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Alimentary Tract

Effectiveness and safety of Ustekinumab for Crohn's disease; systematic review and pooled analysis of real-world evidence

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ABSTRACT

Background: Ustekinumab [UST] is effective in Crohn's disease (CD) in the UNITI studies. Several real-world experience (RWE) studies with UST have been published to date. Our aim was to summarize the available RWE data for UST effectiveness and safety.
Methods: A systematic review of the available RWE studies of UST for CD and pooled analysis of the available effectiveness and safety data was performed.
Results: Eight relevant studies of 6 RWE were included for analysis. Data from 578 patients were pooled for analysis. Most patients (97.7%) were anti-TNF experienced. Pooled clinical response rate was 60%, 62%, 49% at 12, 24 and 52 weeks respectively (95% CI (0.42–0.77), (0.48–0.75), (0.37–0.62)). Pooled remission rate was 39% (95% CI (0.18–0.65)) at 24 weeks and pooled endoscopic response rate was 63% (95% CI (0.53–0.72)) after approximately one year of UST; 134 adverse events (AE) were reported in total, pooled proportion 21% (95% CI (0.12–0.35)). Serious AE were reported in 19 patients, pooled proportion 5% (95% CI (0.03–0.08)). Infections were reported in 38, pooled proportion 6% (95% CI (0.04–0.11)).
Conclusion: Pooled analysis of the RWE data suggests that the real-world effectiveness and safety are comparable to that reported in the randomized control trials.

1. Introduction

Although medical treatment options in inflammatory bowel disease (IBD) have improved dramatically over the last few decades with the introduction of anti-TNF antibodies and selective anti-integrin therapy, patients with refractory disease, as well as primary and secondary non-responders, still pose a major clinical challenge. A substantial number of primary responders to anti-TNF agents (as high as 46%) relapse despite continued treatment or dose escalation, with quite a substantial rate of early discontinuation of anti-TNF therapy [1–3].

There is a growing demand for novel therapeutic agents targeting alternative disease mechanisms. Although effective and relatively safe for the treatment of Crohn's disease (CD), the efficacy of vedolizumab for treatment of anti-TNF-resistant CD appears to be quite modest. In real-world cohorts of patients with CD whose disease has failed to respond to previous anti-TNF therapy, approximately one-third of patients achieved steroid-free clinical remission after 14 weeks of treatment with vedolizumab. Discontinuation rate at 52 weeks was also significant (up to 42%) [4–11].

Interleukin (IL)-12 and IL-23, 2 heterodimeric cytokines sharing the common p40 subunit, are over-produced in IBD and play a major role in promoting the pro-inflammatory cytokine response. These observations together with the demonstration that IL-12 and IL-23 drive pathogenic responses in animal models have paved the way for the development of IL-12p40 blockers [12,13].

Ustekinumab (UST) is a monoclonal antibody that targets the standard p40 subunit of the cytokines IL-12 and IL-23 (IL-12/23p40), which are involved in the pathogenesis of CD [14–16]. UST was shown to be effective in inducing and maintaining clinical remission in CD patients with moderate to severe CD [14]. UST has a favorable safety profile and a substantial body of safety data is available from psoriasis studies [15,17]. Several studies describing real-world experience (RWE) with UST have been published demonstrating effectiveness and safety comparable to those

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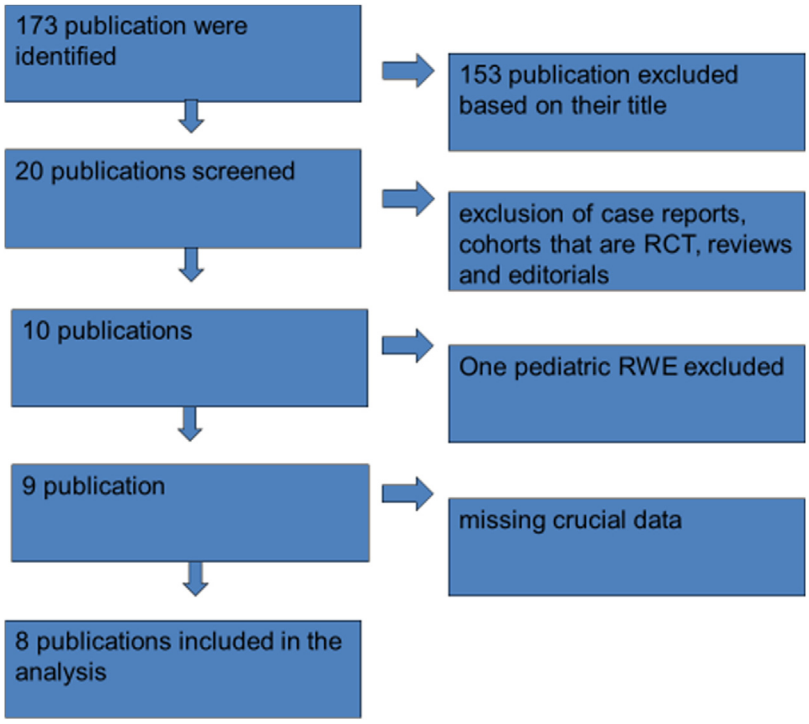

