EDITORIAL

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Immunephenotype Predicts Response to Vedolizumab: Integrating Clinical and Biochemical Biomarkers in the Treatment of Inflammatory Bowel Diseases

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In the past decades, biological agents (engineered monoclonal antibodies [mAbs]) have emerged as essential therapy for moderate-to-severe inflammatory bowel disease (IBD). More recently, the mAb tumor necrosis factor-α antagonists (anti-TNFα), infliximab, adalimumab, golimumab, and certolizumab pegol have been supplemented by newer clinically approved biological agents that target different inflammatory pathways. Vedolizumab is a humanized mAb and the first in class of selective anti-α4β7 integrin that has gained approval for the treatment of moderate-to-severe IBD in adult patients who fail to respond to, lose response to, or are intolerant to conventional therapies (corticosteroids and immunomodulators) or to TNFα mAbs [1]. Natalizumab is another anti-α4 mAb that in contrast to vedolizumab binds both the α4β7 and-α4β1 heterodimers and is therefore less selective. The α4β7 integrin an adhesion molecule expressed on a variety of circulating leukocytes, including cluster of differentiation (CD)4+ and CD8+ naive T cells, CD4+ and CD8+ memory T cells, B cells, eosinophils, natural killer (NK) cells, that is essential for the migration these cells from the systemic circulation to the inflamed intestine. The counterpart of α4β7 integrin is