DOI: 10.1002/ueg2.12278

EDITORIAL

UNITED EUROPEAN GASTROENTEROLOGY ueg journal WILEY

Ustekinumab in ulcerative colitis- insights from the real-world data

The therapeutic arsenal for ulcerative colitis (UC) has increasingly expanded over the past years, along with improved comprehension of the pathogenesis and identification of key cytokines promoting bowel inflammation.[1] Interleukin (IL) −12 and IL23 are two key cytokines in the pathogenesis of intestinal inflammation. IL12 promotes the differentiation of naïve T cells in Th1 effectors, while IL23 exerts its effect by perpetrating the pro-inflammatory functions of Th17 cells.[2,3] Ustekinumab is a humanised monoclonal igG1 kappa antibody directed against the common P40 subunit of interleukin-12 and interleukin-23.[4] It was first approved in 2019 as treatment for moderate to severe UC following the UNIFI study, which demonstrated its efficacy and safety.[5] Since then, several studies evaluate ustekinumab efficacy among UC patients, including patients with refractory disease. Ochsenkühn et al. described the efficacy and safety of ustekinumab in refractory UC patients with a history of multiple biological therapies.[6] In pediatric population, Dhaliwal and colleagues reported the efficacy of ustekinumab in pediatric anti-TNF experienced patients.[7]

In their study "Real-world outcomes of ustekinumab treatment in ulcerative colitis: results from the Swedish Inflammatory Bowel Disease Quality Register" Thunberg and colleagues[8] analyzed prospective data from the Swedish Inflammatory Bowel Disease quality Register (SWIBREG), and reported the short- and long-term outcomes in UC patients treated with ustekinumab. In this study, which included 133 patients, the primary outcome of ustekinumab persistence rate at 16 weeks was 86%, and 67% after a median follow-up of 32 weeks. It should be mentioned that only three patients were naïve to biologics and tofacitinib in this study. The persistence rate reported here is lower than reported in the UNIFI maintenance study, however, the latter included only patients who responded to the induction therapy.[5] Recent studies among Crohn's disease patients treated with ustekinumab demonstrated comparable persistent rates comparable to those reported by Thunberg and colleagues.[8–10]

In accordance to previously published real-world data, ustekinumab treatment was associated with improvements in clinical biochemical parameters. In addition, this is the first real-world experience study to report the effect of ustekinumab treatment on health-related quality of life in UC. Importantly, the effect was demonstrated in a highly resistant population, with the majority of patients failing at least 2 previous biologics or small molecules.

As duly noted by the authors, the main limitations of the study system form retrospective non-controlled design. Importantly, the primary outcome of the study was treatment persistence and not clinical efficacy, and this as early as 16 weeks (correlating to 3rd treatment in most cases). Data on clinical outcomes was missing in a large proportion of the patients.

Given the variety of available treatments, clinicians may face difficulty in when and in what order to position different drugs. Although randomized clinical trials are considered as "gold standard" for the evaluation of efficacy and safety of new therapies, they usually required strict inclusion and exclusion criteria leading to a study population that might not properly embody the patient populations encountered in clinical practice.[11] On the other hand, real-world studies utilize large datasets across diverse populations, including those forgone by clinical trials, and pragmatic clinical outcomes, providing complimentary post marketing data that may assist in positioning and sequencing of the available therapeutic agents.

The future of IBD management is expected to evolve in the upcoming years with the introduction of additional and novel treatment options. While this evolution has a great potential for improving IBD care, the physicians will face a significant challenge in tailoring the right treatment to each patient. Real world studies assessing treatment efficacy, safety and treatment persistence provide crucial pieces for the solution of the treatment sequencing puzzle.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare. Uri Kopylov received speaker and advisory fees from Abbvie BMS Jannsen Takeda Pfizer Sandoz/Novartis Medtronic; and research support from Jannsen Takeda Medtronic.

Ido Veisman
Uri Kopylov

Department of Gastroenterology, Sheba Medical Center Ramat Gan and Tel Aviv University, Tel Aviv, Israel

Correspondence
Uri Kopylov, Department of Gastroenterology, Sheba Medical Center Ramat Gan and Tel Aviv University, Tel Aviv, Israel.
Email: ukopylov@gmail.com

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Uri Kopylov https://orcid.org/0000-0002-7156-0588

REFERENCES

1. Marafini I, Sedda S, Dinallo V, Monteleone G. Inflammatory cytokines: from discoveries to therapies in IBD. Expet Opin Biol Ther. 2019;19(11):1207–17. https://doi.org/10.1080/14712598.2019.1652267
2. Mannon PJ, Fuss IJ, Mayer L, Elson CO, Sandborn WJ, Present D, et al. Anti-interleukin-12 antibody for active Crohn's disease. N Engl J Med. 2004;351(20):2069–79. https://doi.org/10.1056/nejmoa033402
3. Aggarwal S, Ghilardi N, Xie MH, de Sauvage FJ, Gurney AL. Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17. J Biol Chem. 2003;278(3):1910–14. https://doi.org/10.1074/jbc.m207577200
4. Benson JM, Peritt D, Scallon BJ, Heavner GA, Shealy DJ, Giles-Komar JM, et al. Discovery and mechanism of ustekinumab: a human monoclonal antibody targeting interleukin-12 and interleukin-23 for treatment of immune-mediated disorders. mAbs. 2011;3(6):535–45. https://doi.org/10.4161/mabs.3.6.17815
5. Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2019;381(13):1201–14. https://doi.org/10.1056/nejmoa1900750
6. Ochsenkühn T, Tillack C, Szokodi D, Janelidze S, Schnitzler F. Clinical outcomes with ustekinumab as rescue treatment in therapy-refractory or therapy-intolerant ulcerative colitis. United European Gastroenterol J. 2020;8(1):91–8. https://doi.org/10.1177/2050640619895361
7. Dhaliwal J, McKay HE, Deslandres C, Debruyn J, Wine E, Wu A, et al. One-year outcomes with ustekinumab therapy in infliximab-refractory paediatric ulcerative colitis: a multicentre prospective study. Aliment Pharmacol Ther. 2021;53(12):1300–8. https://doi.org/10.1111/apt.16388
8. Thunberg J, Bjorkqvist O, Hedin C, Forss A. Real-world outcomes of ustekinumab treatment in ulcerative colitis: results from the Swedish Inflammatory Bowel Disease Quality Register. United European Gastroenterology Journal. 2022.
9. Biemans VBC, van der Woude CJ, Dijkstra G, van der Meulen-de Jong AE, Lowenberg M, de Boer NK, et al. Ustekinumab is associated with superior effectiveness outcomes compared to vedolizumab in Crohn's disease patients with prior failure to anti-TNF treatment. Aliment Pharmacol Ther. 2020;52(1):123–34. https://doi.org/10.1111/apt.15745
10. David R, Irene M, Severine V, Danese S, Kwok KK, et al. Worldwide post-marketing safety surveillance experience with tofacitinib in ulcerative colitis. Aliment Pharmacol Ther. 2021;55(3):302–10. https://doi.org/10.1111/apt.16619
11. Blonde L, Khunti K, Harris SB, Meizinger C, Skolnik NS. Interpretation and impact of real-world clinical data for the practicing clinician. Adv Ther. 2018;35(11):1763–74. https://doi.org/10.1007/s12325-018-0805-y