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Letter: choosing between ustekinumab and vedolizumab in anti-TNF refractory Crohn's disease - *the devil is in the detail*

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Editors,

We read the study by Alric *et al* with great interest.[1] There are few large-scale 'real-world' studies examining head-to-head clinical outcomes of second- or third-line biologic choices. Hence the reimbursement environment between May 2014 and August 2018 in France presented a unique opportunity to study the relative effectiveness of vedolizumab and ustekinumab across a Crohn's disease (CD) patient cohort refractory to adalimumab and/or infliximab.

Ustekinumab was found to be associated with higher rates of treatment persistence and clinical remission in patients with anti-TNF refractory CD, particularly amongst those with ileal and penetrating disease. While no differences in the rates of clinical remission or steroid-free clinical remission were found across either cohort at week 14 in the intention-to-treat weighted analysis, there were higher rates of clinical remission in the ustekinumab group at week 48. It is important to

consider factors that may have contributed towards differences in remission rates between these timepoints. We note that a higher proportion of vedolizumab (42.4%) treated patients were on combination therapy at biologic initiation compared to ustekinumab (23.4%), and note that combination therapy at biologic initiation was positively associated with clinical remission at week 48 on multivariate analysis. Therefore, it would be interesting to assess whether cessation of immunomodulator co-therapy between week 14 and week 48, particularly within the vedolizumab cohort, may have contributed to this difference. Moreover, it would also be helpful to understand factors that influenced treatment persistence versus treatment failure between week 14 and 48, to help identify predictors of therapeutic success or failure at week 48.

We also note that there was a higher proportion of perianal disease across the vedolizumab (51.5%) relative to the ustekinumab (44.9%) cohort, perhaps suggestive of a more refractory patient cohort. However, we appreciate that there were no differences between both cohorts after propensity scoring with inverse probability of treatment weighting.

Nevertheless, it remains important to clarify whether biologic therapy was initiated to treat predominantly perianal or luminal disease to accurately interpret this study's findings for several reasons. Firstly, the Harvey Bradshaw Index was not designed to assess clinical remission outcomes of predominantly perianal rather than luminal CD. Secondly, the recent study by the GETAID BioLAP Study Group demonstrated low rates of response to vedolizumab in patients with active perianal Crohn's disease, with nearly one third of patients with inactive perianal Crohn's disease experiencing perianal recurrence.[2] Conversely, preliminary data presented by the same group suggested that ustekinumab is potentially effective in perianal CD.[3] Hence it is difficult to ascertain whether the effectiveness of ustekinumab and/or ineffectiveness of vedolizumab in perianal disease might have impacted the study's findings; highlighting the importance of distinguishing outcomes between disease phenotypes such as perianal CD. Finally, it was uncertain whether vedolizumab or ustekinumab dose optimisation was more frequently undertaken amongst patients with perianal CD.

We look forward to similar head-to-head biologic studies in inflammatory bowel disease that can assist clinicians with complex therapeutic decision-making with respect to suitability and sequence of biologic therapies.

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