Fig. 1. Inclusion of the studies for pooled analysis of UST efficacy and safety.

reported in the RCT's. RWE allows bridging of some data gaps and describing real-world patient experiences that are lacking in RCTs that tend to exclude certain groups of patients (such as patients with isolated small bowel disease inaccessible to ileocolonoscopy, patients with multiple comorbidities and other special population) [18]. Real world experience series add substantial data on safety, efficacy, optimal treatment interval and dosing [19–27].

Our aim was to summarize the currently available knowledge and to perform a pooled analysis of the effectiveness and safety of UST in CD patients, as reported by the real-world studies.

2. Methods

A structured search of the Pubmed and Embase database was performed, on March 1, 2018, to identify all studies that describe a real-world experience with UST. Search terms that were used: Ustekinumab, Crohn's disease. For the purposes of the pooled analysis of effectiveness and safety, only reports published in complete form in peer-reviewed literature were included. We extracted the baseline characteristics, efficacy, and safety data from the manuscripts. When further clarifications were required, we contacted the original study authors. We excluded publications based on RCT cohorts and studies missing well-reported efficacy data on long term maintenance (Fig. 1).

For several topics covered in a narrative form, we reviewed case reports and case series from the literature [19–27].

3. Definitions

Clinical response and remission were defined as a reduction in Harvey Bradshaw Index (HBI), physician global assessment (PGA) or both for all cohorts as per the definition used in the original publication. Two cohorts used PGA [21,26], two used both PGA and HBI [19,20,27] and the rest used only HBI for definition of clinical response and remission [22–25].

An endoscopic response was defined as a significant reduction in the number of visible ulceration and mucosal healing was defined as lack of any visible ulceration and normalization of the mucosa as per definitions used in the original publications.

Most studies used subjective endoscopic assessment for definition of endoscopic response and remission [21–24,26] only one study used the Simple Endoscopic Score for Crohn's Disease (SES-CD) for this purpose [27].

4. Statistical methods

For each outcome measure, the pooled proportion of patients (with 95% confidence intervals) for the outcome in question was calculated. We examined the pooled proportions of patients who had responded to UST at various time points following initiation of treatment, and the pooled proportions of patients who had experienced adverse events. The fixed effects (Mantel–Haenszel) and random effects (DerSimonian–Laird) models were used for pooling, depending on heterogeneity. Statistical heterogeneity was determined using the Q statistic of I2 which describes the percentage of total variation across studies attributable to heterogeneity rather than chance. An I^2 value greater than 50% was taken to represent significant statistical heterogeneity. If studies were relatively homogeneous, the fixed effects model was used whereas the random effects model was preferred in instances of significant heterogeneity [28].

Where there was significant statistical heterogeneity between outcomes, the forest plots were examined for obvious outliers, to see if elimination of these studies had a significant effect on the overall pooled outcomes.

Statistical analyses were carried out using the "meta" and "metafor" packages in R statistical software version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) [29,30].

5. Results

The literature search identified 173 publications. After excluding duplicates and ineligible studies by title/abstract screening, 20 studies underwent full-text review. Excluding case reports, cohorts

not based on real-world patients, reviews and editorials, one pediatric paper, and one study missing crucial data (time point for response and remission) [25]. Eight studies were included in a quantitative meta-analysis (Fig. 1).

Two of the 8 relevant studies included in the pooled analysis consisted of patients from the same cohort and hence were included in the meta-analysis as single studies [19,20,22,23].

Clinical characteristics of patients included in RWE studies

Data from 578 patients from 8 studies from 6 cohorts were pooled for analysis. The vast majority of patients (97.7%) were anti-TNF experienced; 60% had previous experience with at least 2 or more biologic agents and only 13 (2.2%) patients were anti-TNF naïve. Disease duration was longer than 6 years for all cohorts and 61% of patients had at least one previous surgery. Among the pooled cohort, 190[32.8%] patients were on concomitant systemic steroids and 200 [34.6%] were on concomitant immunomodulators at the beginning of therapy. Additional details regarding the included studies appear in Table 1.

