	3	FM6/12; EMS	Naïve	X	Excluded: Open-label			RR	GOL200/100	FM response	54	63	GOL100	Hibi et al[43]
PURSUIT-M (NCT00488631)	3	FM6/12; EMS2	Naïve		Induction in PURSUIT-SC			RR	GOL400/200 GOL200/100	FM response	54	464	GOL100 GOL50	Sandborn et al[44]

Table continued

Table I *(Continued)*. Overview of the 22 RCTs included in the NMA.

Study	Phase	UC severity	Bio-experienced	Asian study population	Induction Phase			Maintenance Phase						Primary (bold) and secondary publication(s)
					Duration (weeks)	Total N	Included regimen(s) (+PBO)	RCT design	Induction treatment	Induction status	Duration (weeks)	Total N	Included regimen(s) (+PBO)	
SELECTION (NCT02914522)	2b/3	FM6/12; EMS2; RBS1; SFS1; PGA2	Mixed		10	1348	FIL200 FIL100	RR	FIL200 FIL100	FM response/ AM2 remission	47	571	FIL200 FIL100	Feagan et al[46]; Loftus et al [47]; Peyrin-Biroulet et al[48]; Schreiber et al[49]; Vermeire et al [50]; Feagan et al1[51]; Peyrin-Biroulet et al[52]; Peyrin-Biroulet et al [53]
SERENE-UC (NCT02065622)	3	FM6/12; EMS2	Mixed		Excluded: Intervention ADA HIR			RR	ADA HIR ADA160/80	All (efficacy evaluated in FM responders)	44	371	ADA40Q2W ADA40QW (ADA TDM excluded; no PBO)	Panes et al[54]; Colombel et al[55]
U-ACCOM PLISH (Study M14-675; NCT03653026)	3	AFM5/9; EMS2	Mixed		8	522	UPA45	Induction in U-ACHIEVE Study 3						Vermeireet al[56]
U-ACHIEVE Study 2 & 3 (Study M14-234; NCT02819635)	3	AFM5/9; EMS2	Mixed		8	474	UPA45	RR	UPA45	AM response	52	451	UPA30 UPA15	Sandborn et al[16]
ULTRA-1 (NCT00385736)	3	FM6/12; EMS2	Naïve		8	390	ADA160/80 (ADA80/40 excluded)	No maintenance						Reinisch et al[57]
ULTRA-2 (NCT00408629)	3	FM6/12; EMS2	Mixed		8	518	ADA160/80	TT	ADA160/80 PBO	All	44	518	ADA40Q2W	Sandborn et al [58]; Ghosh et al[59]; Colombel et al[60]; Sandborn et al[61]; D'Haens et al[62]; Sandborn et al[63]; Panaccione et al[64]
UNIFI (NCT02407236)	3	FM6/12; EMS2	Mixed		8	961	UST6 (UST130 excluded)	RR	UST130 UST6	FM response	44	523	UST90Q12W UST90Q8W	Sands et al[65]; Van Assche et al[66]; Sands et al[67]; Alcala et al[68]; Danese et al[69]; Panaccione et al[70]
VISIBLE 1 (NCT02611830)	3	FM6/12; EMS2	Mixed		Excluded: Open-label			RR	VED300	FM response	46	216	VED300Q8W (VED108Q2W SC excluded)	Sandborn et al [71]

