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Editorial

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Tofacitinib De-escalation Strategy in Ulcerative Colitis: Is It the End of the Story?

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Therapeutic goals in inflammatory bowel disease [IBD] are evolving, and sustained steroid-free remission is now recognized as a target to reduce the burden of IBD.[1] Once remission has been achieved and sustained over time, the question of a de-escalation or withdrawal of treatment can be raised, either by physicians or by patients.

The main reason for a de-escalation of therapy is improvement of the risk–benefit profile of a given therapeutic strategy. Since tofacitinib was approved in ulcerative colitis [UC],[2] a dose-dependent increased risk for herpes zoster has been highlighted. Patients treated with 10 mg twice daily [BID] vs 5 mg BID showed an increased risk of this infection.[2,3] Pending the implementation of vaccination strategies into routine practice to prevent this risk, reducing the maintenance dose of tofacitinib could help reducing this risk.[4] Although the risk of venous thromboembolism [VTE] is still debated in UC patients, this might represent another reason to consider the use of the lowest approved dose in the long term.[5] Accordingly, the European Medicines Agency [EMA] recommended to use tofacitinib at the lowest dosage possible for patients who are at high risk of VTE or with cardiovascular risk factors.[6] Finally, such a strategy may be associated with reduced healthcare costs by using the cheapest dose.

The RIVETING study, by Vermeire *et al.*,[7] is a de-escalation trial in 140 patients from the ongoing OLE trial [OCTAVE Open; NCT01470612], treated by tofacitinib 10 mg BID for two or more consecutive years and in stable remission on that dose for ≥ 6 months. Remission was defined as a partial Mayo score ≤ 2 [without subscore > 1, and rectal bleeding subscore of 0], and an endoscopic assessment [with a confirmed Mayo endoscopic score of 0 or 1] was required in the 6 months prior to randomization. Patients were randomly assigned to continue 10 mg tofacitinib BID or to de-escalate to 5 mg BID. Vermeire *et al.*[7] reported safety and efficacy data of the first 6 months on a 42-month follow-up. The authors reported no difference between the two groups for the occurrence of adverse events and serious adverse events. However, herpes zoster cases were numerically higher in the 10 mg BID group [three vs one].[7] Only one case of VTE [one pulmonary embolism] was registered. Interestingly, the authors reported the first case of VTE in a patient without a medical history or risk factors for VTE, except a body mass index of 29.8 kg/m^2 and an age of 59 years.[7] Regarding efficacy, Vermeire *et al.*[7] demonstrated that most patients in stable remission on 10 mg tofacitinib BID maintained remission after dose de-escalation compared to patients who continued at 10 mg BID [77.1% vs 90.0%]. Their results are in line with current data in this field.[8,9] With regard to reducing therapy, it is essential to make a strict selection of patients eligible for such a strategy.[10] For patients treated with tofacitinib, it was demonstrated in a post-hoc analysis of the OLE trial that the maintenance of remission increased with the time spent in remission before de-escalation.[8] In the RIVETING trial, the authors reported better results for maintenance of remission in patient subgroups with a Mayo endoscopic score of 0 and without prior failure to anti-tumour necrosis factor alpha.[7] These findings emphasize the importance of selecting eligible patients for such an approach. However, remission was assessed at 6 months, which is slightly too short a time to draw definitive conclusions. The long-term data promise to be very interesting and informative.

The acceptability of patients is a key point in the discussion of a de-escalation or stopping treatment strategy. In a recent survey, 48–66% of patients were considering stopping combination therapy if recommended by their doctor.[11] A majority of patients would not accept a risk of relapse higher than 25% to be able to de-escalate therapy, and the proportion of time that patients were willing to accept having a flare ranged from none to more than 20% over a 2-year time frame.[11] The relapse risk and the success of dose escalation are the main concerns when de-escalating a drug. Interestingly, a recapture of clinical response after dose escalation with tofacitinib was achieved in about 60% of cases in recent studies.[9,12] The next step is to go beyond drug de-escalation and to consider drug withdrawal in IBD patients who have achieved deep and durable remission. Stopping drugs remains challenging with biologics due to their immunogenicity even though the STORI trial from the GETAID[13] and recent Italian experience showed that this is a feasible approach.[14]

Importantly, the efficacy of tofacitinib retreatment for UC after treatment interruption was recently assessed in the OCTAVE Open trial; a clinical response was recaptured in almost 70% of patients.[15] Similar to thiopurine, one key feature of tofacitinib is its lack of immunogenicity, probably explaining its good results after re-treatment.[15,16] Together with its oral administration, this makes tofacitinib an ideal candidate for an 'on–off' treatment based on intermittent administration. More data from studies assessing de-escalation or stopping strategies with tofacitinib, such as the RIVETING trial, are needed before implementing this strategy in routine practice. Whether the 'start and stop' strategies with small molecules such as JAK inhibitors could be become the new standard in the coming years will require further investigation in terms of long-term efficacy [disease relapse and disease modification] and safety [malignancy and infectious risks].

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Author Contributions

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