

STATE OF ART TO THE MAIN CLINICAL OBJECTIVE:

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract affecting the predominantly young population. With their typical presentation between the ages of 20 and 40 and chronic, life-long character, rising incidence, they represent an important burden for the health care system worldwide. The etionathogenesis of the disease is not fully understood, but the concept of aberrant mucosal immune system reaction to intestinal luminal antigens is generally accepted. As such, IBD is considered to be part of the spectrum of autoimmune disorders and therefore the standard therapeutic approach is using immune suppressive drugs. In the last two decades, the therapeutic armamentarium used in the treatment of IBD has substantially increased. Conventional immune suppressive drugs such as systemic corticosteroids and thiopurines are used as first-line remission induction and maintenance. In patients with specific disease phenotypes and aggressive behaviour or patients failing on steroids and/or thiopurines, biologics with various mechanisms of action are used (Macaluso & Rodriguez-Lago, 2020). Biologics represent a great step forward in the treatment of IBD but approximately one-third of patients are primary non-responders to these therapeutics and subsequently, a significant proportion of patients lose their response over time. Hence, new therapeutic approaches are highly needed and one of the promising lines that has recently been approved for the treatment of IBD consists of agents blocking intracellular pathways involved in signalling of the proinflammatory cytokines. These so-called small molecules are acting through the inhibition of Janus kinases blocking thereby among others the signal of mostly all proinflammatory cytokines. Thus far, three drugs have been approved for the treatment of IBD from this therapeutic group, tofacitinib and filgotinib for the treatment of ulcerative colitis and upadacitinib for treatment of both conditions comprised by general term of IBD, ulcerative colitis and Crohn's disease (Soliotano et al., 2023)

Based on the results of registration trials, the recommended dose of JAKi differs in the induction period of treatment and the maintenance phase of treatment; the induction dose being double or triple of the maintenance dose. In the treatment of UC, the induction phase is 8 weeks for tofacitinib and upadacitinib and 10 weeks for filgotinib, with the recommendation to prolong the use of the higher induction dose during an additional 8 (tofacitinib and upadacitinib) or 12 weeks (filgotinib) (Herrera-deGuise et al., 2023). In CD, the higher induction dose is used for 12 weeks, with the recommendation to prolong the treatment with a higher dose for another 12 weeks if the response has not been reached. Thus, in daily practice, a substantial proportion of patients who do not respond to the treatment with JAKi remain treated for 4 up to 6 months. It is currently unclear what proportion of these patients are primary non-responders, i.e., they have adequate drug levels but there are other pathways involved in the immunopathogenesis that are not sufficiently influenced by JAKi. These patients would benefit from an early switch to another medication and could be identified early in the therapeutic process if the cut-off of drug levels associated with clinical and endoscopic response is known (Nash, P. et al. 2021).

On the other hand, the above-mentioned approach to treatment with JAKi involves the reduction of the dose to maintenance dose in case the patients respond to induction treatment. Data from real-world studies suggest that a substantial proportion of patients with initial response to induction dose relapse after the dose is reduced to a maintenance dose. Again, it is unclear whether this phenomenon has a clear dose-related pharmacokinetic background. If the cut-off levels associated with long-term response are known, the patients unsuitable for dose reduction in the maintenance phase could be detected and the treatment could be personalized accordingly (Spiewak & Patel, 2022).

In addition, JAKi exert a great interindividual variability concerning bioavailability. For example, the metabolism of tofacitinib has a great interindividual variation with 31.4% variability in clearance and is mediated by CYP3A4 and, to a lesser extent, by CYP2C19. In addition, in animal models, it has been shown that the pharmacokinetics of tofacitinib are strongly associated with the severity of intestinal inflammation and that the intestinal first-pass effect greatly influences the bioavailability of tofacitinib (Dowty et al., 2014). So far, it is unclear whether levels in peripheral blood, which is the gold standard of pharmacokinetics assessment, represent an accurate way to assess pharmacokinetics and whether not other

compartments, intestinal tissue, would not be more suitable to predict the response to the drug from pharmacokinetics point of view. Concluding, the bioavailability of JAKi is subject to important interindividual variation. Development and validation of laboratory methodology allowing for therapeutic drug monitoring to enter the clinical practice is crucial in the attempt to optimize the treatment of IBD .

Given the underlying mechanisms of interindividual variabilities in the bioavailability of JAKi, it is probable that these variabilities are prone to change over time, depending on the changes in inflammatory load, hepatic metabolism as well and co-medication. There is thus a need to establish the therapeutic drug monitoring protocol to be used to monitor the stability of the pharmacokinetics in the long term.

References:

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