AMS=Adapted Mayo score; AM5/9=AMS 5 to 9; AM response=decrease in AMS ≥2 points and ≥30% from baseline, and a decrease in RBS ≥1 or an absolute RBS≤1; AM2 remission=SFS≤1 and ≥1-point decrease from baseline, RBS=0, and EMS≤1; EMS=endoscopic Mayo sub-score; EMS2=EMS≥2; FMS=Full Mayo score; FM6/12=FMS 6 to 12; FM response=decrease in FMS ≥3 points and ≥30% from baseline, and a decrease in RBS ≥1 or an absolute RBS ≤1; HIR=higher induction dosing regimen; N=number of patients randomized; NR=not reported; PBO=placebo; PGA=Physician's global assessment sub-score; PGA2=PGA≥2; RBS=Rectal bleeding sub-score; RBS1=RBS≥1; RCT=randomized clinical trial; RR=re-randomized responder; SFS=Stool frequency sub-score; SFS1=SFS≥1; TDM=therapeutic drug monitoring; TT=treat-through; UC=ulcerative colitis; X=applicable. Dose for interventions in NMA (as extensively described in Appendix 1): UPA45=upadacitinib 45 mg QD (once daily); UPA15=upadacitinib 15 mg QD (once daily); UPA30=upadactinib 30 mg QD (once daily); FIL100=Filgotinib 100 mg QD (once daily); FIL200=Filgotinib 200 mg QD (once daily); TOF10=tofacitinib 10mg BID (twice daily); TOF5=tofacitinib 5 mg BID (twice daily); UST6=ustekinumab 6 mg/kg single dose; UST90Q12W=ustekinumab 90 mg every 12 weeks; UST90Q8W=ustekinumab every 8 weeks; VED300=vedolizumab 300 mg at weeks 0, 2, and 6; VED200Q8W=vedolizumab 300 mg every 8 weeks; VED300Q4W=vedolizumab 300 mg every 4 weeks; ADA160/80=adalimumab 160/80 mg; ADA40Q2W=adalimumab 40 mg every other week; ADA40QW=adalimumab 40 mg every week or 80 mg every other week; GOL200/100=golimumab 200/100 mg; GOL50=golimumab 50 mg every 4 weeks; GOL100=golimumab 100 mg every 4 weeks; INF5=infliximab 5 mg/kg; INF10=infliximab 10 mg/kg

Table II. Clinical remission NMA results – induction (RE model).

Intervention	Median OR *vs.* PBO median (95% CrI)	SUCRA	Predicted absolute outcome rate median (95% CrI)
UPA45	10.18 (5.32, 24.91)	97.30%	22.5% (11.7, 43.4)
UST6	6.05 (2.68, 17.05)	76.50%	14.7% (6.4, 34.2)
TOF10	5.41 (2.83, 12.74)	72.10%	13.3% (6.6, 28.1)
FIL200	3.35 (1.39, 7.65)	47.30%	8.6% (3.5, 19.3)
VED300	3.30 (1.33, 7.38)	45.50%	8.5% (3.3, 18.8)
ADA160/80	2.77 (0.85, 7.60)	37.90%	7.2% (2.2, 18.9)
FIL100	2.01 (0.79, 4.78)	21.80%	5.4% (2.0, 12.9)
PBO	Reference	1.80%	2.7% (1.8, 4.1)

CrI=credible interval; OR=odds ratio; PBO=placebo; SUCRA=Surface Under the Cumulative Ranking; UPA45=upadacitinib 45 mg QD (once daily); FIL 100=Filgotinib 100 mg QD (once daily); FIL 200=Filgotinib 200 mg QD (once daily); TOF10=tofacitinib 10 mg BID (twice daily); UST6=ustekinumab 6 mg/kg single dose; VED300=vedolizumab 300 mg at weeks 0, 2, and 6; ADA160/80=adalimumab 160/80 mg. Results in bold are statistically significant.

intervention with regards to all AEs, above INF5 (SUCRA=3.8%) (**Appendix 4**). The median OR of all AEs during induction of UPA45 *vs.* PBO was not statistically significant. In the pairwise comparisons reported in the league table, UPA45 was associated with a significant increase in the odds of all AEs *vs.* GOL200/100 (**Appendix 7**).

Induction-Safety Outcomes: Discontinuation Due to AEs

The evidence network available for discontinuation due to AEs during the induction phase is shown in **Appendix 2**.

NMA results of discontinuation due to AEs during the induction phase are described in **Appendix 4**, and the corresponding league table for pairwise comparisons is shown in **Appendix 8**. UPA45 was found to have the highest probability of being the safest intervention with regard to discontinuation due to AEs during induction (SUCRA=89.3%) with a significant OR *vs.* PBO (**Appendix 4**). Pairwise comparisons from the league table also showed that UPA45 was associated with a statistically significant decrease in the odds of discontinuation due to AEs compared to TOF10 and ADA160/80 (**Appendix 8**).

