Interleukine-23 as a pharmacological target in ulcerative colitis

Wilson C. Santos.[1,2]

[1] Programa de Pós-Graduação em Ciências Aplicadas a Produtos Para Saúde, Faculdade de Farmácia, Universidade Federal Fluminense, Brasil.

[2] Instituto Teófilo Hernando, Departamento de Farmacología y Terapéutica, Facultad de Medicina, Universidad Autónoma de Madrid, Spain.

The proinflammatory cytokine Interleukin-23 (IL-23) belongs to the IL-12 family, which is a unique family of cytokines that is comprised only by heterodimeric molecules. Such feature favours for a unique set of functional interactions not shared by other cytokine families (Fig.1). IL-23 is a 59 kDa heterodimer of IL-23p19 and IL-12p40 subunits. The p19 alone lacks any biological activity, but it combines with p40 to form biologically active IL-23. The IL-23 interacts with a receptor composed of the IL-12Rβ1 subunit and the IL-23-specific subunit IL-23R (Aminoff and Daroff, 2014).

The IL-12 and IL-23 (IL12/23) are proinflammatory cytokines that contribute to multiple aspects of human immunity. Preclinical data as well as clinical trials have demonstrated the relationship between IL-12, IL-23 and the generation of pathogenic T-Helper cells capable of generating tissue inflammation. The clinical evidences until now have set that IL-12p40 subunit is critical to some illnesses. As a matter of fact, Interleukine-23 is recognized to contribute for some autoimmune inflammatory diseases as for instance, psoriasis, inflammatory bowel diseases (IBD; such as ulcerative colitis – UC, and Crohn's disease - CD), rheumatoid arthritis, multiple sclerosis and tumor growth (Xiong *et al.*, 2022). Therefore, considering all the above quoted evidences, aiming at controlling the IL-12/23 signaling pathways is a pharmacological strategy for the development of a number of potential therapeutics.

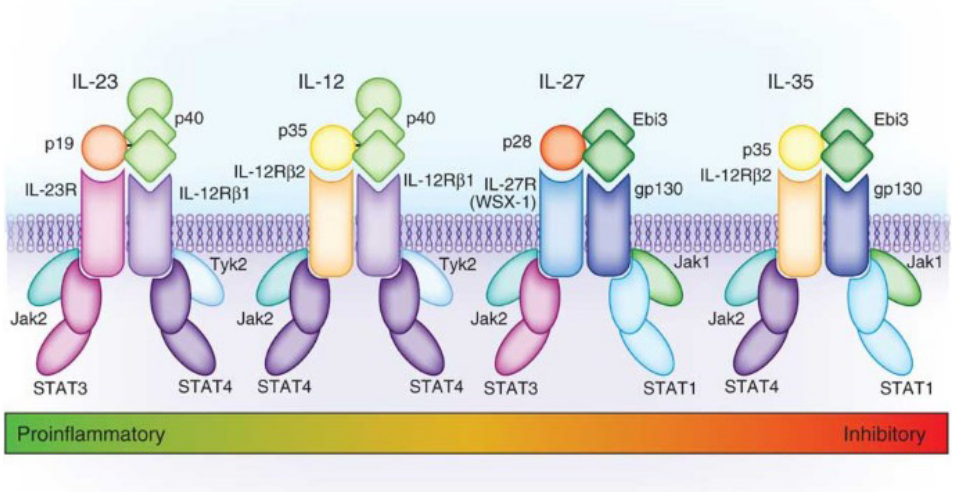

Figure 1: *Architecture of the IL-12 cytokine family. Members of the IL-12 family of cytokines are presented together with their receptors and Jak-STAT signaling partners. Key (bottom) indicates the functional spectrum of these cytokines, from most proinflammatory (IL-23) to most inhibitory (IL-35). Tyk2, kinase of the Jak family.*

Extract from: Vignali & Kuchroo, IL-12 family cytokines: immunological playmakers. https://doi.org/10.1038/ni.2366

