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Review

Targeting IL12/23 in ulcerative colitis: update on the role of ustekinumab

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***Abstract*:** As our comprehension of the pathogenic mechanisms of inflammatory bowel disease (IBD) increases, the therapeutic armamentarium for its treatment can expand, and novel target therapies join the treatment pipeline. Interleukin (IL)-12 and IL23 are two key cytokines responsible for promoting and perpetuating bowel inflammation in IBD. Ustekinumab is a monoclonal antibody directed against the shared p40 subunit of both cytokines, and it was recently approved for the treatment of ulcerative colitis (UC). In the pivotal phase III UNIFI trial, ustekinumab showed a superiority over placebo in both clinical and endoscopic outcomes; furthermore, it was characterized by a favorable safety profile, with a similar rate of adverse events as compared with placebo. Recent evidence from real-life experiences have started accumulating, generally confirming the effectiveness and safety figures emerged from the registration studies. However, most of these observational studies enrolled multirefractory patients; moreover, comparative data with other target therapies are lacking, leaving physicians without clear indications about the appropriate positioning of ustekinumab in the therapeutic pipeline for UC. This review examines the basis of targeting IL12-23 in UC therapy and summarizes the data from both clinical trials and real-life studies, to highlight the main evidence already available and the research gaps that need to be filled for the optimal usage of ustekinumab in UC.

Keywords: inflammatory bowel disease, biologics, randomized controlled trials, real-world studies

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Introduction

Ulcerative colitis (UC) is an idiopathic, chronic inflammatory bowel disease (IBD), starting in the rectum and involving up to the whole colon, characterized by a relapsing–remitting clinical course. According to the most accredited pathogenetic theories, a dysregulated immune response arises against the gut microbiome, in genetically predisposed hosts, to determine chronic intestinal inflammation.[1] Bloody diarrhea, tenesmus, and fatigue represent the most frequent symptoms, responsible for severe impairment of the quality of life and limitation of daily and working activities.[2] The main objective of medical therapies is inducing long-term symptomatic remission, but mucosal healing (MH), commonly defined as a Mayo endoscopic subscore $\leqslant 1$,[3] is also recognized as an essential target to pursue. Several observational studies have indeed shown that achieving MH is associated with lower rates of clinical relapse, hospitalization, cancer development, and, ultimately, colectomy.[4] Recently, histological remission has been identified as a favorable prognostic factor,[5] but the absence of a univocal definition limits its application in clinical practice as a therapeutic target;[6] however, regulatory agencies have recommended the inclusion of histology-based outcomes in future randomized controlled trials (RCTs) among secondary endpoints.

Over the years, the therapeutic armamentarium for UC has progressively expanded, along with an improved understanding of its pathogenesis and with the identification of key cytokines promoting

and perpetuating bowel inflammation.[7,8] Tumor necrosis factor (TNF)-α blockers are the first biological drugs developed for the treatment of IBD, and, 16 years after the ACT1&2 trials that led to the approval of infliximab,[9] they still represent a cornerstone of the therapy for patients with moderate-to-severely active UC. However, the burden of patients with primary and secondary nonresponse[10] or intolerance[11] to TNF-α antagonist has encouraged the development of new drugs targeting alternative inflammatory pathways. Currently, non-anti-TNF-α drugs already licensed for the treatment of moderate-to-severe UC include vedolizumab, belonging to the anti-integrin class, tofacitinib, from the superfamily of Janus kinase (JAK) inhibitors, and ustekinumab, a cytokine inhibitor; more recently, ozanimod (a selective sphingosine-1-phosphate receptor modulator) and filgotinib (a selective JAK1 inhibitor) have also received the final approval.

Interleukin (IL)-12 and IL23 have been identified as key cytokines in intestinal inflammation: specifically, IL12 promotes the differentiation of naïve T cells in Th1 effectors, whereas IL23 exerts its effect by perpetrating the pro-inflammatory functions of Th17 cells.[12,13] Ustekinumab is a monoclonal IgG1 kappa antibody directed against the shared p40 subunit of IL12 and IL23,[14] approved for the treatment of psoriasis, psoriatic arthritis, Crohn's disease (CD) and, more recently, UC – following the results of the Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Participants With Moderately to Severely Active Ulcerative Colitis (UNIFI).[15] However, the results of RCTs should always be interpreted with caution due to their low external validity: first, because patients enrolled in RCTs are not representative of the whole IBD population attending our clinics, but also due to the strict limitations on concomitant medications allowed (e.g. topical therapies are always forbidden) and optimization strategies.[16–18] Currently, few real-life data have been reported on the effectiveness of ustekinumab for UC treatment and, as it usually happens with new drugs, most of these studies included patients with prior exposure/failure to multiple biological drugs.[19–22]

The expansion of the therapeutic armamentarium, with the advent of drugs with different mechanisms of action (MoA), raises several issues about the proper positioning of each molecule, such as the following: (1) What MoA should be used first and what MoA should be chosen after treatment failure? (i.e. the right sequencing); (2) How to choose the best MoA for each specific patient? (i.e. identification of predictors of response); and (3) How to effectively combine different molecules (specifically balancing hopes for increased effectiveness and concerns regarding safety)? In this narrative Review, we discuss the therapeutic implication of targeting IL12/23 and the positioning of ustekinumab in therapeutic algorithms for UC.

The pathway of IL12 and 23

Our knowledge of immune-mediated inflammatory diseases (IMIDs) has been constantly increasing over the last decades, in parallel with a deeper understanding of the molecular mechanisms that lie behind their pathophysiology. In their recent paper, Schett *et al.* proposed a molecular approach for the classification of IMIDs, focused on the inflammatory pathways involved in their pathogenesis.[23] In this conceptualization, TNF-α serves as the common downstream effector of several IMIDs (including IBD itself), whereas IL23 represents a specific hub cytokine for IBD, psoriasis, and psoriatic arthritis. Indeed, data reporting a link between polymorphisms in the *IL23R* gene and susceptibility to IBD,[24,25] higher serum levels of IL23,[26] and increased transcription of mucosal IL23[27] in IBD patients collectively point at the importance of IL23 signaling in UC.