Induction-Safety Outcomes: SAEs

The evidence network available for SAEs during the induction phase is shown in **Appendix 2**.

SAEs NMA results during induction are described in Table III (sorted by descending SUCRA score), and the corresponding league table for pairwise comparisons is shown in

Table III. SAEs NMA results – induction (RE model).

Intervention	Median OR *vs.* PBO median (95% CrI)	SUCRA	Predicted absolute outcome rate median (95% CrI)
GOL200/100	0.42 (0.16, 1.08)	77.50%	2.9% (1.1, 7.1)
UST6	0.47 (0.19, 1.15)	72.00%	3.2% (1.3, 7.6)
UPA45	0.55 (0.25, 1.17)	63.80%	3.7% (1.7, 7.7)
ADA160/80	0.60 (0.33, 1.06)	58.90%	4.0% (2.2, 7.1)
VED300	0.61 (0.26, 1.42)	56.80%	4.1% (1.8, 9.2)
TOF10	0.63 (0.31, 1.33)	53.90%	4.3% (2.1, 8.7)
INF5	0.66 (0.23, 1.83)	51.40%	4.4% (1.5, 11.6)
FIL200	0.93 (0.40, 2.27)	28.80%	6.2% (2.7, 14.0)
FIL100	1.08 (0.47, 2.59)	18.60%	7.1% (3.2, 15.6)
PBO	Reference	18.00%	6.6% (5.7, 7.6)

CrI: credible interval; OR: odds ratio; PBO: placebo; SUCRA: Surface Under the Cumulative Ranking; UPA45=upadacitinib 45 mg QD (once daily); FIL100=Filgotinib 100 mg QD (once daily); FIL200=Filgotinib 200 mg QD (once daily); TOF10=tofacitinib 10 mg BID; UST6=ustekinumab 6 mg/kg single dose; VED300=vedolizumab 300 mg at weeks 0, 2, and 6; ADA160/80=adalimumab 160/80 mg; GOL200/100=golimumab 200/100 mg; INF5=infliximab 5 mg/kg. No statistically significant differences were observed.

Appendix 9. UPA45 was found to have the 3rd highest probability of being the safest intervention for SAEs (SUCRA=63.8%), with GOL200/100 and UST6 having a greater rank (Table III). However, no median OR *vs.* PBO showed any statistically significant difference in the odds of SAEs. Similarly, no statistically significant difference in the odds of SAEs was observed between interventions in pairwise comparisons (**Appendix 9**).

Induction-Safety Outcomes: Serious Infections

The evidence network available for serious infections during the induction phase is shown in **Appendix 2**.

NMA results regarding serious infections during induction are described in **Appendix 4** and the corresponding league table for pairwise comparisons is shown in **Appendix 10**. UPA45 ranked 7th with regards to being the safest intervention in terms of serious infections (SUCRA=32.7%), followed by ADA160/80 and FIL100 (both with a SUCRA score of 31.3%) (**Appendix 4**). No median OR *vs.* PBO showed any statistically significant difference in the odds of serious infections. Similarly, no statistically significant difference in the odds of serious infections could be found between interventions in pairwise comparisons (**Appendix 10**).

Maintenance-Efficacy Outcomes: Clinical Remission

The evidence network available for clinical remission during the maintenance phase in bio-exposed populations is shown in **Appendix 11**.

Clinical remission NMA results during maintenance are described in Table IV (sorted by descending SUCRA score), and the corresponding league table for pairwise comparisons is shown in **Appendix 12**. UPA30 and UPA15 were in the highest positions concerning their probability of achieving clinical remission during maintenance, as demonstrated by SUCRA scores of 92.7% and 86.0%, respectively, followed by VED300 formulations (Table IV). Both UPA formulations, VED300 formulations, FIL formulations, and UST90Q8W showed a statistically significant improvement in clinical remission *vs.* PBO. Results from the pairwise comparisons in the league table show that UPA15 and UPA30 were associated with a statistically significant improvement in the odds of clinical remission compared to both UST formulations (UST90Q8W and UST90Q12W) and TOF5 (**Appendix 12**).

