

Editor in Chief
Alimentary Pharmacology & Therapeutics

Dear Editor

Editorial: gut selective immunosuppression - is it a double edged sword? - authors' reply

The Editorial on the safety of vedolizumab by Sheridan and Doherty [1] in response to our safety review [2] is thoughtful and well balanced, but there are post-marketing data on malignancy after >25000 patient-years of experience with vedolizumab that they do not mention [3].

Post-marketing surveillance data should be interpreted with caution. Nevertheless, the tendency to under-report malignancy in patients exposed to novel therapy is likely to be lower than for other adverse events. The study on 25831 patient-years of post-marketing exposure to vedolizumab reported 25 malignancies [3]. Half (12/25) were gastrointestinal and 7 colorectal (including one adenoma), which is about what one would expect in such a large cohort [4,5]. Where reported, vedolizumab exposure was of short duration (≤ 6 months' treatment, or after ≤ 7 infusions at the time of malignancy diagnosis). Confounding factors included prior use of immunosuppressants including anti-tumour necrosis factor therapy, smoking history and previous malignancy prior to initiating treatment with vedolizumab.

Although $\alpha 4\beta 7$ inhibition may affect intestinal NK cell activity, the authors haven't elaborated on what pro-malignant 'theoretical concerns' that they vaguely intimate are at play. There is no biologically plausible carcinogenic pathway that would be specifically activated by $\alpha 4\beta 7$ inhibition. Thus vedolizumab is unlikely to have any greater effect on the development of dysplasia than other immune modulators. The frequencies of dysplasia in the trials and post-marketing data are within the bounds of what one would expect in longstanding IBD. It is conceivable that there is a minimum exposure time per patient to identify any risk. Only time will tell. Meanwhile watchfulness rather than concern about the potential for vedolizumab to increase the risk of gastrointestinal malignancy is appropriate.

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[words: 452; refs: 5]

References

1. Sheridan J, Doherty GA. Gut selective immunosuppression: is it a double-edged sword? *Alimet Pharmacol Ther* 2017;xx:yyy-zzz.
2. Bye WA, Jairath V, Travis SPL. Systematic review: Safety of vedolizumab for the treatment of inflammatory bowel disease. *Alimet Pharmacol Ther* 2017;doi. 10.1111/apt.14075
3. Bhayat F, Blake A. Post-marketing safety experience with vedolizumab: Malignancy. *Am J Gastroenterol* 2016;111:S260-S335
4. Madanchi M, Zeitz J, Barthel C, Samaras P, Scharl S, Sulz MC, Biedermann L, Frei P, Vavricka SR, Rogler G, Scharl M. Malignancies in patients with inflammatory bowel disease: A single-centre experience. *Digestion* 2016;94:1-8.

5. Bernstein CN, Blanchard JF, Kliewer E, Wajda A. Cancer risk in patients with inflammatory bowel disease: a population-based study. *Cancer* 2001;91:854-62.

The authors' declarations of personal and financial interests are unchanged from those in the original article [2].

Acknowledgements: Thanks to Professor Simon Leedham, Wellcome Trust Centre for Human Genetics and Translational Gastroenterology Unit, Oxford, for informal discussion.