IL12 and IL23 – belonging to the IL12 family of cytokines, part of the IL6 superfamily – are heterodimeric cytokines that share a common subunit (p40) that interacts with either p19 (unique to IL23) or p35 (unique to IL12).[28] Their receptors transduce the signal via the JAK/STAT pathway – specifically, JAK2 and TYK2 are activated, then STAT4 is phosphorylated in response to IL12, while IL23 determines the phosphorylation of STAT3 and 4.[29,30] Figure 1 highlights the role of the IL12/23 pathway in UC and the mechanism of action of ustekinumab.

Macrophages and dendritic cells represent the main intestinal source of IL12 and IL23,[28] but little is known about the signals that promote their production.

T cells constitute the main targets of IL12 and IL23 signals. Specifically, IL12 acts on naïve T cells and promotes their differentiation in Th1 cells that produce TNF-α and IFNγ;[31] conversely,

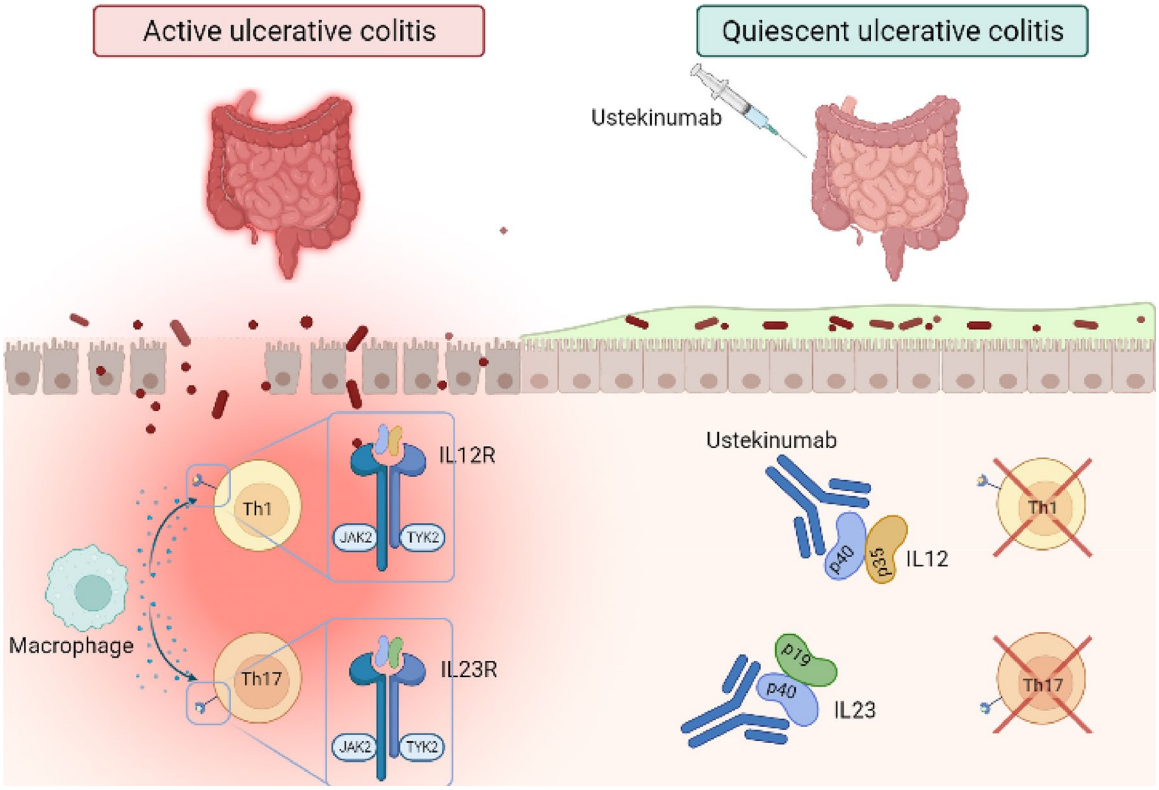

Figure 1. The IL12/23 pathway in ulcerative colitis. During active ulcerative colitis, tissue-resident macrophages represent the main source of intestinal IL12 and IL23. These two cytokines, respectively, induce the differentiation of Th1 cells and sustain the pro-inflammatory phenotype of Th17 cells, thereby promoting and perpetrating intestinal inflammation. Ustekinumab targets and blocks the p40 subunit (shared by IL12 and IL23), and can therefore dampen intestinal inflation, reduce UC symptoms, and induce clinical remission. IL, interleukin; JAK, Janus kinase, TYK.
Source: Created with BioRender.com.

IL23 binds to already differentiated Th17 cells [primed to express IL23R by IL1, IL6, and tumor growth factor (TGF) β[32]], to induce the production of IL17A, IL17 F, TNF-α, and IL22.[28,33] Th17 cells are characterized by significant functional plasticity – as they can act as either colitogenic or anti-inflammatory cells – and IL23 might be paramount in skewing them toward a pro-inflammatory phenotype.[34,35] Interestingly, while the IL23-dependent production of IL17 plays a detrimental role in several IMIDs, the pathogenic effect of IL23 appears to be decoupled from IL17 secretion in IBD. Controversies exist regarding the protective or pathogenic effect(s) of IL17A and IL17F in experimental colitis.[36] Evidence from clinical studies revealed that IL17 inhibition can worsen ongoing intestinal inflammation and even trigger IBD relapse:[37] indeed, it has been reported that IL17A promotes intestinal barrier integrity by upregulating epithelial tight junctions, and that its production is independent from IL23 in the intestinal mucosa,[38] thus challenging the paradigm of IL23-IL17 cascade in the context of intestinal inflammation. Studies also suggest that IL23 can dampen the production of IL10 from mucosal Treg cells, thereby impairing the barrier integrity and defensive functions of the intestine.[33] Innate lymphoid cells (ILCs) have been identified as another important target of IL12 and IL23. ILC1 responds to IL12 by producing TNF-α and IFNγ; conversely, RORγt+ ILC3 produces IL22, IL17A and granulocyte-macrophage colony-stimulating factor (GM-CSF) upon IL23 stimulation.