5.1. Clinical response and remission

5.1.1. Week 12

Data for clinical response were available from 5 studies with a pooled clinical response rate of 60% (95% CI 0.42–0.77). Data from 493 patients were analyzed [19,21–24,26]. Data for clinical remission at week 12 were only available from 2 cohorts and was not suitable for analysis [20,22] (Figs. 2 and 3).

5.1.2. Week 24

Based on data from 473 patients in 6 studies, a pooled proportion of 62% (95% CI; 0.48–0.75) responded to UST at week 24 [19,21–24,26,27].

Remission rates were available for analysis from 3 studies, enrolling 281 patients, with 39% pooled remission rate (95% CI; 0.18–0.65). [19,20,22,23,27] (Figs. 2 and 3).

5.1.3. Week 52

Three hundred and twenty-one (321) patients from 5 cohorts were analyzed for week 52 clinical response rate: pooled proportion 49% (95% CI;0.37–0.62) [19–24,26].

Steroid-free response rates, based on 4 cohorts with a total of 261 patients, yielded a pooled proportion of 51% (95% CI;0.37–0.62) [19,20,22–24,26].

Remission rates (45/161) were available from only 2 RWC (Ma C and Wils) and were not adequate for pooled statistical analysis (Figs. 2–4).

5.2. Endoscopic response and mucosal healing

Six studies (all included cohorts) reported endoscopic response and five reported mucosal healing with UST, with totals of 190 and 187 patients respectively. The pooled endoscopic response rate was 63% (95% CI; 0.53–0.72) after approximately one year of UST treatment among those continued treatments.

Mucosal healing was achieved in 29 of 133 patients at 24–26 weeks (21.8%) and in 19 patients out of 71 (26.7%) after one year [22,24]. The pooled proportion of mucosal healing rates after one year, analyzed from 4 cohorts, was 31% (95% CI; 0.22–0.41) [19,22,24,26] (Fig. 4).

5.3. Predictors of clinical response

Six studies assessed predictors for short and long-term response. Two cohorts found no predictive factors associated with

Table 1
Characteristics of the real-world experience e studies of UST in CD.

Study Author	Journal	type	year	countr y	N	median or mean age (year)	disease duration median (month)	previous surgery (n)	Perianal disease	baseline CRP>5 sd	prior TNF treatment total number n (%)	Tumor necr osis anti-TNF agents, total n (%)	Concomitant immunomodulat or TIOFAL n(%)	Corticosteroid treatment at onset	response at week 12	response at week 24	response at week 52	remission at week 12	remission at week 24	remission at week 52	Non steroid response at week 52	steroid free remis sion at week 24	mucosal healing at week 24	mucosal healing at week 52	endoscopic response at week 52	Efficacy of UST on perianal lesions	dose escalation	escalation was effective
Wils P	*CCH+APT* 2018	retrospective	2016-2018	France	122	33.8(27.5-43.9)	11.5(6.9-17.1)	75\122	71\122	72(110(+5)	3\122	112\122	28\122	19\122	47\104	22\68	16\50	19\104	20\68	14\50	20\47 (36m)			11\28	8\21	8\12		3\79	3\8
Greenup AJ	Scand J Gastroenterol. Dec 2017	retrospective	2017	Canada	73	37 (30-50)	17 (10-23)	51\73	32\73	38\98(+5	1\73	9\73	30\73	19\73	38\68	30\55	21\53									24\36		16\73	
Batat r	Clin Gastroenterol Hepatol	retrospective	2017	Canada	62	39(+)	13.6(mean)	32\62	17\62	28±40.6 (mean)	1\62		25\62	19\62		50\62 (week26)			41\62(w26)		31\62(w26)	12\62(w26)		36\62				
Ma C	*APT*2017+IBam mBowel Dis	retrospective	2017	Canada	167	44.6(31.8-55.5)	14.3(8.84-21.8)	111\167	45\167	7.8(2.2-23)	8\167	93\167	73\167	74\167	65\167	91\151	68\111	25\167	38\151	31\111	69\111	91\151	17\71	13\45	32\45	14\45			
Khorram i 3	IBD J	retrospective	2016	Spain	116	37(28-48)	10(6-17)	56\116	58\116	74(89+5 MEDIAN (5)	0	10\116	42\116	37\116	97\116	81\106	59\88				32\88			4\13	9\13	11\18	11\116		8\11
Koyfov U	JCC	retrospective	2014	Canada	38	35.5(22.5)	13 (6.5)	17\38	13\38	22\32	0	36\38	4\38	22\38	28\38	20\31	9\19				11\15			2\13	10\13	9\13	16\38	11\16	
SUM					578							351															48\306		

