

Review

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Review

Ustekinumab in the Treatment of Inflammatory Bowel Diseases: Evolving Paradigms

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Abstract: Inflammatory bowel diseases, comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing and remitting immune-mediated inflammatory diseases affecting the gastrointestinal tract. Ustekinumab (UST) is a monoclonal antibody blocking the p40 subunit of the anti-interleukin (IL) 12/23. Pivotal trials (CERTIFI and UNITI-IM for CD, UNIFI for UC) established the efficacy of UST for the induction and maintenance of remission in both CD and UC, with the most favorable results in naïve patients to biologics. In recent years, a wealth of 'real-world' data has emerged supporting positive clinical, endoscopic, and histological outcomes in patients treated with UST, as well as reassuring safety data. More recently, the results of the first head-to-head trials of UST and tumor necrosis factor (TNF) antagonists have been reported. Moreover, a number of studies exploring the role of UST in specific clinical settings, such as perianal CD, postoperative complications and recurrence, extraintestinal manifestations, chronic antibiotic-refractory pouchitis, and pregnancy, have been reported. This review explores results reported to date on UST, including those from pivotal trials, real-world data, and emerging studies regarding therapeutic drug monitoring and immunogenicity. The safety profile of UST was also reviewed.

Keywords: Crohn's disease; inflammatory bowel diseases; mucosal healing; safety; remission; ulcerative colitis; ustekinumab

1. Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are the two most common forms of inflammatory bowel disease (IBD). The IBDs are commonly observed in the Western world and are caused by a complex interaction between genetic and environmental factors [1]. Given that both diseases have a relapsing and remitting course, an aggressive therapeutic approach is frequently required to prevent complications [2].

After discovering the critical pathogenetic role of tumor necrosis factor- α (TNF- α) in IBD, monoclonal anti-TNF- α antibodies have been developed and successfully adopted in clinical practice. However, a number of patients do not respond or experience a secondary loss of response or intolerance to anti-TNF- α treatment. Thus, novel therapeutic agents targeting alternative pathogenetic pathways have been investigated and approved for IBD treatment [3–6].

Ustekinumab (UST) is a monoclonal antibody blocking the p40 subunit of the anti-interleukin (IL) 12/23 [7], showing significant efficacy and safety in treating psoriatic arthritis [8]. Since IBD and chronic arthritis share similar pathogenetic mechanisms, researchers tried to use UST in managing IBD.

The IL-12 family is a cluster of cytokines, including IL-12, IL-23, IL-27 and IL-35. Although these molecules share structural features, they have different actions and properties. In particular, IL-23

and IL-12 are mainly pro-inflammatory cytokines produced in response to gut pathogens, which are essential for the differentiation of CD4⁺ T naïve cells [9]. 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 causes the phosphorylation of STAT3 and 4 [10]. IL-12 drives cell-mediated immunity by activating T-cell proliferation by Th1 cells [11,12]. This cytokine has a heterodimer structure composed of p40 and p35 protein subunits, and these, in turn, bind to a heterodimeric receptor complex consisting of IL-12 receptor (IL-12Rb1) and IL-12Rb2 chains expressed on the surface of T cells or natural killer (NK) cells [13]. IL-23 plays a major role in the expansion of committed Th17 cells [10,14]. This cytokine also is heterodimeric with p40 (common to both IL-12 and IL-23) and p19 protein subunits [15]. The specific intracellular signaling results in the expansion of committed Th17 cells [14]. As a consequence, the pharmacological blockade of the IL-12/23 axis interferes with the adaptive immune responses mediated by Th1 and Th17, which are highly relevant in the pathogenesis of CD [16], as well as UC [17].

More in detail, IL-12 induces the differentiation of a naïve cluster of CD4⁺ T cells into Th1 cells, producing interferon (IFN)- γ [9,13], whereas IL-23 specifically induces the differentiation of naïve CD4⁺ T cells into Th17 cells, with the activation of several proinflammatory cytokines, including IL-6, IL-17, and TNF- α [18]. Finally, IL-23 is capable of inducing a strong pro-inflammatory action through the activation of various target cells of the immune system, including CD8⁺ T cells, innate lymphoid cells, γ/δ T cells, and natural killers [19].

