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Commentary

TREM1 predicts response to anti-tumor necrosis factor in inflammatory bowel diseases: Towards precision medicine

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Several biological agents are currently approved for the treatment of inflammatory bowel diseases (IBD), such as anti-tumor necrosis factor (TNF) alpha (infliximab, adalimumab, golimumab only for ulcerative colitis -UC-), gut-selective anti-integrin (vedolizumab) and anti-IL12/23 (ustekinumab only for Crohn's disease -CD-). However, patients may not respond or they may lose clinical benefit over time to these drugs and then need to be switched to another agent, with consequent uncontrolled disease, poor quality of life and high health-related costs. Moreover, the possibility to obtain clinical and endoscopic benefit from a treatment seems to decrease in non-biologic naïve patients [1]. Therefore, the identification of non-invasive predictors of response would significantly help to tailor the therapeutic strategy to each patient. A significant amount of scientific data has been published so far at this regard, but their application in clinical practice is still lacking. For example, longer disease duration, stricturing behavior, history of previous intestinal resection, active smoking and low body mass index (BMI) were identified as risk factors for inadequate response to anti-TNFs in CD patients [2–4]. A Matrix-based model was developed by Billiet et al., showing that the combination of three independent predictive factors (age > 65 years, BMI < 18.5 and previous surgery) was able to predict a rate of 53% of primary non-response to infliximab [5]. However, none of these clinical characteristics absolutely contraindicates the use of anti-TNFs in clinical practice and no specific data are available about their possible effects on clinical response to other biological agents, such as vedolizumab and ustekinumab. The importance of serological biomarkers in this context is still controversial. For example, most of the studies investigating the role of C-reactive protein (CRP) showed that higher values at baseline predict better outcomes in CD patients treated with infliximab, whereas opposite results (lower CRP values for higher response rates) were found in CD candidates to vedolizumab [6]. In a small cohort of patients treated with vedolizumab, higher levels of interleukin-6 were found in non-responders to therapy; also, lower osteocalcin and increased soluble CD40-ligand were associated with poor outcomes in UC and CD patients, respectively [7]. However, despite the interesting prompts emerged during the last years, the need for validated, non-invasive, biologic-specific and easily reproducible predictors of therapeutic benefit transposed into clinical practice is still unmet.

In this regard, the study recently published by Verstockt et al. [8] in *EBioMedicine* offers an important contribution. Baseline TREM1 (Triggering Receptor Expressed on Myeloid cells 1) was found to be significantly reduced in IBD patients who achieved mucosal healing following induction with anti-TNF (infliximab and adalimumab) therapy in comparison with those who did not achieve it ($p < .001$). First, the gene expression of TREM1 in whole blood was analyzed by qPCR, using all available TREM1 transcripts; then, TREM1 was also quantified through RNA-seq in baseline mucosal tissue and as protein level in the serum by ELISA: all experiments led to the same results [8]. The authors also proposed a possible pathophysiologic mechanism to support these findings: in particular, they hypothesized that low TREM1 expression may be associated with a strengthened autophagy pathway and with a consequent reinforcement of anti-TNF response [8]. Such hypothesis was based on recent animal models of colitis in TREM1 knock-out mice, which showed a significant decrease of inflammatory activity at clinical, endoscopic and histological levels [9]. Interestingly, Verstockt et al. compared TREM1 expression also in patients treated with vedolizumab or ustekinumab, without finding any significant difference between endoscopic responders and non-responders and therefore leading to the conclusion that TREM1 may represent a predictor of response specifically to anti-TNF agents. This is exactly what we need in daily clinical practice: a highly specific, non-invasive and easily analyzable predictor of clinical benefit to tailor therapeutic decisions to each patient.

However, despite these very useful results, the study by Verstockt and coauthors [8] also has some limitations: first of all, the number of patients included in the analysis is low (54 IBD patients receiving anti-TNFs, 51 treated with vedolizumab and 22 CD subjects with ustekinumab) and endoscopic remission was evaluated only in the short-term (after a median of 27.1 weeks in CD and 8.4 week in UC). Also, a table with comparison of clinical, laboratory and endoscopic baseline characteristics between responders and non-responders to anti-TNFs is not showed, therefore it is not possible to rule out that TREM1 different expression is depending on any further factor. Moreover, a recent study showed opposite results (low whole blood TREM1 expression associated with better clinical response), although patients included were even fewer (5 non-responders and 17 responders) and only infliximab was considered among biological agents [10].

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In conclusion, Verstockt et al. added a significant contribution to the search of predictors of response to specific biological agents, however future studies including a greater number of patients and evaluating also long-term outcomes are urgently required before any application of these results into daily clinical practice.

Disclosure

The authors declared no conflicts of interest.

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