We previously mentioned that TNF-α and IL23 can be considered signature cytokines of IBD, and it has been observed that IL23 is an upstream regulator of TNF-α production in the inflammatory cascade.[33] Bloemendaal *et al.*[39] observed that TNF-α inhibition could dampen the production

of IL12 and IL23 from intestinal macrophages in IBD patients, with a negative feedback mechanism. Schmitt *et al.*[40] identified a specific subpopulation of T cells that, in response to IL23, express IL23R and demonstrate resistance to anti-TNF-α-mediated cell death. Therefore, it appears that, while TNF-α and IL23 can be a part of the same inflammatory pathway, IL23 can also mediate the development of pharmacodynamic escape from TNF-α blockade.

The exact contribution of IL12 in IBD pathogenesis is up to debate. Preclinical studies seemingly suggest that the main driver of intestinal inflammation is represented by IL23, as various animal studies report that the inhibition of p19, rather than p35, can effectively prevent or block experimental colitis;[41–43] nevertheless, it has been observed that IL12 is responsible for wasting disease and serum cytokine production in colitic mice, thus suggesting that this cytokine might be implicated in (some of) the systemic manifestations associated with intestinal inflammation.[44] Furthermore, a recent work revealed that IL12 stimulates a subpopulation of pathogenic IL8$^+$ T cells that co-express either IL17 or IFNγ and that are specific to UC.[45] The potential clinical implications of these observations are still to be clarified.

Methods

We searched for relevant publications using Medline/PubMed up to 31 December 2021. The following terms 'ulcerative colitis', 'ustekinumab' alone or matched with the Boolean operators 'AND' or 'OR' were used. Two authors (D.P. and G.P.) independently examined titles and abstracts to identify eligible studies. In addition, a hand-search of the bibliographic lists of selected manuscripts was performed to identify studies missing from the electronic search. Any disagreements were resolved through collegial discussion between all co-authors. The inclusion criteria were (1) confirmed diagnosis of UC, (2) treatment with ustekinumab, (3) full paper, and (4) study published in English.

Efficacy and safety of ustekinumab in RCTs: the UNIFI program

The efficacy of ustekinumab for the treatment of UC was tested in the phase III UNIFI program, consisting of a double-blind, randomized, placebo-controlled 8-week induction phase, followed by a 44-week-long maintenance study.[46] Eligible patients were adults with moderate-to-severely active UC [defined as Full Mayo Score (FMS) ranging from 6 to 12, with a minimum endoscopic subscore of 2] and a history of inadequate benefit/intolerance to conventional or biological drugs or both. At baseline, 961 patients were randomized into three induction arms: a single i.v. (intravenous) infusion of ustekinumab – at fixed (130 mg) or weight-based (6 mg/kg) doses – or placebo. Overall, about 48.0% of patients had previously failed biological therapies (13.4% both anti-TNF-α drugs and vedolizumab) and 51% of them were on concomitant steroids at enrollment. The primary endpoint was clinical remission at week 8 (FMS $\leqslant 2$, with no single subscore >1) that was met in 15.5%, 15.6%, and 5.3% of patients, respectively ($p<0.001$ for both comparisons with placebo), with no differences related to previous anti-TNF-α exposure.

Of note, histo-endoscopic MH (namely, the combination of histological and endoscopic improvement) was included among secondary endpoints, and it was achieved in a significantly higher proportion of patients receiving the active drug (18.4%, 20.3%, and 8.9% of patients treated with ustekinumab 130 mg or 6 mg/kg or placebo, respectively, $p<0.001$ for both comparisons against placebo). Moreover, a post hoc analysis showed that, among patients who responded to ustekinumab induction and were subsequently randomized to subcutaneous ustekinumab during maintenance, those with histo-endoscopic MH at week 8 were more likely to achieve clinical remission ($p=0.001$), corticosteroid-free clinical remission ($p=0.0038$), histological improvement ($p=0.0053$), endoscopic improvement ($p=0.0023$), and histo-endoscopic MH ($p=0.0006$) at week 44.[47]

Week 8 clinical responders were re-randomized into three different maintenance arms: subcutaneous 90 mg ustekinumab every 12 weeks (q12w), q8w, or placebo. Clinical remission was recorded in 38.4% of q12w, 43.8% of q8w, and 24% of placebo patients ($p<0.001$ and $p=0.002$ *versus* placebo, respectively). Moreover, a significantly higher percentage of patients maintained clinical response through week 44 (71.0%, 68.0% *versus* 44.6%, $p<0.001$ for both comparisons), achieved endoscopic improvement (51.1%, 43.6% *versus* 28.6%, $p<0.001$ and $p=0.002$, respectively),

steroid-free clinical remission (42.0%, 37.8% *versus* 23.4%, $p < 0.001$ and $p = 0.002$), and histo-endoscopic MH (45.9%, 38.8% and 24.1%, $p < 0.001$ and $p = 0.002$, respectively) at week 44.

After completing the maintenance phase, patients who received ustekinumab entered the long-term extension study until week 220, maintaining the same treatment regimens. At week 152, 54.1% and 56.3% of patients were in symptomatic remission in the ustekinumab q12w and q8w groups, respectively (p = ns).[48]

Pharmacokinetics analysis showed that serum ustekinumab concentrations (SUCs) were dose-proportional and unaffected by concomitant immunomodulators and prior exposure to biological therapies. The exposure-response analysis showed a positive relationship between SUCs and clinical response, clinical remission, endoscopic improvement, and normalization of inflammatory biomarkers at week 8, and with clinical remission, endoscopic improvement, and normalization of inflammatory biomarkers at week 44. A week 8 target concentration threshold ⩾ 3.7 mg/ml and a steady-state trough level ⩾1.3 mg/ml were identified by receiver operating characteristic (ROC) curves to best correlate with clinical response at week 8 and clinical remission at week 44, respectively. On the contrary, no significant correlations were found between SUCs and adverse events. Regarding immunogenicity, antibodies to ustekinumab were detected only in 39 patients (5.7%) who received ustekinumab during the entire follow-up, in particular: 28.2% were neutralizing and 43.6% transient. No significant correlations were observed between the presence of antibodies and efficacy outcomes, injection site reactions, or adverse events.[49]

Overall, the safety of ustekinumab in UC was consistent with the already known safety profile in all other approved indications, and rates of key safety events, including infections, were similar between ustekinumab and placebo.