Genome-wide association studies (GWAS) have identified IL-12 and IL-23 as key cytokines in the pathogenesis of IBD [20], and therefore, therapies targeting the IL-12/IL-23 pathways have emerged and are in development.

Ustekinumab is a fully humanized IgG1k monoclonal antibody that binds to the p40 subunit of IL-12 and IL-23 and prevents their interaction with the IL-12 receptor, subsequently inhibiting IL-12 signaling and further activation of the Th1 cells subset. At the same time, it blocks the immune responses mediated by IL-23 and, in turn, the activation of the Th17 cells subset [7].

Pivotal trials (CERTIFI and UNITI-IM for CD, UNIFI for UC) established the efficacy of UST for the induction and maintenance of remission in both CD and UC, with the most favorable results in naïve patients to biologics [21–25]. In recent years, a wealth of ‘real-world’ data has emerged supporting positive clinical, endoscopic, and histological outcomes in patients treated with UST confirming its safety [26–59]. More recently, results of the first UST and an anti-TNF- α head-to-head trial have been reported [60]. Moreover, a number of studies exploring the role of UST in specific clinical settings, such as perianal CD [61–63], postoperative complications and recurrence [64–66], extraintestinal manifestations (EIMs) [67], chronic antibiotic-refractory pouchitis [68,69], and pregnancy appeared in the literature.

The aim of this review is to summarize the current literature regarding the mechanism of action of UST, data from registrational trials on safety and efficacy, including open-label extension (OLE), observational and emerging real-world (RW) evidence on its effectiveness in the treatment of IBD, and evolving paradigms with UST.

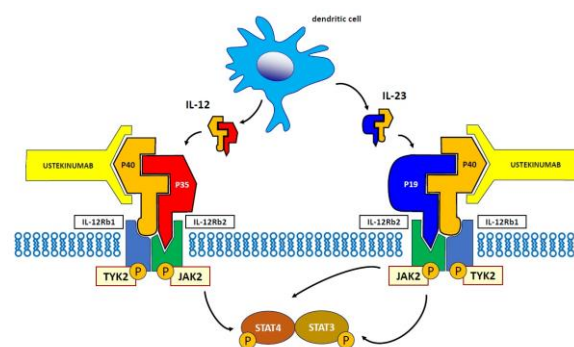


Figure 1. Mechanism of action of ustekinumab.

2. Materials and Methods

A thorough literature search was conducted using PubMed to identify all relevant articles published until November 2023. Original articles and reviews were identified using the following search terms: “inflammatory bowel disease,” “Crohn’s disease,” and “Ulcerative colitis” matched with each of the following keywords: “Ustekinumab,” “Real life,” “Real world.” Additional articles were identified by reviewing the reference lists of selected pertinent articles. As a second step, we analyze and critically evaluate our sources, particularly RW studies with a significant number of patients.

3. Results

3.1. UST in CD

3.1.1. Evidence from Randomized Controlled Trials (RCTs)

The efficacy of UST in CD was initially investigated in two phase-2 RCTs. The first one was published in 2008, and it was a double-blind, cross-over trial on the clinical effects of UST in 104 patients with moderate-to-severe CD [70]. More specifically, patients were assigned (1:1:1:1) to subcutaneous (s.c.) placebo at weeks 0–3, then UST s.c. 90 mg at weeks 8–11; UST s.c. 90 mg at weeks 0–3, followed by placebo at weeks 8–11; intravenous (i.v.) placebo at week 0, then i.v. UST 4.5 mg/kg at week 8; or i.v. UST 4.5 mg/kg at week 0, followed by placebo at week 8. The primary endpoint of clinical response at week 8 (70-point decrement and at least 25% reduction from the baseline in the CD activity index [CDAI] score) was achieved in 49% and 40% ($P = 0.34$) of those who received UST and placebo, respectively. In a subgroup of patients who were previously treated with infliximab (IFX) (neither primary nor secondary nonresponders), clinical response at week 8 was significantly greater with UST compared with placebo ($P < 0.05$). Higher baseline serum C-reactive protein (CRP) values predicted larger treatment effects with UST, especially in IFX-experienced patients, with a decrease in the CRP concentration paralleling clinic response observed with UST [71].