ORCID: https://orcid.org/0000-0001-9971-094X

E-mail: wsantos@id.uff.br

Concerning to the disease UC, a considered body of evidences have pointed towards to a causal dysregulated immune response to gut microbiota in genetically prone individuals. Also, genetic studies have shown that polymorphisms of IL-23R are associated with CD and UC, and mutations of IL-23R are protective towards intestinal inflammation (Duer *et al.*, 2006). Still, increased levels of IL-23 and IL-17A were found in murine models of IBD, and confirmed in UC patients (Fujino *et al.*, 2003). Considering that, blockade of IL-23 and IL-17 might be an effective therapeutic strategy, given the role of these cytokines in the pathogenesis of IBD. Indeed, several agents specifically targeting IL-23 are currently under investigation for both CD and UC. For instance, Mirikizumab is a humanized IgG4-variant monoclonal antibody selectively targeting the IL-23 p19 subunit that has been approved by FDA for the treatment of moderately to severely active ulcerative colitis (UC) in adults. Mirikizumab binding to IL-23 p19 subunit prevents it from binding to the IL-23 receptor and inhibiting downstream release of proinflammatory cytokines and chemokines. It is the first selective IL-23 antagonist to be approved for UC (The Medical Letters, 2024). The efficacy of Mirikizumab in UC was assessed in the AMAC study, a randomized, double-blind, placebo-controlled phase 2 clinical trial, conducted in 14 countries between 2016 and 2017 (Sandborn *et al.*, 2020). Although several trials of Mirikizumab in UC have been ongoing in the last few years (Parigi *et al.*, 2022), the FDA approval was based on the results of two randomized, double blind trials: a 12-week induction trial (LUCENT I) and a subsequent 40-week maintenance trial (LUCENT II).

Briefly, the tests and trials were reported by The Medical Letters (2024) as:

> *"…In LUCENT I, 1062 patients with moderately to severely active UC who had an inadequate response to or could not tolerate at least one conventional drug, biologic drug, or JAK inhibitor received IV treatment with mirikizumab 300 mg or placebo at weeks 0, 4, and 8. The rate of clinical remission at week 12, the primary endpoint, was significantly higher with the active drug than with placebo (24% vs 15%; NNT ~11). Patients who received mirikizumab also had significantly higher rates of clinical response (65% vs 43%) and endoscopic improvement (34% vs 21%)."*

And:

> *"…In LUCENT II, 544 patients who had experienced a clinical response to mirikizumab in LUCENT I were rerandomized to receive SC injections of mirikizumab 200 mg or placebo once every 4 weeks. After 40 additional weeks (52 total weeks of treatment), the rate of clinical remission, the primary endpoint, was significantly higher with the active drug than with placebo (51% vs 27%; NNT ~4). Patients who received mirikizumab also had significantly higher rates of glucocorticoid-free clinical remission (50% vs 27%) and endoscopic improvement (58% vs 30%). "*

Mirikizumab showed a favourable safety profile in the phase 2 trials in both UC and CD. During the maintenance phase in UC, although treatment-emergent Adverse Events were observed in around 70% of patients the great majority were mild, such as nasopharyngitis, headache and arthralgia. Therefore, the FDA approval has recommended, concerning to adverse effects that:

> *"…Mirikizumab can increase the risk of infections. Injection-site reactions, arthralgia, rash, and headache can also occur. Serious hypersensitivity reactions, including anaphylaxis during IV infusion of the drug, and hepatotoxicity have been reported."*

Concerning to dosage and administration, the US agency has pointed out the following:

> *"…Mirikizumab is supplied in 300 mg/15 mL vials for IV induction and in 100 mg/1 mL prefilled pens for SC maintenance treatment. Before starting the drug, patients should receive all appropriate vaccinations and be evaluated for tuberculosis (TB) infection; those with latent TB should receive anti-TB therapy. Liver enzyme and bilirubin levels should be measured at baseline and monitored for at least 24 weeks of treatment. The recommended induction dosage of mirikizumab is 300 mg infused IV over at least 30 minutes at weeks 0, 4, and 8. For maintenance treatment, the recommended dosage is 200 mg (two injections) injected SC at week 12 and every 4 weeks thereafter. The injections should be given in separate locations in the abdomen, thigh, or the posterior upper arm; patients may self-inject after receiving training. Prefilled pens should be stored in the refrigerator; they should be left at room temperature for 30 minutes before injection".*

Taking the results of the quoted trials, one should consider that the interleukin (IL)-23 antagonist Mirikizumab is an effective option for induction and maintenance of clinical remission in adults with moderately to severely active ulcerative colitis. However, a critical point is that direct comparisons with other biologic drugs used for ulcerative colitis are lacking in the clinical tests. Nevertheless, monoclonal antibodies are not the only class of drugs targeting the IL-23 pathway under investigation. PTG-200, an orally administered peptide targeting IL-23R has shown encouraging results in animal models and healthy volunteers (Cheng *et al.*, 2019). Achieving positive results on it, might represent an expansion on the available drug for approaching some IBD's like UC and CD.

As a future perspective, Stankey *et al.* (2024) have recently described that the gene ETS2 is a central regulator of human inflammatory macrophages and delineate disease mechanism that amplifies ETS2 expression. Genes regulated by ETS2 were prominently expressed in diseased tissues with upregulation of multiple drug targets, including TNF and IL-23. Therefore, a plenty of drugs that might modulate this pathway and with anti-inflammatory activity might be identified in the near future with the application of functional genome studies.

REFERENCES

1. Vignali, D., Kuchroo, V. IL-12 family cytokines: immunological playmakers. Nat Immunol 13, 722–728 (2012). https://doi.org/10.1038/ni.2366
2. Aminoff M. J. and Daroff R. B. Encyclopedia of the Neurological Sciences, 2nd edition, 2014. ISBN 978-0-12-385158-1
3. Xiong DK, Shi X, Han MM, Zhang XM, Wu NN, Sheng XY, Wang JN. The regulatory mechanism and potential application of IL-23 in autoimmune diseases. Front Pharmacol. 2022; 13:982238. doi: 10.3389/fphar.2022.982238
4. Duerr RH, Taylor KD, Brant SR, *et al.* A genome-wide association study identifies IL-23R as an inflammatory bowel disease gene. Science 2006; 314: 1461–3. doi: 10.1126/science.1135245
5. Fujino S, Andoh A, Bamba S, *et al.* Increased expression of interleukin 17 in inflammatory bowel disease. Gut 2003;52:65–70. doi: 10.1136/gut.52.1.65
6. The Medical Letter on Drugs and Therapeutics, Volume 66 (Issue 1698), p46, 2024.
7. Sandborn WJ, Ferrante M, Bhandari BR, *et al.* Efficacy and safety of Mirikizumab in a randomized phase 2 study of patients with ulcerative colitis. Gastroenterology 2020; 158: 537–49.e10. doi: 10.1053/j.gastro.2019.08.043
8. Parigi, T. L., *et al.* Blockade of IL-23: What is in the Pipeline? J Crohns Colitis. 2022 Apr; 16(Suppl 2): ii64–ii72. doi: 10.1093/ecco-jcc/jjab185
9. Cheng X, Lee TY, Ledet G, *et al.* Safety, tolerability, and pharmacokinetics of PTG-200, an oral GI-restricted peptide antagonist of IL-23 receptor, in normal healthy volunteers. Am J Gastroenterol 2019; 114: S439
10. Stankey, C.T., Bourges, C., Haag, L.M. *et al.* A disease-associated gene desert directs macrophage inflammation through ETS2. Nature (2024). https://doi.org/10.1038/s41586-024-07501-1