Maintenance-Efficacy Outcomes: Clinical Response

The evidence networks available for clinical response during the maintenance phase in bio-exposed populations are shown in **Appendix 11**.

Table IV. Clinical remission NMA results – maintenance (RE model).

Intervention	Median OR *vs.* PBO median (95% CrI)	SUCRA	Predicted absolute outcome rate median (95% CrI)
UPA30	**19.03 (5.84, 77.58)**	92.70%	67.0% (37.3, 89.5)
UPA15	**15.08 (4.46, 61.54)**	86.00%	61.6% (31.4, 87.1)
VED300Q8W	**8.40 (3.02, 27.10)**	73.20%	47.2% (23.5, 75.0)
VED300Q4W	**8.23 (2.34, 33.97)**	71.50%	46.7% (19.2, 78.9)
TOF10	**4.69 (1.79, 12.97)**	54.30%	33.3% (15.3, 59.2)
FIL200	**4.40 (1.39, 16.46)**	51.40%	31.9% (12.4, 64.4)
FIL100	**3.79 (1.12, 14.56)**	45.10%	28.8% (10.3, 61.7)
UST90Q8W	**3.17 (1.29, 8.12)**	39.10%	25.3% (11.5, 47.7)
ADA40Q2W	2.69 (0.60, 15.59)	34.80%	22.2% (5.8, 62.9)
TOF5	2.56 (0.94, 7.36)	29.80%	21.5% (8.7, 45.1)
UST90Q12W	1.91 (0.74, 5.07)	19.70%	16.9% (7.0, 36.2)
PBO	Reference	2.30%	9.6% (7.2, 12.7)

CrI: credible interval; OR: odds ratio; PBO: placebo; SUCRA: Surface Under the Cumulative Ranking; UPA15=upadacitinib 15 mg QD (once daily); UPA30=upadactinib 30 mg QD (once daily); FIL100=Filgotinib 100 mg QD (once daily); FIL200=Filgotinib 200 mg QD (once daily); TOF10=tofacitinib 10 mg BID (twice daily); TOF5=tofacitinib 5 mg BID (twice daily); UST90Q12W=ustekinumab 90 mg every 12 weeks; UST90Q8W=ustekinumab every 8 weeks; VED200Q8W=vedolizumab 300 mg every 8 weeks; VED300Q4W=vedolizumab 300 mg every 4 weeks; ADA40Q2W=adalimumab 40 mg every other week. Results in bold are statistically significant.

Clinical response NMA results for the bio-exposed populations during maintenance are described in **Appendix 13** and the corresponding league table for pairwise comparisons is shown in **Appendix 14**.

UPA30 and UPA15 ranked 1st and 3rd, respectively, with regards to their probability of being the best interventions in achieving clinical response during maintenance in bio-exposed populations (SUCRA score of 92.7% and 75.7%, respectively), while TOF10 ranked 2nd (**Appendix 13**). Both UPA formulations, VED300 formulations, and TOF formulations, as well as FIL200 and UST90Q8W, showed a statistically significant increase in the odds of clinical response *vs.* PBO. Results from the pairwise comparisons in the league table also showed that UPA30 had a statistically significant increase in the odds of clinical response during maintenance *vs.* both UST90 formulations and FIL100 (**Appendix 14**).

Maintenance-Efficacy Outcomes: Endoscopic Improvement

The evidence networks available for endoscopic improvement during the maintenance phase in the bio-exposed population are shown in **Appendix 11**.