The second phase-2 RCT (CERTIFI) [21] assessed UST in 526 patients with moderate-severe CD resistant to anti-TNF treatment. Patients were assigned to receive i.v. UST at a dose of 1, 3, or 6 mg/kg, or placebo at week 0. The proportions of patients who reached the primary endpoint (clinical response at 6 weeks) were 36.6%, 34.1%, and 39.7% for 1, 3, and 6 mg of UST per kg, respectively, compared with 23.5% for placebo ($P = 0.005$ for the comparison with the 6 mg/kg group). One hundred forty-five patients who responded to UST at 6 weeks were randomly assigned to s.c. UST 90 mg or placebo at weeks 8 and 16. The UST achieved significantly increased rates of clinical remission (41.7% vs. 27.4%, $P = 0.03$) and a response (69.4% vs. 42.5%, $P < 0.001$) at 22 weeks compared with placebo.

The promising results obtained in the two phase-2 trials paved the way for a phase-3 trials program, which was called UNITI. More in detail, two 8-week phase-3 induction trials (UNITI-1 and 2) and one 44-week phase-3 maintenance trial (IM-UNITI) were conducted [21–23]. The UNITI-1 trial included patients who were nonresponders or with unacceptable side effects to anti-TNF- α . In contrast, patients in the UNITI-2 trial were either naïve to biologics or anti-TNF- α experienced without failing. In the IM-UNITI, less than half (44%) of the patients had prior treatment with anti-TNF- α [21–23]. In these trials, UST was administered at 130 mg or approximately 6 mg per kg e.v., while at 90 mg s.c. every 8 or 12 weeks in maintaining remission.

The results of these pivotal studies were significant: the rates of response at week 6 among patients receiving UST e.v. were significantly higher than those enrolled in the placebo group (in the UNITI-1, 34.3%, 33.7%, and 21.5%, respectively, $P \leq 0.003$ vs. placebo; in the UNITI-2, 51.7%, 55.5%, and 28.7%, $P < 0.001$ for both doses); the rate of remission at week 44 in the groups receiving UST every 8 weeks or every 12 weeks, 53.1% and 48.8%, respectively, were in remission at week 44, compared with 35.9% of those receiving placebo ($P = 0.005$ and $P = 0.04$, respectively).

Continued treatment with UST s.c. to maintain clinical response and remission through three years was investigated by another study (UNITI Long-Term Extension, UNITI-LTE). The IM-UNITI trial found that 38.0% of UST induction responders receiving the drug every 12 weeks and 43.0%

receiving the drug every eight weeks were in remission at week 152 [22]. Finally, 34.4% of patients in the every-8-weeks group and 28.7% in the every-12-weeks group were in clinical remission at week 252 [23].

The SEAVUE is the first clinical trial to directly and prospectively compare two approved biologic treatments for CD, UST and adalimumab (ADA), in a randomized, double-blind, treat-through design [60].

In this study 386 patients who had failed conventional therapy and were biologic naïve were randomized to ADA or UST induction followed by maintenance therapy with a primary endpoint of clinical remission at week 52 (CDAI score ≤ 150). There was no significant difference in the proportion of patients in clinical remission between UST and ADA-treated patients (65% vs. 61%, $P=0.42$). ADA-treated patients had high rates of anti-drug antibodies compared to UST-treated patients (74% vs. 2%); however, the presence of anti-drug antibodies did not modify treatment response. Regarding endoscopic remission, at 52 week rates of endoscopic remission, defined as SES-CD ≤ 3 , were largely equivalent (31% with adalimumab vs. 29% with UST) regardless of baseline SES-CD score.