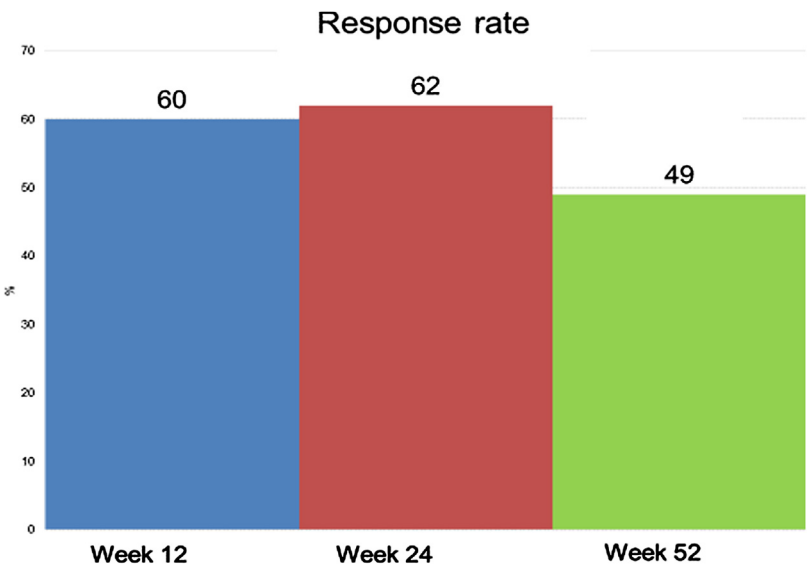

Fig. 2. Pooled efficacy of UST, response rate week 12, 24 and 52.

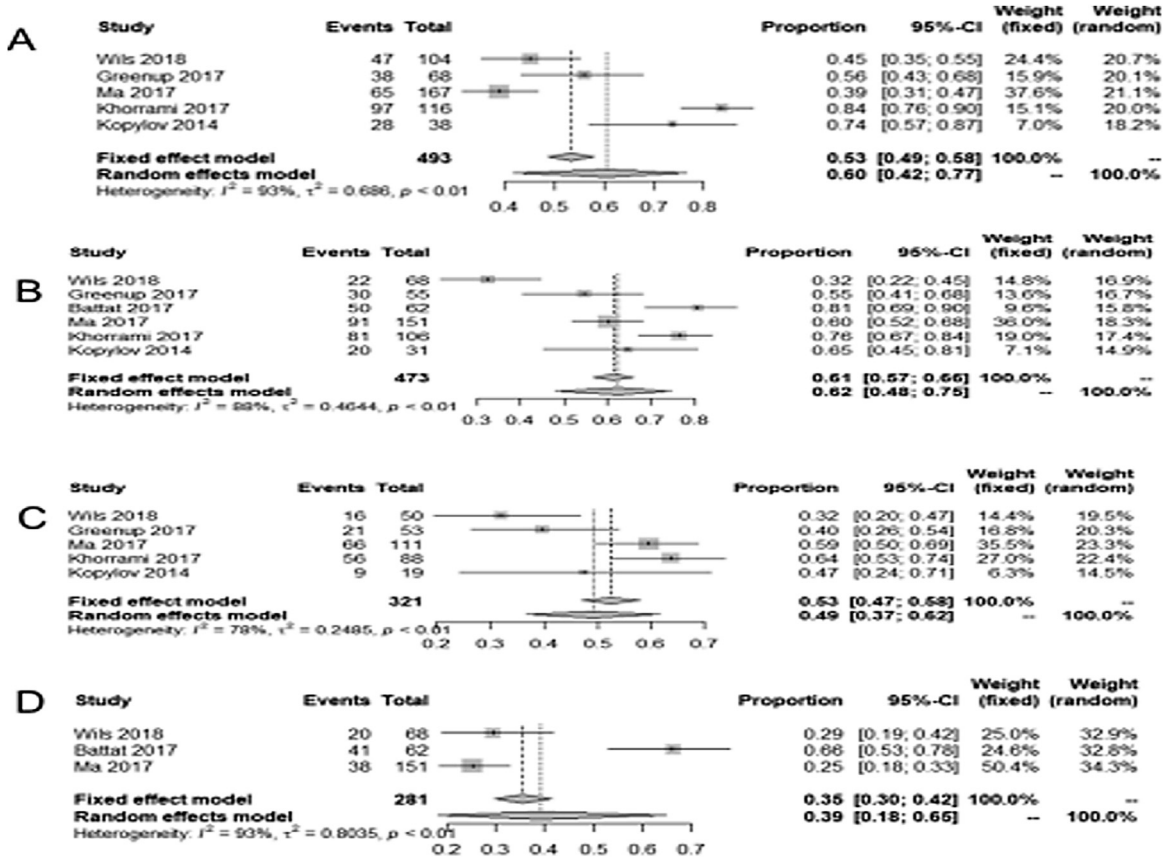

Fig. 3. Pooled response rates with UST treatment in CD. (A) 12 weeks (B) 24 weeks (C) 52 weeks and remission rate at 24 weeks (D).