Endoscopic improvement NMA results for the bio-exposed populations during maintenance are described in **Appendix 13**, and the corresponding league table for pairwise comparisons is shown in **Appendix 15**. UPA30 and UPA15 ranked 1st and 3rd, respectively, concerning their probability of being the best interventions in achieving endoscopic improvement during maintenance in bio-exposed populations (SUCRA scores of 92.2% and 79.2%, respectively) (**Appendix 13**). VED300Q4W and VED300Q8W ranked 2nd and 4th, respectively. Both UPA formulations, VED300 formulations, TOF formulations, and UST90Q8W showed a statistically significant increase in the odds of endoscopic improvement *vs.* PBO. Results from the pairwise comparisons in the league table showed that UPA15 performed better than UST90Q12W with regards to the endoscopic improvement and that UPA30 performed better than either of the two UST90 formulations, better than either of the FIL formulations and better than TOF5, as reported by statistically significant median ORs **Appendix 15**.

Maintenance-Safety Outcomes: all AEs

The evidence network available for all AEs during the maintenance phase is shown in **Appendix 11**.

All AEs NMA results during maintenance are described in the **Appendix 13** and the corresponding league table for pairwise comparisons is shown in **Appendix 16**. UPA15 and UPA30 ranked about mid-table (8th and 9th, respectively) with regards to their probability of being the safest interventions in terms of all AEs during maintenance, with SUCRA scores of 51.2% and 47.1%, respectively (**Appendix 13**). There were preceded by UST90Q12W (90.1%), TOF5 (71.6%), VED300Q4W (68.2%), FIL100 (67.6%), UST90Q8W (66.0%) and VED300Q8W (55.8%) (the % reflects the probability of being the safest intervention). Apart from GOL100, which ranked last, none of the interventions were associated with a statistically significant increase in the odds of all AEs *vs.* PBO. Pairwise comparisons in the league tables also showed that GOL100 had a statistically significant increase in the odds of all AEs compared to UST90Q12W (**Appendix 16**).

Maintenance-Safety Outcomes: Discontinuation Due to AEs

The evidence network available for discontinuation due to AEs during the maintenance phase is shown in **Appendix 11**.

Discontinuation due to AEs NMA results during maintenance are described in **Appendix 13** and the corresponding league table for pairwise comparisons is shown in **Appendix 17**. UPA15 ranked 2nd in terms of its probability of being the safest intervention with regards to discontinuation due to AEs during maintenance (SUCRA=78.9%), only preceded by UST90Q8W (89.3%) which also showed a statistically significant decrease in the odds of discontinuation due to AEs *vs.* PBO. VED300Q8W (4th rank) was also associated with a statistically significant decrease in these odds *vs.* PBO. UPA30 ranked about mid-table (8th, 58.6%) (**Appendix 13**). Pairwise comparisons in the league table also showed that UPA15 was associated with a statistically significant decrease in the odds of discontinuation due to AEs *vs.* ADA40Q2W and FIL100. ADA40Q2W and FIL100 were also associated with greater odds of discontinuation due to AEs compared to both VED300 formulations and UST90Q8W (**Appendix 17**).

Maintenance-Safety Outcomes: SAEs

The evidence network available for SAEs during the maintenance phase in the bio-exposed population is shown in **Appendix 11**.

SAEs NMA results during maintenance are described in Table V (sorted by descending SUCRA score) and the corresponding league table for pairwise comparisons is shown in **Appendix 18**. Although UPA30 and UPA15 were found to have the highest probability of being the safest intervention with regards to SAEs during maintenance (SUCRA=84.9% and 79.1%, respectively, followed by VED300 formulations), none of the interventions showed any statistically significant difference *vs.* PBO in terms of SAEs. Pairwise comparisons in the league table showed that UPA30 was found safer than ADA40Q2W with a statistically significant decrease in the odds of SAEs (**Appendix 18**).

Maintenance-Safety Outcomes: Serious Infections

The evidence network available for serious infections during the maintenance phase is shown in **Appendix 11**.

Serious infections NMA results during maintenance are described in **Appendix 1** and the corresponding league table for pairwise comparisons is shown in **Appendix 19**. UPA30 and UPA15 ranked 5th and 8th, respectively, in their probability of being the safest interventions in terms of serious infections during maintenance (SUCRA scores of 64.6% and 54.2%) (**Appendix 13**). UPA30 was preceded by VED300Q4W (70.9%), ADA40Q2W (70.4%), TOF10 (69.6%), and INF5 (67.5%). None of the interventions showed any statistically significant difference *vs.* PBO. No statistically significant difference between interventions could be observed in the pairwise comparisons from the league table (**Appendix 19**).