3.2. 'Real-world' experience in CD

Real-world data provide greater insights into the effectiveness of therapy in a heterogeneous and more complex patient population representative of clinical practice. A growing body of evidence from RW data for UST provides credible evidence for its effectiveness and safety. After the UNITI pivotal trials' publication, several real-life studies from Europe, Asia, North and South Americas have been conducted, confirming its efficacy in daily practice.

3.2.1. UST for bio-experienced patients

In most real-life studies UST was used in the setting of anti-TNF- α failure or refractory to this treatment [72,73]. The RW studies in this specific setting reported that clinical remission at 24 weeks and (when available) at 52 weeks, ranged from 31% to 75%, and 25% to 60%, respectively [26–54]. In addition, other parameters, ranging from mucosal healing (MH) to fecal calprotectin (FC) level, improved significantly under UST treatment [26–54]. Interestingly, the results comparison of studies conducted on different continents, showed that UST works in the same way: between 24 and 52 weeks, the remission rate was about 25% in North America [32,34], 39% in South America [43], 25–60% in Europe [26–30,35–37,40–42,46–48], and 31–84% in Asia [31,38,39,45].

Two meta-analyses confirmed these results. In a systematic review and pooled analysis of real-world evidence only, Engel et al. found that the pooled remission rate at week 24 was 39% (range 18–65%) [74], and Macaluso et al. observed a pooled remission rate of 34% (range 18–65%) at week 24, and 40% at 52 weeks [75]. These results are superior to those obtained in pivotal trials, confirming a better response rate in RW studies.

In the absence of prospective, randomized clinical trials comparing available treatments, some RW studies often tried to overcome this limit using the propensity score, a statistical method able to reduce the selection bias, to compare head-to-head UST versus other biologics in this population setting. Ahmed et al. found that UST was not superior to ADA at week 56 (27% vs. 25%, $P=0.820$) [76]; Alric et al. found a higher response rate with UST than Vedolizumab (VDZ) at week 48 (54.4 vs. 38.8, $P=0.03$) [77]. Lenti et al. found UST not superior to VDZ at week 14 ($P=0.631$) and week 52 ($P=0.157$) [78]. Singh et al. compared UST vs. anti-TNF- α and VDZ in a large population of CD patients. The UST was better than TNF- α antagonists and VDZ in term of response, however, differences in the hospitalization or surgery risk were not detected [79]. Onali et al found UST slight but not significant than better VDZ in obtaining clinical remission [80]. Finally, Kappelman et al. did not observe a difference in treatment persistence between UST and VDZ. Still, UST was associated with a lower rate of all-cause hospitalisation (adjusted hazard ratio [aHR] 0.73), nonsurgical CD hospitalisation (aHR 0.58), and hospitalization for infection (aHR 0.56) [81].

3.2.2. UST for bio-naïve patients

Real-world studies have also investigated UST in CD patients never exposed biologics. Overall, the remission rate was higher in this setting.

In a retrospective, multicenter, multinational consortium of UST-treated CD patients, the authors found a higher remission persistence at week 52 in bio-naïve vs. bio-experienced CD patients (55% vs. 40%, respectively). Significantly, prior anti-TNF- α (HR, 0.72) and VDZ exposure (HR, 0.65) were independently associated with lower likelihoods of achieving response to UST [82]. A Belgian study found a 12-month remission of about 74% [83], and a very recent Spanish study reported a remission at weeks 16 and 52 of 93% and 82%, respectively in CD patients [84]. These results were confirmed by a Canadian study reporting a clinical remission in 59% of bio-experienced and 79% of bio-naïve CD patients [85]. In contrast, in a Brazilian study, statistically significant differences were not observed in the remission rate recorded at one year between bio-experienced and bio-naïve CD patients treated with UST or VDZ (39.4 vs. 39.8; $P=0.96$), respectively [45].