UST efficacy on univariate and multivariable analysis 1926 Colonic disease was associated with better clinical and endoscopic outcome and a lower chance for loss of response in two different cohorts [22,27]. One cohort found that the initial response to UST and history of 2 or more different immunosuppressive drugs were associated with a clinical benefit at the end of follow-up [24]. In 2 studies, concurrent immunomodulators were associated with lower risk for loss of response and with greater effectiveness and the clinical benefit of UST (OR 0.39 CI 0.17–0.92) [20,22]. This was not supported by other RWE series.

In contrast, patients with stricturing phenotype (B2) tended to have worse outcomes [22]. History of previous intestinal resection was associated with long-term failure of UST (OR 2.09 CI 1.16–3.79) [24].

In an additional study on univariate analysis, age and type of preceding nonresponse to an anti-TNF agent (primary vs. sec-

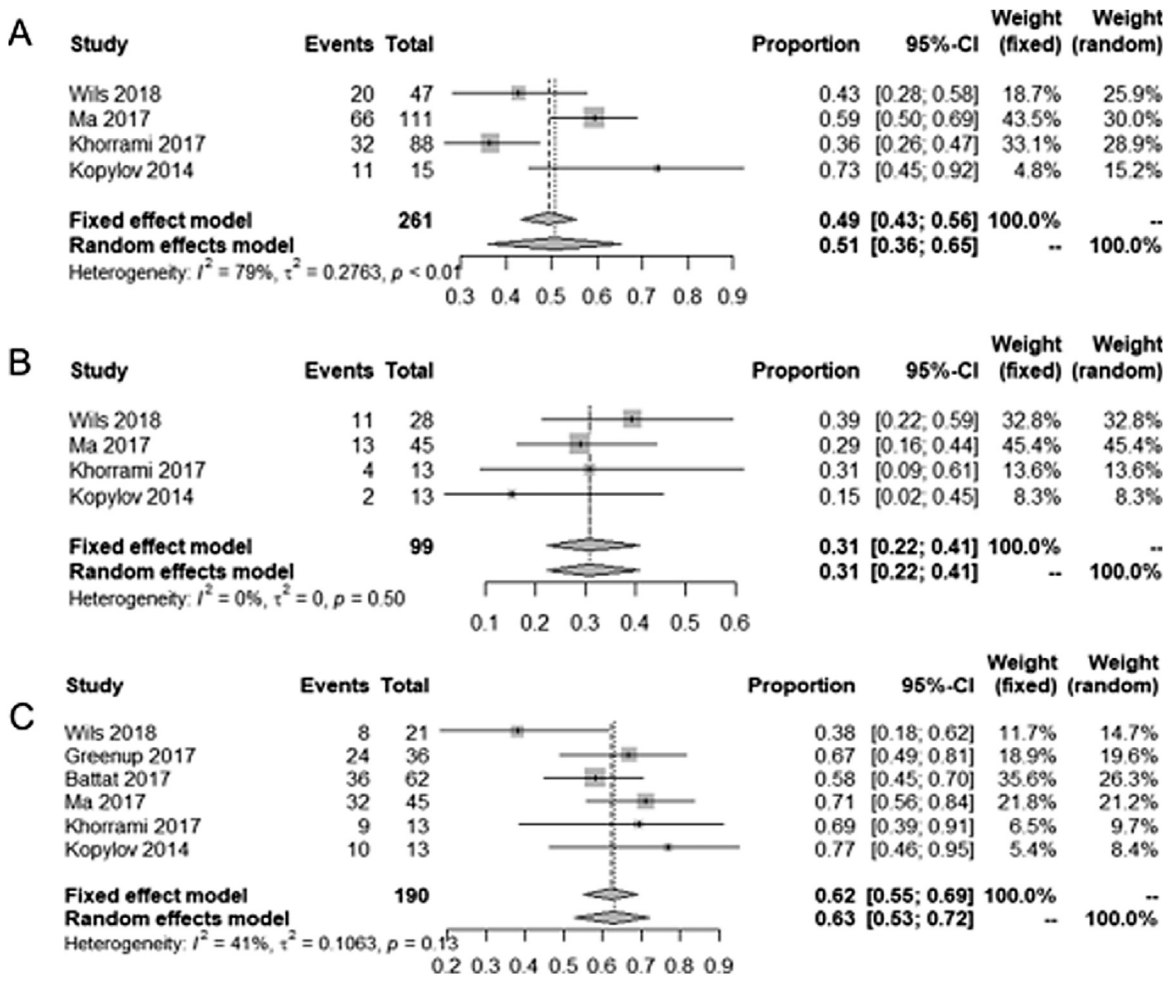

Fig. 4. Pooled rates at 52 weeks for: (A) steroid free response rate, (B) mucosal healing and (C) endoscopic response with UST treatment in CD.

ondary; primary vs. intolerance) were predictors of short-term symptomatic response (OR 17.3 CI (2.34–128.47) and 26.5 CI (3.46–203.62)) [21].

