Journal of Crohn's and Colitis, 2022, **16**, ii1–ii2
https://doi.org/10.1093/ecco-jcc/jjab188
Editorial

Evolution of IL-23 Blockade in Inflammatory Bowel Disease

The hallmark of inflammatory bowel diseases [IBD] is chronic intestinal inflammation resulting in a pathological response in both the innate and the adaptive immune systems.[1] The pathogenesis of both Crohn's disease [CD] and ulcerative colitis [UC] is caused by the interplay of many factors including genetic susceptibility, the external environment, the commensal enteric flora, and immune system dysfunction.[2]

The diverse array of possible triggers and the complex immune response that results offers many therapeutics targets, which are reflected in the wide array of drugs for IBD that have been developed, are in development, or have failed to demonstrate efficacy.[3]

The most popular approach to IBD has been to target the surplus or excessive activity of the adaptive immune system, using biologic agents such as monoclonal antibodies against tumour necrosis factor-alpha [TNF-α] or interleukin [IL] 12/23.[3–6]

After anti TNF-α agents' approval [infliximab, adalimumab, certolizumab, and golimumab], the first anti-IL 12/23 ustekinumab has been developed and approved for patients with both moderate and severe CD and UC, providing not only an effective treatment but also a very safe therapeutic option.[7,8] However, it has been demonstrated by preclinical work that the therapeutic efficacy observed in dampening intestinal inflammation is mainly due to IL-23 rather than IL-12 blockade.[9] Consistently, the development of IL-12 antibodies was stopped in CD. Therefore new selective IL-23 inhibitors are under development for both forms of IBD[10] [Figure 1].

In this special issue of *JCC*, IL-23 will be reviewed in depth, particularly focusing on its key role in IBD pathogenesis and the strategic relevance for therapeutic intervention. In addition, besides the lessons learned by our colleagues in dermatology and their key experience gained as first users of IL-12/23 blockers, the emerging data regarding ustekinumab on the STARDUST and the SEAVUE trials will be summarised in order to better understand ustekinumab positioning in CD.

Furthermore, the evolving landscape of IL-23 blockers will be reviewed, including the new monoclonal antibodies under development and the first in class oral anti-IL23 small molecules.

Finally, the state of the art regarding biomarkers and potential personalised medicine applied to the future IL-23 blockers will be put into perspective.

In conclusion, it is an exciting time for our patient with CD and UC, because many drugs are likely to be successful and soon approved, blocking the IL-23 pathway in intestinal inflammation. A special effort on positioning and strategic trials should be made in order to understand proper timing and correct use in the IBD therapeutic armamentarium.

Funding

This paper was published as part of a supplement financially supported by AbbVie.

Conflict of Interest

Dr. Silvio Danese reports consultancy fees from AbbVie, Alimentiv, Allergan, Amgen, AstraZeneca, Athos Therapeutics, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Dr. Falk Pharma, Eli Lilly, Enthera, Ferring Pharmaceuticals Inc., Gilead, Hospira, Inotrem, Janssen,

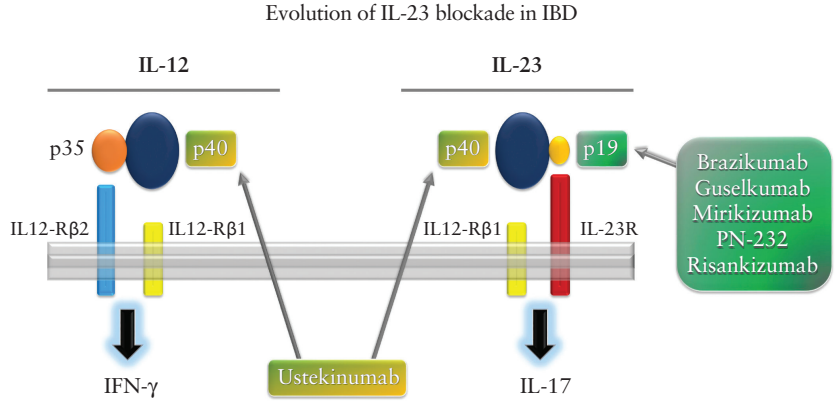

Figure 1. IL-12 and 23 share the same subunit p-40 that is blocked by ustekinumab, leading to both IL-12 and IL-23 inhibition. Brazikumab, guselkumab, mirikizumab, PN-232, and risankizumab selectively block IL-23 by inhibiting the p-19 subunit of IL-23.

Johnson & Johnson, MSD, Mundipharma, Mylan, Pfizer, Roche, Sandoz, Sublimity Therapeutics, Takeda, TiGenix, UCB Inc., and Vifor. Dr. Silvio Danese reports lecture fees from Abbvie, Amgen, Ferring Pharmaceuticals Inc., Gilead, Janssen, Mylan, Pfizer, Takeda.

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