Finally, UST with other biologics was also compared in a number of RW studies. In a retrospective study conducted in two tertiary centers, Rivière et al. compared UST with anti-TNF- α in bio-naïve CD patients with luminal disease. Authors found that anti-TNF- α as first-line biological therapy was better than UST at three months ($P=0.02$), whereas no difference was observed during a 40-month follow-up ($P=0.29$) [86]. These results were probably linked to the effect of IFX rather than ADA. Zhdanova et al. found that, at 12 months, bio-naïve UST-treated CD patients showed a significantly higher treatment persistence rate than ADA-treated CD patients [87]. On the other hand, a Belgian study was unable to detect differences in the clinical remission rate between ADA vs. UST bio-naïve CD patients at week 26 (adjusted odd ratio [aOR] 1.30; $P=0.72$) and at week 52 (aOR, 1.60; $P=0.41$) [88].

3.3. UST in UC

3.3.1. Evidence from Randomized Controlled Trials (RCTs)

More recently, UST has been approved by the European Medicines Agency (EMA) and the Food and Drugs Administration (FDA) to treat moderate to severe active UC patients with inadequate response, lost response to, or intolerance to either conventional therapy or biologic, or with medical contraindications to such therapies. UST efficacy and safety have been investigated in a double-blind, randomized phase-3 trial (UNIFI) among patients with moderate to severe active UC. This study consisted of a single protocol combining 8 weeks of induction therapy and 44 weeks of maintenance therapy, accounting for a total of 52 weeks of therapy [24]. 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. According to the endpoints, induction and maintenance were analyzed. In the ongoing long-term extension study, participants will continue with the same treatment regimen received at the end of the maintenance study [24].

At baseline, 961 patients were randomly assigned to either a single i.v. infusion of UST 130 mg, a dose based on weight that approximated to 6 mg/kg (260 mg, weight ≤ 55 kg; 390 mg, weight >55 kg and ≤ 85 kg; 520 mg, weight >85 kg), or placebo. Overall, nearly 48.0% of patients had previously failed biological therapies (13.4% both anti-TNF- α drugs and VDZ) and 51% of them were on concomitant steroids at enrollment.

Intravenous UST was more effective than placebo (15.6% vs. 5.3%) for inducing clinical remission in patients at week 8. Week 8 clinical responders were re-randomized into three different maintenance arms: 90 mg UST s.c. every 12 weeks (q12w), q8w, or placebo. Subcutaneous UST q12w or q8w was more effective than placebo (38.4% or 43.8% vs. 24%) for maintaining clinical remission in responders at induction at week 44. No significant differences were observed in patients with or without previous treatment failure with biologics [24].

After completing the maintenance phase, patients who received UST entered the long-term extension study until week 220, maintaining the same treatment regimens. At week 200, 55.2% were

in symptomatic remission, with a greater proportion of biologic naïve patients (67.2%, 117/174) than those with a history of biologic failure (41.6%, 67/161). Finally, among patients in symptomatic remission at week 200, 96.4% were corticosteroid-free [89].

3.3.2. 'Real-world' experience in UC

The first real-life experiences date back to a few years before the drug was approved for the treatment of UC. An Italian multicenter, retrospective study including seventy patients (64 CD and 6 UC) exposed to UST for concomitant active psoriasis, especially paradoxical forms, and psoriatic arthritis, UST s.c. showed a good effectiveness profile, irrespective of IBD activity, with a cumulative probability of maintaining UST treatment of 97.1% at 6 months and 77.1% at 12 months [33]. However, in that setting, patients received UST s.c. 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 UST for UC, some retrospective, observational studies, including unselected patients, have evaluated the effectiveness and safety of UST for UC in clinical practice [49–59,90]. Overall, although limited by the small sample sizes enrolled and the short follow-up time, these studies provided further credible evidence for effectiveness and safety of UST. A recent systematic review of thirteen real-life studies [86] noted that clinical remission and clinical response at induction were achieved in 24% to 61% of cases, and in 47% to 77% of cases, respectively. Moreover, clinical remission was achieved in 33% to 79% of cases at 52 weeks of follow-up, whereas steroid-free remission was reported in 6 studies and ranged from 14% to 67%. Finally, lack of effectiveness, refractory disease, and loss of response were the main reasons for UST discontinuation.