5.4. Dose escalation

Four cohorts (306 patients) addressed escalation rates; 48/306 (15.6%) needed dose escalation with effectiveness rates ranging between 50%–72% [19,21,24,26].

5.5. Pharmacokinetics and immunogenicity

Only one study examined the effects of UST levels. Two patient cohorts were analyzed. A longitudinal cohort prospectively received UST 90 mg SC induction at weeks 0, 1, and 2, followed by UST 90 mg SC maintenance Q8 weeks and a cross-sectional cohort, already on UST ≥ 26 weeks. UST drug trough and anti-UST antibody concentrations were analyzed using a drug-tolerant liquid phase homogeneous mobility shift assay (Prometheus Laboratories Inc, San Diego, CA).

At week 10 mean trough concentrations were 3.4 ± 2.1 μg/mL, no patient had detectable antibodies but trough level did not correlate with clinical or endoscopic response nor with biomarkers outcome. Nevertheless, at week 26, during maintenance, drug mean trough level was 4.4 ± 2.2 μg/mL and correlated with endoscopic response. Endoscopic response was more frequent in patients with level above 4.5 μg/mL (5.9% vs 40.7% (n = 27; P = 0.008)) but clinical outcomes did not correlate with UST concentrations [27].

5.6. Surgery

Among the reported cohorts 34/578(6%) patients needed surgery (small bowel resection, colectomy, and surgical abscess drainage) during UST treatment.

5.7. Perianal disease

Perianal disease phenotype was reported in 236 patients in some point of their disease, but only 4 papers reported outcome for patients receiving UST for active perianal disease, enrolling 88 patients with 43 patients responded to treatment by the end of the studies. Wils et al. reported remission of perianal disease in 6 out of 9 patients (66.6%), Khorrami et al. reported improvement in 11 out of 18 patients (61.1%), Kopylov et al. reported initial response in 9/13 (69.2%) and Ma et al. reported complete perianal disease healing in 14/45 (31.1%) as demonstrated by pelvic MR or dedicated pelvic contrast-enhanced ultrasound [19,22,24,26].

5.8. Pregnancy

Since many of CD patients are a young female in childbearing age, its consequences on pregnancy and fetus outcome are critical. Currently, UST is classified as Pregnancy FDA category B and

our knowledge pertaining to the safety of UST for CD in pregnancy is very limited since most of the available data regarding this issue comes mainly from psoriasis patients. Clinical outcomes from the UST clinical trials were recently published reporting a total of 26 maternal pregnancies. In all cases, treatment was discontinued upon the report of pregnancy. Pregnancy outcomes were reported for 24 of 26 pregnancies, including 15 (62.5%) live births, 4 (16.7%) spontaneous abortions (all 4 occurred in the 1st trimester) and 5 (20.8%) elective abortions comparable to the rate previously reported in the psoriasis clinical trials data [31]. Reports on UST from RWE during pregnancy are scarce. Cortes and Venturin both reported RWE cases and reviewed the issue nicely. Venturin et al. reported a case of a patient, already experienced an obstetrical history of miscarriage in the past, who became pregnant during treatment with UST for a refractory CD and which ended in miscarriage [32]. On the contrary Cortes et al. reported a case of a pregnant patient with refractory CD who was successfully treated with UST and azathioprine maintenance therapy throughout her pregnancy and delivered a baby boy without any congenital abnormalities [33]. Galli-Novak et al. reported a case of a patient with CD, who developed psoriasis during IFX treatment which eventually was switched to UST with a rapid and complete remission of psoriasis and control of CD and became unintentionally pregnant. The patient continued on UST towards the 33rd week of gestation and delivered a healthy baby [34]. Likewise, Rowan et al. reported a case of CD patient who was treated with UST throughout her pregnancy up to 33 weeks and delivered a healthy baby by Cesarean section at week 37. Cord blood UST levels were almost 2-fold higher than UST levels in maternal serum [35].

The numbers of exposed pregnancies are too small to draw any conclusions, bearing in mind that active CD itself carries gestational and fetal risk, teratogenic and abortion risks must be balanced and discussed with the patient [36].

5.9. Pediatric experience

Data from pediatric psoriasis patients suggest UST is effective and safe in managing severe pediatric psoriasis although based on a relatively modest number of reports and long term safety data remains scarce [37].