Effectiveness and safety in real-world studies

The first real-life experiences date back to more than 5 years ago, when ustekinumab was prescribed to UC patients with concomitant dermatological or rheumatological conditions (i.e. psoriasis, especially paradoxical forms, and psoriatic arthritis).[50,51] However, in that setting, patients received subcutaneous ustekinumab at the dosages and intervals approved for those conditions – specifically, they did not receive i.v. induction and the standard maintenance dosage was 45 mg q12w. More recently, after the approval of ustekinumab for UC, some retrospective, observational studies, including unselected patients (most of whom ineligible in the UNIFI program), have explored its effectiveness and safety in the real-life setting.

Chaparro *et al.* reported the outcomes of 95 patients, from the ENEIDA registry, treated with ustekinumab for active UC (Partial Mayo Score, PMS > 2), of whom 80% had previously failed two anti-TNF-α agents and vedolizumab, and 30% two anti-TNF agents, vedolizumab and tofacitinib. At week 16 after the induction, 33 of 95 patients (34.7%) were in clinical remission, and 50 of 95 (52.6%) showed clinical response (including those ones in clinical remission). Clinical remission and steroid-free clinical remission were achieved in 38.6% (32/83) and 30.1% (25/83) at week 24, and in 33.3% (18/54) and 31.5% (17/54) of patients at week 52. The probability of maintaining ustekinumab therapy was 87% at week 16, 63% at week 56, and 59% at week 72. Overall, 34 patients (35.8%) discontinued ustekinumab after a median follow-up of 31 weeks [interquartile range (IQR) = 18–59]. The main reasons for discontinuation were primary nonresponse (22%) and loss of response (13%). Among 66 patients who started the maintenance phase with the standard doses (q12w or q8w), 18 patients (27.2%) required dose escalation: 10 patients (55.6%) due to primary failure (with benefit in only 1 of them), 3 (16.7%) due to partial response (none with benefit), and 5 (27.8%) for loss of response (benefit in 1 patient). These discouraging results after dose optimization (effectiveness only in 11% of patients) might potentially be attributed to the prevalence of primary nonresponders and to the clinical features of patients enrolled (i.e. multirefractory patient, with four out of five refractory to both anti-TNF-α, and almost one-third also to tofacitinib). Nine patients (9.5%) underwent colectomy after a median time of 14 weeks (IQR = 7.5–18). Looking at potential predictors of response, multivariate analysis showed that baseline C-reactive protein (CRP) over the upper normal value was associated with a significantly lower probability of clinical remission at week 16 [odds ratio [OR] = 0.3, 95% confidence interval [CI] = 0.1–0.7].[22]

Amiot *et al.* performed a retrospective analysis on 103 UC patients (70% previously exposed to ⩾2 anti-TNF-α agents and 85% to vedolizumab) treated with ustekinumab across 20 French centers affiliated with the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif (GETAID). Patients who received ustekinumab with an extraintestinal manifestation as the primary indication were excluded. Conversely, 10 patients who received a subcutaneous induction were included, because they had received a total dose of at least 270 mg within the first 8 weeks. Steroid-free clinical remission and clinical remission at weeks 12–16 were achieved in 35.0% (36/103) and 39.8% (41/103) of patients, respectively. According to patient-reported outcomes (PROs), 19.4% of patients had normal stool frequency (SF) with the absence of rectal bleeding (RB). Before the week 12–16 visits, 16 patients (15.5%) were optimized to the q4w regimen due to inadequate response, and 10 patients (9.7%) discontinued ustekinumab due to lack of efficacy. Overall, 49 patients had an endoscopic evaluation at both week 0 and weeks 12–16. The Mayo endoscopic subscore decreased from 2.7 ± 0.5 to 2.2 ± 1.0 ($p = 0.001$), with nine patients (18.4%) achieving MH. The UCEIS decreased from 5.0 ± 1.2 to 3.8 ± 1.9 ($p < 0.001$), and eight patients (16.3%) reached a Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score of 0 or 1. Multivariate analysis showed that a more severe disease (PMS > 6) and previous exposure to anti-TNF-α agents and vedolizumab were significantly associated with a lower likelihood of achieving steroid-free clinical remission at weeks 12–16 (OR = 0.10, 95% CI = 0.01–0.90, $p = 0.04$ and OR = 0.03, 95% CI = 0.01–0.42, $p = 0.01$, respectively). Serious adverse events occurred in four patients (3.9% of the cases), including three cases of UC exacerbation and one case of pneumonia requiring hospitalization. Among them, three patients (2.9%) patients discontinued ustekinumab.[19]

In a subsequent study, the authors reported the long-term data of the same cohort up to week 52. Overall, 45 patients (43.7%) discontinued ustekinumab, mainly due to lack of efficacy (91.0%). The cumulative probabilities of ustekinumab persistence after 3, 6, 9, and 12 months were 96.1%, 81.6%, 71.7%, and 58.4%, respectively. At week 52, steroid-free clinical remission and clinical remission were recorded in 32.0% (33/103) and 34.0% (35/103) of patients, respectively. Both SF and RB of 0 were reported by 24.3% patients. Sixty-five patients (63.1%) had an endoscopic reassessment performed between weeks 26 and 52. Mayo endoscopic subscore decreased from baseline 2.7 ± 0.5 to 2.0 ± 1.0 ($p > 0.005$) and UCEIS from 5.0 ± 1.1 to 3.6 ± 1.1 ($p < 0.001$). During the whole follow-up period, 65 patients (63.1%) required optimization to q4w, with clinical response and clinical remission obtained in 20 (30.7%) and 17 (26.1%) patients, respectively. Ten patients underwent colectomy after a median time of 6.7 months (IQR = 4.3–10.6). Sixteen adverse events occurred in 15 patients (14.8%), four of which severe: three UC exacerbation requiring hospitalization and one death for myocardial infarction 4 months after ustekinumab initiation.[52]