Regarding predictive factors that might predict clinical remission and response with UST, Hong et al. showed that a history of TNF-antagonist primary nonresponse and a baseline Mayo endoscopic score of 3, were negative predictors of clinical remission at three months [53]. Chaparro et al. showed that CRP serum concentration over the upper limit of the normal range was the only factor significantly associated with a lower probability of achieving remission [49].

Another recent systematic review with meta-analysis of RW included 19 studies, with 3786 patients, of which over 92% previously treated with any biologic, 61.1% with both anti-TNF and VDZ and 16.4% with any biologic and tofacitinib [91]. Among the UC patients, 45.4% were in clinical remission by weeks 8, 43.8% (38.4%–49.2%) by weeks 12–16, 44.6% by month 6, and 50.6% by month 12. Overall, 58.2% of patients displayed endoscopic improvement at month 12. Clinical response was achieved in 61.2%, 59.4%, 65.2%, and 76.8% at week 8, 12–16, month 6 and 12, respectively, and corticosteroid-free remission was achieved in 18.7%, 36.8%, 34.5% and 39% at week 8, weeks 12–16, month 6 and 12, respectively. Overall, in 58.2% of patients endoscopic improvement at month 12 was observed. Interestingly, almost 30% of the patients needed dose escalation, which was effective in 40% of them. However, this meta-analysis suffers from several biases, ranging from high heterogeneity (>80%) in achieving remission at week 8 and one year to limited sample size in some included studies. Additionally, studies enrolling a higher proportion of patients with previous biological agents' failure had a lower clinical remission rate. Parakkal et al. [55] and Honap et al. [54] reported remission rates of 23.9% and 20% at week 8 and 40.4% and 43.6% at week 26, respectively.

3.4. Safety

The safety profile of UST is very favorable. The pivotal trials UNITI-1 and -2 showed an adverse events (AEs) rate similar to placebo, both as overall rate (65.9% and 55.6% vs. 64.9% and 54.3%, respectively), and for serious AEs (7.2% and 2.9% vs. 6.1% and 5.8%, respectively). The IM-UNITI showed a similar safety profile of UST vs. placebo (81.7% vs. 83.5% for overall AEs, and 9.9% vs. 15.0% for severe AEs, respectively). Serious infection occurred in only 2.3% of the patients receiving UST and in the placebo group [21–23].

Regarding UC, overall, the UST safety in the UNIFI trial was consistent with the already known safety profile in all other approved indications, and rates of key safety events, including infections, were similar between UST and placebo. No deaths occurred among the primary population in the

maintenance study. The rates of infection were similar across the treatment groups, and serious infections were infrequent: 1.7% in the q8w group; 3.5% in the q12w group; 2.3% with placebo. The number of AEs leading to discontinuation of the study agent was 20 in the placebo group; 5 and 9 in the q8w and q12w groups, respectively [24].

This favorable profile has also been confirmed in real life. In CD, overall, the mean rate of the AEs is about 11%, the large majority of them mild, and not requiring stopping treatment. Only one study reported an AEs rate of about 44%: a retrospective cohort study performed at a large single tertiary referral center in the US and analyzed the effect of UST in complex perianal disease [62]. The authors studied a challenging population: 61.3% reported prior perianal surgery, 36.2% taking concurrent immunomodulators at UST induction, and all patients were already treated with ≥ 2 anti-TNF [62]. Therefore, it was hypothesized that the population's characteristics could influence this high AEs rate.

In UC, a recent systematic review of RW data found that patients with AEs ranged from 2.6% to 32% [92]. In another recent systematic review with meta-analysis of RW the incidence rates (IRs) of colectomy, mild AEs, serious AEs and serious infections were 4.8, 7.9, 0.8 and 0.3 per 100 patient-years, respectively [91]. The most common non-infectious AE, except IBD exacerbation, was arthralgia (1.94%), followed by skin rash (1.55%).

3.5. UST in special situations

3.5.1. UST for perianal disease

UST has also been evaluated in specific clinical contexts, such as fistulizing perianal disease. UST seems to be less performing when used in managing fistulizing perianal CD. For example, a recent meta-analysis of controlled trials found UST effective in the induction of response but not in the induction of remission in those patients [93].