No pediatric patients were included in the UST clinical trials for CD and RWE is also very limited with only 4 reports published in the literature describing only 7 patients.

Rinawi et al. reported in 2016 the successful treatment with UST of a 7-years-old boy with refractory CD colitis and arthritis who previously failed IM and both ADA and IFX. Cameron et al. reported a case of an 11-years-old boy with refractory ileocolonic CD who failed IM and IFX but did not respond to UST and eventually required a colectomy and end ileostomy, resulting in surgically-induced clinical remission [38,39].

Bertrand et al. reported a case of a 13-year-old girl with CD who developed a severe anti-TNF-induced psoriatic rash with ADA and was treated successfully with UST [40]. Bishope et al. reported the use of UST for 4 patients (age 12, 13, 16 and 17) with pediatric CD. All patients were previously exposed to corticosteroids, IM and both IFX and ADA. Two of 4 patients showed clinical improvement within 4–8 weeks after initiation and remain on UST while the other 2 discontinued therapy due to lack of response [41].

5.10. Safety

A total of 134 adverse events were reported in the real-world cohorts, pooled proportion 21% (95% CI (0.12–0.35)). The most common adverse events were musculoskeletal pain and symptoms (n = 41/134, 30%) followed by headache (n = 23/134, 17%) and skin eruption (n = 18/134, 13.4%). Infections were reported in 38/134 (28%), the vast majority were mild upper respiratory infection with 2 cases of severe pneumonia. Two cases of new onset perianal abscess were reported and 3 cases of Clostridium difficile infection. No cases of tuberculosis were reported (Table 2).

Serious adverse events were reported in 19 patients (3.2%). Among them, one patient developed amyotrophic lateral sclerosis (causal relationship not concluded), another reported severe neuropathic pain which resolved after discontinuation of UST and there was one case of pancreatitis requiring hospitalization.

Three cases of malignancy and dysplasia were reported in two cohorts. A case of anal adenocarcinoma developed in a 32 YO male with long-standing pediatric-onset Crohn's disease. A case of colon adenocarcinoma was found in a patient who had dysplasia prior to treatment and was diagnosed with cancer more than 6 months after UST discontinuation; another case of colonic carcinoma developed in a patient with severe colitis and low-grade dysplasia prior to UST treatment who was found to have carcinoma at colectomy while on UST treatment.

One mortality was reported, an 86-year-old patient who died from complications of pre-existing cardiac and pulmonary comorbidity.

6. Discussion

Data from randomized controlled trials have demonstrated that UST is an effective agent for the treatment of moderate-to-severe CD with a good safety profile and favorite response rates for anti-TNF experienced patients. Herein, the current pooled analysis of the RWE data suggests that the real-world effectiveness and safety are comparable and even somewhat better to what reported in the CERTIFI and UNITI studies [14,17,42,43].

The vast majority of patients in the included studies had a long duration of disease and failed at least 2 lines of previous biologic therapy, making these favorable results even more appealing. Importantly, RWE data frequently suggests higher response rates in comparison to RCT [4]. The main explanation for this discrepancy is not unique to our analysis or specific to UST and most likely stems from the less stringent definition of response in RWE studies. In addition, in many patients UST was the "last resort" treatment after failing all previously available lines of treatment. In this setting, it is quite likely that the treatment could have been extended even when there was no initial clear evidence of benefit (as demonstrated for example by the study by Ma et al. where 6-month response rates were much higher that 3-month response), and discontinuation rates could have been higher if additional lines of treatment were readily available [23]. Importantly, less than 3% of the patients that were included in the RWE series included in this analysis; thus the data did not allow for comparison of anti-TNF naïve and experienced patients. Such comparison was also not directly available from the UNITI1 and 2 data.

Moreover, our pooled analysis suggested a rather favorable rate of endoscopic response and remission; importantly the number of patients with available endoscopic data was quite limited and mostly biased by the exclusion of patients that stopped treatment before arriving at follow-up endoscopy. Data regarding the efficacy of UST in perianal disease are very limited. Some of the studies aimed to evaluate predictors of response to UST. However, the data was not amenable for pooled analysis. As expected, the initial response to UST was associated with a long-term maintained clinical benefit. This finding is in accordance with data from the CERTIFI study [42]. Moreover, it appears that the rate of response may further improve with time even in patients lacking initial response; it may be pertinent to wait (even up to 6 months) before discon-

Table 2
Pooled prevalence of main adverse events in real-world cohorts with UST in CD.