Dalal *et al.* explored potential predictors and outcomes of ustekinumab dose intensification in a cohort of 108 UC patients (91.7% previously exposed to anti-TNF-α and 57.4% on concomitant oral corticosteroids) from two American centers. Overall, 39.6% of patients (40/101) achieved steroid-free clinical remission 12–16 weeks after induction. Dose intensification to q4w or q6w was required by 42.6% of patients (46/108) after a median of 95 days (IQR = 65–208). The main reasons were no/minimal response to induction (22 patients, 47.8%) and loss of response (20 patients, 43.4%). After 12–16 weeks from intensification, 55.0% of patients achieved remission (22/40 with Simple Clinical Colitis Activity Index [SCCAI]/Mayo data) and 67.5% (27/40) achieved clinical response. Conversely 30.0% of patients (12/40) required colectomy or drug discontinuation within 16 weeks after dose intensification: notably, most of them (10/12) had no/minimal response after induction. Indeed, multivariate analysis showed that patients with no/minimal response to induction have a lower likelihood of achieving remission after dose intensification (OR = 0.2, 95% CI = 0.04–0.7, $p < 0.05$). Moreover, a shorter time-to-intensification was associated with a higher daily SF [hazard ratio (HR) = 1.1, 95% CI = 1.02–1.2, $p < 0.05$] and biologic exposure to > 2 biologics (HR = 2.5, 95% CI = 1.1–5.8, $p < 0.05$).[53]

Another study from the United States included 66 patients with moderate-to-severely active UC (92.4% with prior exposure to biologics or tofacitinib or both). All patients were treated with standard ustekinumab induction (weight-based single

i.v. infusion) and 90 mg subcutaneous injections q8w during maintenance, most of them through an 'off-label' prescription before ustekinumab approval. The median follow-up was 178 days (IQR = 57–482). Follow-up PMS was available for 47 patients at 3 months and for 20 patients at 12 months, when 42.6% (20/47) and 45.0% (9/20) of patients achieved clinical remission (primary outcome), respectively. Moreover, 31.9% (15/47) and 35.0% (7/20) of patients reached corticosteroid-free clinical remission at 3 and 12 months, respectively, while clinical response was achieved by 48.9% (23/47) of patients at 3 months and 55% (11/20) at 12 months. Overall, 12 patients (18.2%) underwent a follow-up colonoscopy at 12 months, showing endoscopic remission in 6 patients (50%), and histologic-endoscopic healing (defined as a combination of Mayo endoscopic subscore $\leq$1 plus histologic quiescence) in 4 patients (33.3%). At the last follow-up evaluation, 71.2% of patients (47/66) were still on ustekinumab therapy. During follow-up, 43.9% of patients (29/66) required dose escalation (90 mg q4w), regaining response in 38% of the cases. At multivariate analysis, a Mayo endoscopic subscore of 3 (OR = 0.04, 95% CI = 0.01–0.73, $p = 0.03$) and previous primary nonresponse to anti-TNF-α (OR = 0.03, 95% CI = 0.01–0.82, $p = 0.04$) were negative predictors of clinical remission at 3 months. No predictors of clinical remission at week 12 were identified. Adverse events occurred in eight patients (12.1), four of which were serious and required hospitalization: three UC relapse ultimately requiring colectomy and one vasculitis.[54]

Similar clinical characteristics of multiple refractoriness and access through an 'off-label' program characterized 68 patients enrolled in multicenter Italian study and treated with ustekinumab at standard doses. During follow-up, nine patients (13.2%) discontinued the treatment: one patient for primary failure, seven for loss of response, and one for adverse event (notably, the only one reported). Steroid-free clinical remission (defined as PMS $<$ 2 without steroids) at 24 and 52 weeks was recorded in 31.1% (19/61) and 50.0% (19/38) of patients, respectively. In addition, at same timepoints, 83.6% (51/61) and 81.6% (31/38) of patients achieved clinical response (i.e. a reduction of PMS of at least of 3 points from baseline). Among 38 patients with a follow-up endoscopy at week 52, 47.4% showed an endoscopic improvement.[55]

Again, 19 multidrug failure patients had been enrolled in a case series from Germany. Overall, four patients (21.1%) stopped ustekinumab due to refractory disease or one due to side effect (drowsiness). Two patients (10.5%) eventually required colectomy. At 1 year, 52.6% of patients (10/19) achieved clinical remission. The Mayo endoscopic score fell from a median of 2 points at the beginning to a median of 1 point at 1 year, and the median colitis activity index fell from 8.5 points (range 1–12) at baseline to 2 (range 0–5.5) points after 1 year.[20]

Initial data on the effectiveness of ustekinumab among 25 treatment-refractory (100% and 48% with history of anti-TNF-α and vedolizumab failure) pediatric patients have been recently reported from the Canadian Children Network. Overall, five patients (20.0%) stopped ustekinumab at the end of induction and four more (16.0%) during the maintenance phase; furthermore, six patients (24%) underwent colectomy. At week 52, 16 patients (64%) were still on ustekinumab treatment. Steroid-free clinical remission (defined as Pediatric Ulcerative Colitis Activity Index $<$10 and no steroids $\geq$ 4 weeks) was achieved by 11 patients (44.0%) and endoscopic improvement (Mayo endoscopic subscore $\leq$ 1) by 7 patients (28.0%) at week 52. Dose escalation to q4w or 6w was performed in 60.0% of patients (12 and 3 patients, respectively), but data on its effectiveness were not presented. No adverse events were reported.[21]

Dalal *et al.* compared the effectiveness of ustekinumab *versus* tofacitinib in a cohort of 81 UC patients (36 and 45 patients, respectively) with previous exposure to both anti-TNF-α and vedolizumab. To account for potential bias, the authors matched two groups through a propensity score method, including ustekinumab and tofacitinib as independent variables in a multivariable logistic regression model. No significant differences emerged in terms of steroid-free clinical remission after 12–16 weeks (40.0% ustekinumab *versus* 43.9% tofacitinib, $p = 0.82$) and response (48.6% ustekinumab *versus* 46.3% tofacitinib, $p = 1.00$), also after kernel-weighting. There was no significant difference in terms of colectomy-free drug survival ($p = 0.75$ by log-rank test) or rate of adverse events ($p = 0.57$ by log-rank test) between the two treatments.[56]

Finally, it is worth mentioning the case reports of three patients with steroid-refractory acute severe colitis treated with i.v. cyclosporine and successfully bridged to ustekinumab maintenance treatment – of note, they all received ustekinumab i.v. loading dose while on concomitant cyclosporine therapy.[57,58]

Table 1 summarizes the main outcomes of the real-life studies reported.