As explained in the Materials & Methods Section, there is a key limitation on the interpretation of the maintenance NMA, namely that estimates produced are understood to be within the induction responder population. As such, this interpretation may not capture the overall efficacy of a treatment that can induce a large percentage of responders and thus move a relatively larger proportion of a given population into a maintenance dosing period. To address this limitation, results from the treat-through ITT calculations are displayed in **Appendix 20**. The results of ITT analysis were consistent with the induction phase results, showing that UPA is the most efficacious advanced therapy.

Table V. SAEs NMA results – maintenance (RE model).

Intervention	Median OR *vs.* PBO median (95% CrI)	SUCRA	Predicted absolute outcome rate median (95% CrI)
UPA30	0.41 (0.14, 1.18)	84.90%	3.8% (1.2, 11.1)
UPA15	0.48 (0.17, 1.36)	79.10%	4.5% (1.5, 12.6)
VED300Q4W	0.62 (0.23, 1.67)	68.90%	5.6% (1.9, 15.0)
VED300Q8W	0.75 (0.37, 1.60)	58.40%	6.8% (3.0, 14.9)
TOF5	0.76 (0.25, 2.21)	57.60%	6.8% (2.1, 18.9)
UST90Q12W	0.76 (0.27, 2.07)	57.60%	6.8% (2.3, 18.1)
INF5	0.79 (0.32, 1.94)	55.50%	7.1% (2.7, 17.1)
TOF10	0.83 (0.29, 2.42)	51.50%	7.5% (2.5, 20.4)
UST90Q8W	0.86 (0.32, 2.33)	49.80%	7.7% (2.7, 19.8)
GOL50	0.89 (0.31, 2.37)	48.60%	7.9% (2.6, 20.2)
INF10	0.91 (0.38, 2.21)	46.70%	8.1% (3.2, 19.1)
PBO	Reference	38.90%	8.8% (5.8, 13.2)
FIL100	1.22 (0.35, 4.43)	32.90%	10.6% (3.0, 31.6)
FIL200	1.23 (0.36, 4.30)	32.50%	10.6% (3.1, 31.1)
GOL100	1.39 (0.53, 3.20)	23.50%	11.8% (4.4, 25.8)
ADA40Q2W	1.75 (0.82, 3.91)	13.00%	14.5% (6.5, 29.8)

CrI: credible interval; OR: odds ratio; PBO: placebo; SUCRA: Surface Under the Cumulative Ranking; UPA15=15 mg QD (once daily); UPA30=upadactinib 30 mg QD (once daily); FIL100=Filgotinib 100 mg QD (once daily); FIL200=Filgotinib 200 mg QD (once daily); TOF10=tofacitinib 10 mg BID (twice daily); TOF5=tofacitinib 5 mg BID (twice daily); UST90Q12W=ustekinumab 90 mg every 12 weeks; UST90Q8W=ustekinumab every 8 weeks; VED200Q8W=vedolizumab 300 mg every 8 weeks; VED300Q4W=vedolizumab 300 mg every 4 weeks; ADA40Q2W=adalimumab 40 mg every other week; GOL50=golimumab 50 mg every 4 weeks; GOL100=golimumab 100 mg every 4 weeks; INF5=infliximab 5mg/kg; INF10=infliximab 10 mg/kg. No statistically significant differences were observed.

Discussion

The introduction of biological drugs as treatment options available for UC represents a clear added value in the treatment of patients, allowing a considerable improvement in the prognosis associated with ulcerative colitis. However, a high proportion of patients turn out to be refractory to therapy with these biological drugs, and it is estimated that up to half of the patients show an inadequate response to therapy or end up losing the response acquired over time[72,73]. Thus, there is a clear need for new treatments for moderate to severe ulcerative colitis, with alternative mechanisms of action to those currently available and with a non-invasive route of administration that promotes adherence to therapy. This alternative should, ideally, induce a quick and effective response and promote a lasting remission, accompanied by a tolerable and life-adjusted safety profile for patients.