There are currently few RW studies in the literature on UST for perianal disease, reporting overall a modest effectiveness. The *Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif* assessed in detail the UST efficacy in perianal CD. Two hundred patients were included; 99% were previously exposed to at least one anti-TNF- α , and 28% were also exposed to VDZ. Successful treatment was obtained in 38% of patients, and successful seton removal was obtained in 33% of patients with their placement at the start of therapy [61]. In a retrospective cohort studied in a large single tertiary referral center, Godoy Brewer et al. found that, at 6 and 12 months, 48.1% and 55.6% of patients had an improved fistula response, but none achieved fistula remission [62]. Finally, according to the study of Yao et al., radiological healing of perianal fistulas was obtained in 44.8% of patients by using UST [63].

3.5.2. UST for postoperative recurrence

Despite the burden of postoperative recurrence after ileocolonic resection, no treatments have been approved to prevent recurrence in CD. Current ECCO guidelines recommend prophylactic immunosuppression with either thiopurines or anti-TNF- α agents to prevent postoperative recurrence in the presence of at least one of the clinical risk factors for recurrence [94].

Few RW studies are currently available in this specific setting of CD patients. A preliminary, retrospective study found that UST obtained MH, defined as Rutgeerts' score < 2 , in 73.3% of CD patients refractory to anti-TNF- α [65]. A recent prospective and comparative study showed a rate of endoscopic postoperative recurrence of 42% for UST and 40% for VDZ, in a cohort of patients exposed to anti-TNF therapy [64]. Finally, in a recent Italian study, Macaluso et al. confirmed the promising role of UST in preventing postoperative recurrence. The authors found 50% of endoscopic healing after a mean of 14.5 ± 5.5 months following initiation of UST [66].

3.5.3. UST for extraintestinal manifestations.

The occurrence of extraintestinal manifestations (EIMs) during the course of IBD is challenging. Anti-TNF- α agents are well studied and validated in this field [95]. The use of other biologics, such

as UST, as a therapeutic strategy remains unclear. Guillo et al. found recently that UST could be an effective option for the treatment of EIMs of CD, especially for dermatological and rheumatological manifestations [67]. An exciting study assessed the effect of UST on EIMs after the failure of anti-TNF- α agents. Twenty-four CD patients with EIM (17 with articular disease, nine with ankylosing spondylarthritis, three with rheumatoid arthritis, five with seronegative arthritis, four with erythema nodosum, one with uveitis; one with sclerosing cholangitis, and one with hidradenitis suppurativa) were treated with UST, with a significant improvement/remission of these EIMs [96].

More recently, a retrospective cohort study including IBD adult patients treated either with VDZ or UST and with EIMs before treatment initiation, showed clinical response of EIMs at week 52 in 36% (18/50) of patients treated with UST [97]. Moreover, safety profile and efficacy on EIMs also advocate in favor of UST 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 EIMs [98–100]. All these specific topics need further larger and longer studies.

3.5.4. UST for pouchitis

Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) is routinely performed in patients with UC undergoing colectomy [101,102]. Idiopathic inflammation of the pouch —referred to as pouchitis— is the most common long-term complication of IPAA [103,104]; it develops in approximately half of patients within 5 years after surgery [105] and recurs in more than half of affected patients.