Ustekinumab for the treatment of pouch disorders

Chronic antibiotic-refractory pouchitis (CARP), occurring in about 15% of pouch patients,[59] represents an indication to biological therapy, mainly anti-TNF-α, whose short- and long-term (12 months) benefits are estimated to be around 50%.[60] Other MoA are usually recommended for refractory patients or for those who have specific contraindications to anti-TNF-α drugs.[61] Interesting data come from the University of Chicago on 24 CARP patients treated with ustekinumab (other pouch disorders were previously ruled out) at the dosage of 90 mg IV loading dose infusion followed by 90 mg subcutaneous injections q8w. Of note, CARP had been previously treated unsuccessfully with other biologics in 12 patients (50.0%) and with immunomodulators in 6 (25.0%). After a median follow-up of 12.9 months (IQR = 7.9–16), five patients (20.8%) stopped ustekinumab due to ineffectiveness. Follow-up endoscopies were available only for 13 patients (54.2%), after a median time of 7.4 months (IQR = 4.6–10.6) since ustekinumab start. The median Pouchitis Disease Activity Index (PDAI) decreased from baseline 5 (IQR = 4–6) to 4 (IQR = 2–5) follow-up ($p = 0.016$). Moreover, 50.0% of patients achieved clinical response according to physician's judgment and in terms of number of bowel movements per day.[62]

More recently, Dalal *et al.* reported the data on a cohort of 46 patients treated with ustekinumab with mixed pouch disorders, in particular: 6 CARP, 4 cuffitis, and 36 CD of the pouch (CDoP). Among them, 82.6% of patients had been previously treated, after colectomy, with anti-TNF-α drugs and 45.7% also with vedolizumab. According to physician judgment, 80.4% (37/46) of patients achieved clinical response after 8–16 weeks since ustekinumab start. Dose intensification to q6w or q4w was required in 23 patients (50.0%) after median of 223 days, and clinical response was obtained in 60.8% of them within the subsequent 8–16 weeks. Cox-regression analysis showed that lower age at both UC diagnosis (HR = 0.94, 95% CI = 0.90–0.99) and at ustekinumab start (HR = 0.96, 95% CI = 0.92–0.99) was associated with a shorter time to dose intensification. No significant adverse events were reported.[63]

Ustekinumab for special populations

As already stated, a substantial proportion of patients attending IBD clinics are not eligible for RCTs. However, some special populations – including elderly and frail patients, those with history of cancer, childbearing, or willing-to-be pregnant women – are increasingly represented in our daily clinical practice. Few data exist on the effectiveness and safety of ustekinumab in these settings among patients with IBD. With regard to elderly patients (⩾65 years), a small case–control study enrolling 117 CD patients (elderly $n = 39$, nonelderly $n = 78$) showed that elderly patients have a lower rate of clinical remission (28% *versus* 53%, $p = 0.03$) and clinical response based on physician global assessment (23% *versus* 46%, $p = 0.03$), but similar likelihood to achieve steroid-free clinical response, remission, MH and to develop adverse events ($p > 0.05$ for all comparisons) compared with nonelderly ones. Moreover, at multivariate analysis, age has been not associated with any clinical outcome.[64] Similar findings emerged from a Dutch study, showing that comorbidities, but not age, correlated with higher rate of hospitalization among patients treated with ustekinumab. Conversely, higher age at baseline was independently associated with an increased rate of combined biochemical and clinical remission (OR = 1.043, 95% CI = 1.003–1.085, $p = 0.036$).[65] The risk of cancer recurrence with a biological treatment is still a matter of debate. The choice of starting/resuming a biological therapy in a patient with a history of previous cancer is usually made on a case-by-case basis, balancing the estimated intrinsic risk of each neoplasia recurrence, the neoplasia-free survival interval, and the severity of IBD.[66] Recently, two retrospective studies explored the risk of cancer recurrence among IBD patients treated with biologics, including ustekinumab (14 of 390 patients treated with ustekinumab with a median follow-up time of 52 months in the study by Hong *et al.*[67]

Table 1. Summary of real-life studies on ustekinumab for the treatment of ulcerative colitis.

Study	Ustekinumab dosage	Patients followed	Primary outcome	Results
Chaparro *et al.*[22]	IV induction 6 mg/kg, maintenance 90 mg sc every 8 or 12 weeks	95	Durability of ustekinumab treatment	63% at week 56
Amiot *et al.*[19]	IV induction 6 mg/kg (or sc induction 270 mg), maintenance 90 mg sc every 8 or 12 weeks	103	Steroid-free clinical remission at weeks 12–16	35%
Fumery *et al.*[52]	IV induction 6 mg/kg (or sc induction 270 mg), maintenance 90 mg sc every 8 or 12 weeks	103	Steroid-free clinical remission at week 52	32%
Dalal *et al.*[53]	Dose escalation to 90 mg every 4 or every 6 weeks	46	Steroid-free clinical remission after dose intensification	55%
Hong *et al.*[54]	IV induction, maintenance 90 mg sc every 8 weeks	47	Clinical remission at 3 months	42.6%
		20	Clinical remission at 12 months	45.0%
Chiappetta *et al.*[55]	IV induction, maintenance 90 mg sc every 12 or 8 weeks	68	Steroid-free clinical remission at week 24	31%
		68	Steroid-free clinical remission at week 52	50%
Ochsenkühn *et al.*[20]	IV induction 6 mg/kg, maintenance 90 mg sc every 8 or 12 weeks	19	Clinical remission at 1 year	53%
Dhaliwal *et al.*[21]	IV induction, maintenance 90 mg sc every 8 weeks	25 children	Steroid-free clinical remission at 52 weeks	44%
Dalal *et al.*[56]	90 mg every 8 weeks after weight-based induction	36	Steroid-free clinical remission at 12 to 16 weeks – comparison with tofacitinib	40% – *versus* 43.9% with tofacitinib ($p = 0.82$)

IV, intravenous.

and 27 of 341 with a median of 5.2 person-years in the study by Hasan *et al.*[68]). In both studies, there was no increase of cancer recurrence associated with ustekinumab treatment (adjusted HR = 0.96; 95% CI = 0.17–5.41 and HR = 0.88; 95% CI = 0.25–3.03, respectively).

