

LETTER TO THE EDITOR

Combination of vedolizumab and immunomodulators in ulcerative colitis

To the Editor,

Naganuma *et al.*¹ have recently published the results of a post hoc analysis about the potential benefit of immunomodulators over vedolizumab monotherapy for maintenance, but not induction, of remission in Japanese patients with moderate to severe ulcerative colitis (UC).

These results appear to be original and uncommon.

The combination therapy of vedolizumab with an immunomodulator was not associated with better clinical or endoscopic outcomes whether in induction or maintenance in a meta-analysis from Yzet *et al.*² Results from the GEMINI 1 study, whether in the global population or the Asian countries population, did not suggest any favorable benefit, neither in induction nor in maintenance.^{3–5} A study examining the real-world effectiveness of vedolizumab in Korean patients with UC found no benefit in the combination at week 14 but does not include any long-term data.⁶ The American Gastroenterological Association guidelines state that the combined therapy over vedolizumab monotherapy for induction or maintenance of remission is uncertain with a very low-quality evidence.⁷

Naganuma *et al.* have lengthily detailed and discussed their results. It might have been nevertheless of interest to evaluate the combination in conjunction to the exposure or not to steroids, as well as the clinical efficacy kinetic of vedolizumab. Did some of the patients not or poorly initially responding to vedolizumab benefit from the combination to gain efficacy and when? Did some patients with a loss of response (LOR) regain efficacy with the immunomodulators? Increased vedolizumab dosing frequency from every 8 weeks to every 4 weeks for the UC patients with a LOR is not approved yet in Japan, a study (NCT 04738942) is ongoing. Would a combination of vedolizumab and immunomodulators be an alternative?

Ethnicity is of no impact on vedolizumab clinical and pharmacokinetic profiles. Data from GEMINI 1 post hoc analysis have shown widely consistent efficacy and safety of vedolizumab in Asian countries with that of overall study population.^{3,4} Pharmacokinetic profile of vedolizumab was found to be similar between Asians and non-Asians, supporting a flat fixed dose in Asian patients, including Japanese ones.⁸

A consistent difference in extension between patients of different races or ethnicities with UC has not been elicited but tends to exist when considering severity.^{9,10} A difference in genetic factors exists, between Caucasians and Asians, and amongst Asians, in UC. Patients' characteristics of the patients from Naganuma *et al.* present a more severe inflammatory phenotype than those from Feagan *et al.* In such population, notably in the patients who initially slowly or less response to vedolizumab, immunomodulators might have then favored the innate and adaptive immune benefit of vedolizumab.¹¹ Manzini *et al.*¹² have

shown that, in acute colitis NOD-SCID-SGM3 mice humanized with CD34+ cells, the combination of vedolizumab with tacrolimus was more efficient to reduce the immune cell numbers and to increase the therapeutic efficacy than vedolizumab alone.

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[Correction added on 20 December 2021, after first online publication: The copyright line was changed.]