Study author	Journal	Adverse events total (n)	Severe adverse events (n)	Infection (n)	MSK-myalgia arthralgia arthritis (n)	Headaches (n)	Clostridium difficile infection (n)	Skin eruption (n)	Fatigue (n)	Neurologic	Cancer	Death	Other
Wils P	CGH + APT 2018	20/122	4/20	9/122	5/122			3/122			1/122(anal adenocarcinoma)		2/122 (depression, allergic)
Greenup AJ	Scand J Gastroenterol. Dec 2017	18/73	1/18	3/73 (2 abscess and 1 pneumonia)	6/73	1/73		3/73		1/73 (Amyotrophic lateral sclerosis)			
Battat r	Clin Gastroenterol Hepatol	31/62	3/62	3/62	8/62	14/62		6/62	8/62		2/62(HGD CRC)		3/62 (nephrolithiasis)
Ma C	APT2017 +Inflamm Bowel Dis	53/167	11/53	20/167	21/167	6/167	2/167	5/167				1/167	
Khorrami S	IBD J	11/116		3/116	1/116	2/116		1/116					4/116
Kopylov U	JCC	1/38					1/38						
SUM		134/578	19/134	38/578	41/578	23/578	3/578	18/578	8/578	1/578	3/578	1/578	9/578

tinuation of UST for inefficacy; this is somewhat different from the commonly accepted definition of primary response within 12–14 weeks with anti-TNFs [44].

Efficacy of UST for perianal fistulizing CD was reported recently in subgroup analysis of patients included in the clinical studies (CERTIFI and UNITI) with somehow low rate of active fistula disease at baseline (10.8% and 15.5% respectively) but with response rate of 47% at the CERTIFI (9/19) and up to 80% response rate in the UNITI [45]. Our analysis suggests that clinical improvement in perianal fistulae may be achieved in at least half of the patients with active perianal disease. However, these promising findings should be considered with caution because of the small number of patients assessed and the subjective assessment of response in perianal disease (with the exclusion of Ma et al. [22] that defined perianal response as evidence of fistula healing by transrectal ultrasound or pelvic MRI).

Ustekinumab is a potentially usefult therapeutic option in patients with concomitant psoriasis or rheumatological abnormalities. A recent multicenter Italian study by Pugliese et al. [46] included seventy patients with IBD and psoriasis or psoriatic arthritis. Their cumulative probability of achieving clinical remission was 84.7% and 63.9% at 6 and 12 months, respectively.

Recent data analysis from Phase 3 studies looking serum drug concentrations of UST over time found no significant differences between the different induction regimens although median trough drug levels were significantly higher with the 8-week maintenance interval versus the 12-week interval. Drug levels were proportional to dose and reached a steady state by the second maintenance dose. Trough concentrations of UST of 0.8 μg/mL or greater were associated with maintenance of clinical remission in a higher proportion of patients than patients with lower trough concentrations. UST antibodies were found in 2.3% of patients with available sera (27/1154 p). Importantly, patients randomized to maintenance and responders who continued to receive UST maintenance therapy had a lower incidence of anti-UST antibodies than those who did not receive continuous UST treatment. Moreover, patients receiving concomitant immunomodulators had a lower proportion of positive sera for antibodies [47].

Data for RWE was scarce. Only one included study examined the effects of UST levels in two patients' cohorts [27]. Unlike in the UNITI, no patient had detectable antibodies and trough level correlated with endoscopic response only after 26 weeks in maintenance phase but clinical outcomes did not correlate with UST concentrations. It is possible that differences between assays can explain the differences.

The safety profile of UST in the RWE series appears to be very favorable with RCT data. No new safety signals were identified in the included studies. Unfortunately, pediatric and pregnancy data is currently limited to small case reports and series, and additional studies are urgently required.

In summary, RWE data supports the effectiveness and safety of UST in the treatment of CD. Additional studies are merited to assess the role of UST as a first-line biologic, as well as its usefulness in the treatment of pregnant and pediatric patients.

Conflict of interest

Uri Kopylov — Speaker/advisory fees — Avbbvie, Jannsen, Takeda, MSD, Medtronic. Research support — Jannsen, Takeda, Medtronic

Tal Engel — No conflict of interest

Diana E. Yung-No conflict of interest

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Pariente B — Consulting fees from, Abbvie, Janssen, Ferring, Hospira, Takeda, Biogaran, Lilly, Pfizer, Lecture fees from Abbvie, Takeda, Janssen, Ferring.

Wils Pauline — Travel accommodation: Janssen, Biogaran, Hospira. Consulting fees: Ferring

Rami Eliakim — No conflict of interest

Bella Ungar — Received speaker/consultant fees from Abbvie, Jannsen, Takeda and Neopharm.

Shomron Ben — Horin-received consulting and advisory board fees and/or research support from AbbVie, MSD, Janssen, GSK, Takeda and CellTrion.

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