A favorable safety profile of ustekinumab for pregnant women has been initially observed among patients treated for psoriatic diseases.[69] Few data have been reported so far for women affected by IBD, who conventionally receive higher doses compared with the dermatological and rheumatological indications. Wils *et al.*[70] reported data of 73 pregnancies in 68 women (of whom 29 treated with ustekinumab), with no evidence of ustekinumab negatively affecting pregnancy outcomes. The placental transfer of ustekinumab seems to be similar to anti-TNF-α agents (positive correlation between cord blood and maternal trough levels at delivery). Conflicting data exist on the correlation between infant ustekinumab trough levels at delivery and time of the last administration during pregnancy.[71,72] However, it may be suggested, when possible, as for anti-TNF-α drugs, to interrupt drug administration in the last trimester.

Expert commentary on the 'optimal' use of ustekinumab in UC

Evidence from basic science supports the appropriateness of targeting IL12/23 for the management of UC patients, and data from both RCTs

and real-world studies with ustekinumab confirm the efficacy of this approach. However, the poor external validity of RCTs and the striking prevalence of multirefractory patients enrolled in these initial real-world experiences prevent from drawing firm conclusions on the positioning of ustekinumab in the UC treatment algorithm. Drug-specific validated markers to predict the response to therapy are impressively absent: a multiparametric predictive model incorporating genetic, clinical, immunological, microbiological, and pharmacokinetic markers seems the most promising tool, but its feasibility in clinical practice is still inadequate.[73] To date, the choice among different MoA – with the notable exception of pharmacokinetic failures to anti-TNF-α therapy[74] – is empirical and guided by physicians' personal experience and confidence, hospital facilities and setting, pharmacoeconomic considerations, and patient's preference. Ustekinumab could potentially exhibit several advantages over other competitors in UC (anti-TNF-α drugs, vedolizumab, and tofacitinib), including a favorable profile of safety, effectiveness on certain extraintestinal manifestations, and a convenient administration mode (q12w or q8w subcutaneous injection).

Head-to-head trials aim to help physicians and payers to establish the best positioning of each drug, but they suffer from the same limitations of pivotal trials, namely the strict inclusion/exclusion criteria, and the restrictions on the concomitant therapies and optimization strategies that are usually adopted in clinical practice. Real-life comparative studies with large cohorts (ideal number >1000 patients across multiple sites) and propensity score matching (to overcome selection bias and disparity in allocation among treatments arms) are paramount to confirm, in a real-world setting, the observations from randomized studies (i.e. external validation). Moreover, they can explore effectiveness for subgroups of patients (e.g. frail patients) or for specific disease subtype, investigate remarkable 'hard outcomes' (for instance, hospitalization and need for surgery) or optimal optimization strategies (dose escalation, add-on therapy, topical therapy) and long-term safety.

In the absence of head-to-head trials and real-life comparative studies, indirect evidence can be drawn from network meta-analysis. In their 2020 paper, Singh *et al.*[75] analyzed the data from RCTs enrolling adult UC patients treated with biologics or small molecules and reported that ustekinumab ranked below infliximab and vedolizumab for inducing clinical remission in biologic-naïve UC patients, while it is ranked highest (together with tofacitinib) in non-naïve patients. More recently, Burr *et al.*[76] performed a network meta-analysis including the RCTs of recently investigated drugs (upadacitinib, ozanimod, etrolizumab, and filgotinib), where upadacitinib 45 mg/day ranked first in terms of clinical response and clinical remission, and second after infliximab 10 mg/kg in terms of endoscopic improvement; of note, a significant discrepancy in ustekinumab ranking (in terms of both clinical remission and endoscopic improvement but, notably, not for clinical improvement) emerged between patients naïve and exposed to anti-TNF-α, in favor of the latter. In the 2021 network meta-analysis from Welty *et al.*,[77] ustekinumab ranked highest in terms of clinical response, clinical remission, and endoscopic MH at 1 year in naïve UC patients, when compared with TNF-α inhibitors, vedolizumab and tofacitinib; in the biologic-experienced population, data were less robust and clear, but they still pointed toward ustekinumab being superior or at least equal to other treatments. More recently, Lasa *et al.* performed a network meta-analysis including 29 studies on UC patients treated with biologics or small molecules: they reported upadacitinib ranking highest for the induction of clinical remission and endoscopic response, as well as for the maintenance of clinical remission and endoscopic improvement in maintenance studies with re-randomization of responders, while vedolizumab ranked highest for maintenance of clinical remission (together with subcutaneous infliximab) and endoscopic response in treat-through maintenance studies. However, when splitting naïve *versus* biologic-exposed patients, ustekinumab ranked highest for the induction of endoscopic response in the naïve population and for the induction of clinical remission and endoscopic improvement (together with tofacitinib) in biological-exposed patients – of note, upadacitinib was not included in this split analysis.[78]

Despite providing some indications, the intrinsic limitations of meta-analysis and surface under the cumulative ranking (SUCRA) deserve appropriate consideration: heterogeneity in study designs renders indirect comparison not completely reliable, and SUCRA rankings do not reflect the actual magnitude of differences in effects, thus caution is advised in the interpretation of such results. Nevertheless, they surely point out how the correct positioning can be crucial to improve

the outcomes of UC patients. Indeed, the observations on ustekinumab efficacy coming from the two network meta-analyses seemingly suggest that the optimal positioning of ustekinumab in the therapeutic algorithm of UC might be in biologic-exposed patients, while data on bionaïve ones are not homogeneous across different meta-analyses; however, it needs to be acknowledged that evidence coming from this type of analysis cannot be directly exported in clinical practice and needs to be confirmed and validated in prospective, controlled trials.