The conventional treatment for confirmed pouchitis is antibiotics such as ciprofloxacin and metronidazole [103]. Up to 15% of patients, however, develop chronic pouchitis and either become dependent on antibiotics for symptom relief or have continuous symptoms despite chronic antibiotic therapy [103,106–108]. Chronic antibiotic-refractory pouchitis represents an indication to biological therapy, mainly anti-TNF- α , whose short- and long-term (12 months) benefits are estimated to be around 50% [108]. Other treatments are usually recommended for refractory patients or for those with specific contraindications to anti-TNF- α drugs [109]. The real-life data for the use of UST in this setting are still scarce and limited by small sample sizes and large heterogeneity of therapy protocols/outcome definitions [9–21,35,45,47,48,55,61–63,68–74,76–110]. In a retrospective, single-center study, 24 patients with chronic antibiotic-refractory pouchitis received UST (other pouch disorders were previously ruled out) at the dosage of 90 mg e.v. loading dose infusion followed by 90 mg subcutaneous injections q8w [68]. Of note, chronic antibiotic-refractory pouchitis had been previously treated unsuccessfully with other biologics in 12 patients (50.0%) and with immunomodulators in six (25.0%). After a median follow-up of 12.9 months (IQR = 7.9–16), 50.0% of patients achieved clinical response according to physician's judgment and in terms of number of bowel movements per day. In 13 patients (54.2%) pouchoscopies were available post-UST treatment, in these patients, after a median time of 7.4 months (IQR = 4.6–10.6) since UST start, the median Pouchitis Disease Activity Index (PDAI) decreased from baseline 5 (IQR = 4–6) to 4 (IQR = 2–5) ($P=0.016$).

More recently, Dalal et al. reported on a cohort of 46 patients treated with UST with mixed pouch disorders, six chronic antibiotic-refractory pouchitis, 4 cuffitis, and 36 CD of the pouch [110]. Also in this study, all patients had prior anti-TNF exposure, and 24 of 46 (52.2%) with VDZ.

According to physician judgment, clinical response at 8–16 weeks was observed in 80.4% (37/46) of patients. Dose intensification to q6w or q4w was required in 23 patients (50.0%) after a median of 223 days, and a clinical response was obtained in 60.8% of them within the subsequent 8–16 weeks. Lower age at both UC diagnosis (HR = 0.94, 95% CI = 0.90–0.99) and UST start (HR = 0.96, 95% CI = 0.92–0.99) was associated with a shorter time to dose intensification.

In a recent systematic review to evaluate the efficacy of UST in chronic refractory pouchitis [69], clinical response and clinical remission were observed in 63% and 10% of patients, respectively, after 4–12 weeks, whereas endoscopic response was reported in 60% of patients with chronic pouchitis after 24–32 weeks of treatment. Small sample sizes and large heterogeneity of therapy protocols/outcome definitions were significant limitations of the studies.

In conclusion, there is a limited and inconclusive body of evidence suggesting that UST may be a therapeutic option for patients with chronic pouchitis and CD of the pouch refractory to other therapies.

3.5.5. UST in pregnancy

The UST is an IgG1 and therefore crosses the placenta through the FcRn receptor as is the case with anti-TNF- α drugs. A favorable safety profile of UST for pregnant women has been initially observed among patients treated for psoriatic diseases [111]. Few data have been reported up to now for females affected by IBD, who conventionally receive higher doses compared with the dermatological and rheumatological indications. Although UST has not been extensively studied in pregnant women with IBD, existing data suggest it may be safe. Cases have been reported of mothers exposed to UST during pregnancy and lactation without observable negative consequences for them or their children [112,113]. The effects of UST in pregnant women with IBD were also evaluated in 29 pregnancies in the PREGNANCY-GETAID study, without negative effects on maternal or neonatal outcomes. Overall, the 29 pregnancies resulted in 26 (90%) live births, two (7%) spontaneous abortions during the first trimester, and one (3%) elective termination. Mild maternal complications were reported in two patients. Rates of prematurity, spontaneous abortion, congenital malformations and maternal complications were comparable between the UST and anti-TNF- α groups [114]. These data were confirmed by the preliminary results from the DUMBO prospective registry [115]. Although UST appears to be safe during pregnancy, the experience is still limited, and its use should be individualized.

8. Conclusions

UST is a much-needed addition to the increasing armamentarium of IBD therapy, and its effectiveness in patients with other immune-mediated diseases, such as psoriasis and psoriatic arthritis, is particularly appealing. UST has shown efficacy both as a first-line both as a second-line agent for the induction and maintenance of remission in IBD. The safety profile is promising. Real-world data have supported its effectiveness and safety profile. Recent data on pregnancy, prevention of postoperative recurrence, fistulizing CD and pouchitis appear promising.

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