Results from this NMA, which included drugs either approved or in the process of being approved, in Portugal, demonstrated that upadacitinib seemed to be the most effective for treating UC, in both induction and maintenance phases in patients with prior exposure to biologic therapy.

During the induction phase, UPA45 ranked first, in SUCRA analysis, in all the evaluated efficacy outcomes, clinical remission, clinical response, and endoscopic improvement, being superior to almost all the other interventions in the pairwise comparisons. Concerning safety during the induction phase, results showed that all the interventions were similar to placebo and show similarities between them in the pairwise comparisons. Nevertheless, SUCRA analysis showed that, in the different analyzed outcomes, all AEs, discontinuation due to AEs, SAEs, and serious infections, the interventions occupy different positions. GOL200/100 ranked first for all AEs, SAEs, and serious infections, whilst for discontinuation due to AEs, UPA45 ranked first.

In the maintenance phase, UPA30 ranked first, in SUCRA analysis, in the three efficacy outcomes. For safety, in the induction phase, different interventions occupied the first position in the rank (the highest probability of being the safest intervention): UST90Q12W for all AEs and discontinuation due to AEs; UPA30 for SAEs, and VED300Q4W for serious infections. However, all the interventions were similar to placebo, and the pairwise comparisons were also similar between them.

Filgotinib, tofacitinib, and upadacitinib are the three oral interventions for UC[14,16,46]. In the induction phase, they demonstrated similar efficacy and safety. However, UPA45 showed superiority, in the pairwise comparisons, to TOF10 in clinical response and to FIL100/200 in clinical remission and endoscopic improvement. Regarding safety, UPA45 showed superiority to TOF10 in the discontinuation due to AEs (reflecting less discontinuation due to AEs). In the maintenance phase, the efficacy of UPA30 was superior to FIL100 in clinical remission, to FIL200 in clinical response, and TOF5 and FIL100/200 in endoscopic response. Concerning safety, no differences were found between the three small molecules during the maintenance phase.

Maintenance NMA results should be interpreted with caution, given the noted limitations of incorporating a mix of treat-through and re-randomized responder study designs into the analyses, as well as potential concerns surrounding treatment carry-over effects in the maintenance networks' PBO arms. Nevertheless, the treat-through ITT analysis presented in **Appendix 20** demonstrated that the results obtained in the NMA for both the induction and maintenance phases were reliable, and the combination UPA45 x UPA30 (induction x maintenance) achieved the highest predicted absolute outcome rate in the three efficacy outcomes.

Results of this efficacy NMA are following a recently published NMA[74], where upadacitinib was the best-performing intervention for the induction of clinical remission. Although the present work only presented efficacy results from bio-exposed patients, the results in the bio-naïve population were similar (data not shown), which is also in accordance with the recently published NMA.

Limitations

One general limitation of the NMA is that assumptions underlying it, network connectivity, homogeneity, and transitivity or consistency, must be carefully considered, because if any of them is violated, the conclusions of the NMA may be jeopardized. Furthermore, similar to a traditional pairwise meta-analysis[75], conclusions from the NMA are susceptible to the methodological quality of included studies, as well as to reporting biases and choices of study eligibility criteria.

Conclusions

These results, which represent the best comparative evidence that it is possible to generate among the set of interventions, together with the distinct characteristics of upadacitinib in terms of mechanism of action and its route of administration, corroborate its relevance as a therapeutic alternative in this clinical setting. Upadacitinib reflects better efficacy than the available treatments in Portugal, for bio-exposed patients with moderate to severe UC. The safety profile of upadacitinib is similar to most of the interventions in this analysis. These results suggest that upadacitinib has a favorable benefit-risk profile compared to other advanced therapies for moderately to severely active UC. While NMAs are not substitutes for head-to-head comparisons in RCTs, they can be useful tools in healthcare decision-making when such RCT data are lacking.

Conflict of Interest
All authors are employees of Abbvie.

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