Timing for postinduction re-assessment and effectiveness dose escalation/reinduction represents two major topics to address, with respect to ustekinumab use in UC. As mentioned before, in the UNIFI program, week 8 nonresponders were assigned to receive subcutaneous 90 mg and then re-evaluated at week 16, before entering the maintenance phase (with subcutaneous ustekinumab q8w) or being discontinued due to treatment failure. Interestingly, a discernible drop in inflammatory biomarkers (namely, CRP and fecal calprotectin) is preliminary detectable as early as after 4 weeks in ustekinumab-treated patients, compared with the placebo arm (although statistical significance of such a drop was not assessed).[46] Most observational studies assess clinical response between weeks 12 and 24, and a recent work notably reported that more than 20% of CD patients achieve delayed response (at week 24) to ustekinumab.[79] Early observations from retrospective studies (mostly in CD patients[80,81]) suggest that empirical dose escalation beyond q8w (i.e. q6w and q4w) can be effective in the case of uncontrolled disease. Chaparro *et al.*[22] observed that, among UC patients not in remission at week 16, up to a third of them achieved remission in the long term; interestingly, dose escalation was effective in 2/5 patients with loss of response, as opposed to 1/13 of patients with primary nonresponse or partial response. Similarly, the abovementioned study from Dalal *et al.*[53] reported that, after a median time of 95 days, about 40% of their cohort required dose escalation, interestingly reporting that optimization was more likely to be effective in patients experiencing loss of response, compared with primary failures. Collectively, these studies suggest that dose optimization does not appear to significantly impact the outcomes of primary nonresponders. Finally, seminal studies support ustekinumab reinduction as an effective strategy in CD patients with loss of response, even in the case of previous dose escalation to q4w;[82,83] on this matter, no data have been presented for UC patients so far.

Within this frame of reference, it would seem appropriate to have a first, *ad interim* evaluation 8 weeks after induction, assessing clinical improvement and, possibly, CRP and fecal calprotectin decrease, to decide the appropriate maintenance regimen (i.e. q12w *versus* q8 e). In that regard, it will be paramount for future research to investigate whether early changes in biomarkers – especially fecal calprotectin – represent valid predictors of effectiveness, as suggested for other drugs in UC.[84] The STRIDE II consensus proposes normalization of fecal calprotectin and MH as intermediate and long-term targets, respectively; the panel suggests the time required to achieve such goals, with biologics other that ustekinumab, to be around 10–14 for the first and 14–18 weeks for the latter.[6] In accordance with these recommendations, and also bearing in mind the purported existence of 'late responder' subpopulation, the optimal time for an exhaustive, postinduction assessment appears to range between 12 and 24 weeks: clinical remission and normalization of inflammatory biomarkers represent the main parameters to look at, and endoscopic evaluation can also be appropriate at this stage. Dose escalation, with or without preceding reinduction, seemingly represent valid strategies, especially in patients experiencing loss of response; for primary nonresponders, swapping to a different MoA can also be considered.

With respect to safety, no major differences in risk of adverse events emerged among different treatments from network meta-analyses.[75,76,78] A pooled analysis of safety data from phase II and III RCTs of ustekinumab in UC and CD showed a safety profile similar to placebo;[85] furthermore, a recent, registry-based study reported a reduced risk of infections in IBD patients treated with ustekinumab, compared with anti-TNF-α agents.[86] Prospective comparative studies are currently lacking, and additional research is needed to further explore potential differences of safety among treatments. With specific regard to extraintestinal manifestations, it should be noted that ustekinumab is approved for the treatment of psoriasis[87] and psoriatic arthritis,[88] but it failed the phase III trial in axial spondylarthritis.[89] Furthermore, real-life observations support that it can be effectively and safely used in patients who

develop paradoxical psoriasis while receiving anti-TNF-α treatment,[51] as well as for the treatment of hidradenitis suppurativa.[90] Safety profile and efficacy on extraintestinal manifestations also advocate in favor of ustekinumab as a reasonable candidate for the combination of targeted therapies, for patients with medical-refractory IBD without other medical options as well as for those with concomitant IBD and extraintestinal manifestations.[91,92] Moreover, unlike with anti-TNF-α drugs, treatment with ustekinumab is associated with a more durable efficacy over time, mainly due to its low rate of immunogenicity.[93] This feature can explain the lack of advantages of combining ustekinumab with traditional immunomodulators, which is, in our opinion, currently not strictly recommended.

In summary, regarding the optimal use of ustekinumab in UC, (1) there is not enough evidence to support the use of ustekinumab as a standard choice for first-line treatment in place of less expensive drugs (i.e. anti-TNF-α biosimilars); (2) ustekinumab can be considered an appropriate choice for out-of-class swap after anti-TNF-α failure, especially when this is not accompanied by the formation of antidrug antibodies; (3) postinduction assessment should probably be obtained between 16 and 24 weeks, and should be based on clinical response, normalization of inflammatory biomarkers, and, potentially, endoscopic evaluation; (4) dose escalation to q6e or q4w and i.v. reinduction might be a valid options in case of loss of response/nonresponse, but high-quality evidence in that regard is lacking; (5) ustekinumab might present advantages, compared with some competitor drugs in UC, in terms of both safety and effectiveness on extraintestinal manifestations, which can be taken into consideration on a case-by-case basis.

Conclusion

In conclusion, the data from literature show that ustekinumab can be considered an effective and safe option for the management of UC. However, several issues remain unsolved in regard to its optimal use, and these should be crucially addressed by future research: (1) comparison with other MoA, (2) positioning in the therapeutic algorithm (in biologic-naïve *versus* -experienced patients), (3) identification of biomarkers to predict response, (4) effectiveness of combination with other MoA in dual targeted therapies, and (5) effectiveness in UC-related conditions not investigated in RCTs (such as the disorders of the pouch, isolated proctitis, and maintenance therapy following cyclosporine in acute severe UC).

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Author contributions

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