primarily, but not exclusively, represented by the mucosal addressin cell adhesion molecule-1 (MAdCAM-1), whose expression is abundant in intestinal endothelial cells (Fig. 1a, b). Because the α4β7–MAdCAM-1 interaction is highly restricted to the intestine, vedolizumab appears to selectively target recruitment of inflammatory cells to the gastrointestinal tract. The success of vedolizumab in treating IBD has facilitated the development of additional treatments that target the β7 integrin (etrolizumab) or MAdCAM-1 (PF-00547659).
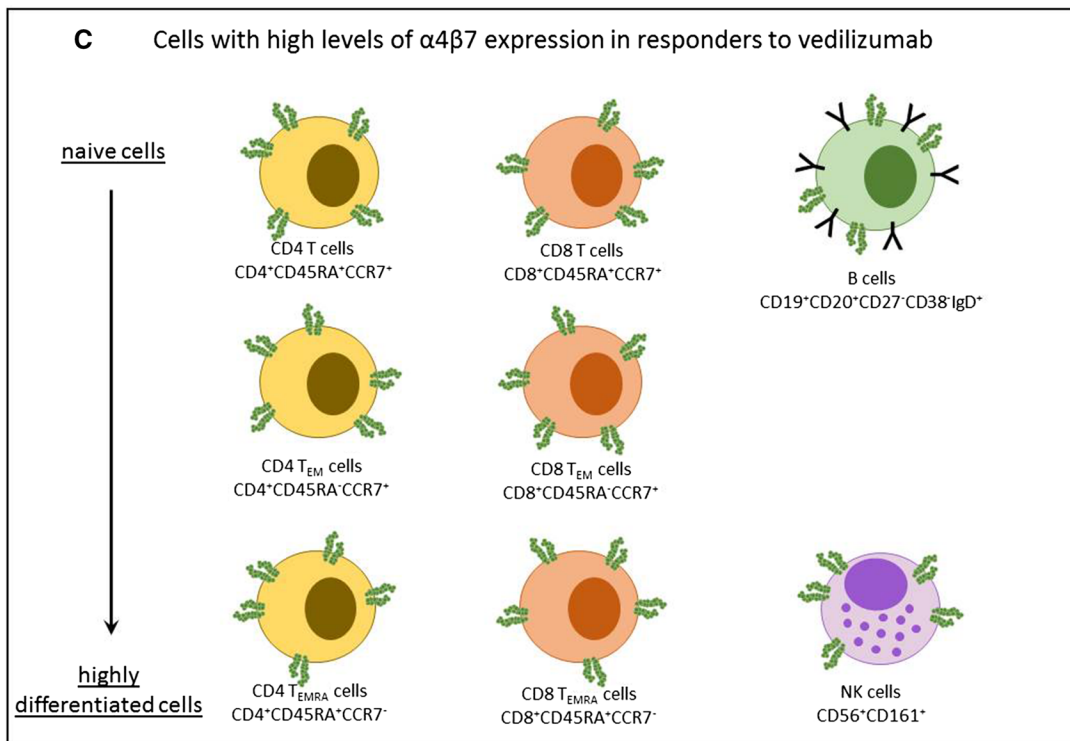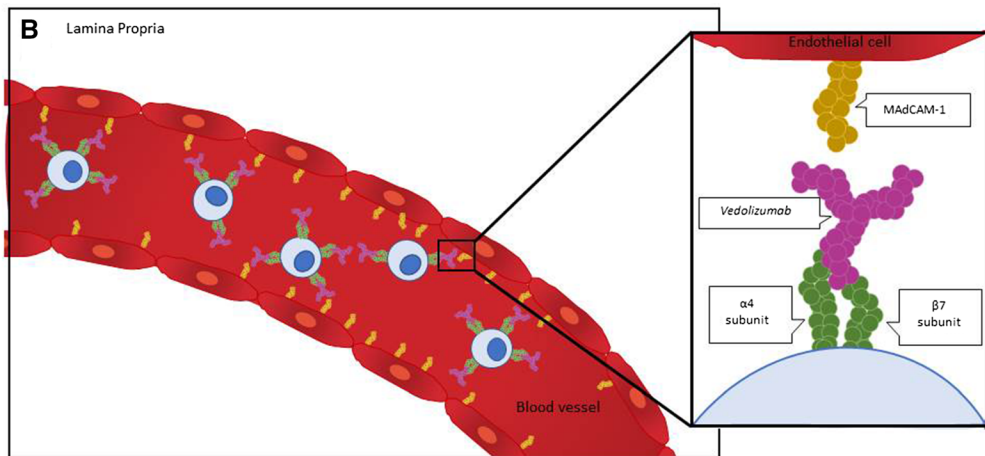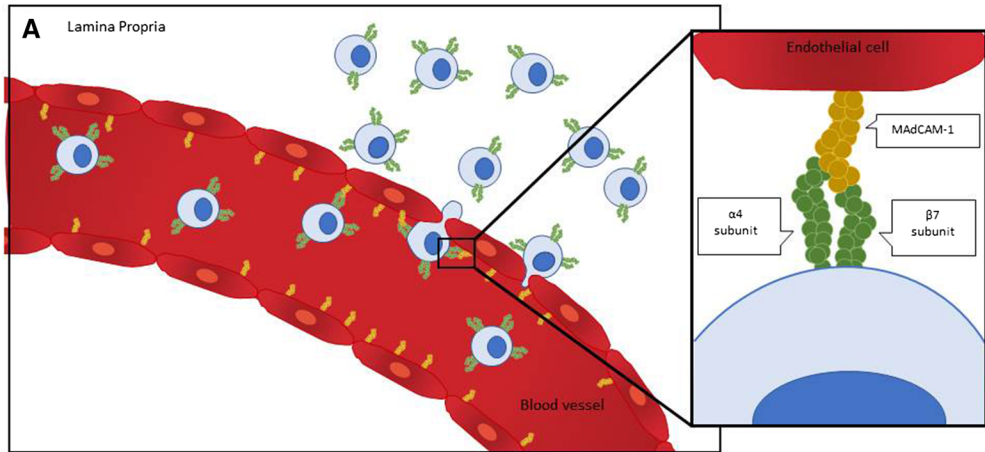
In preclinical models, vedolizumab effectively reduced leukocyte trafficking toward the intestine, thus reducing inflammation and immune dysfunction. These findings were confirmed by results of Phase III trials, in which the anti-α4β7 antagonist successfully induced and maintained remission in patients with Crohn's disease (CD) and ulcerative colitis (UC) [2–4]. Nevertheless, similar to anti-TNFα agents, a significant proportion of patients (≈40%) failed to reach or to maintain remission in response to vedolizumab. In real-word cohorts, the primary response rate to vedolizumab is effectively similar in UC and CD patients, 40–60% of patients [5, 6]. Lack of response or need for dose optimization occurs in 40–60% of IBD patients during the maintenance phase [7, 8]. Due to the above factors, the place of vedolizumab in the management of IBD remains unclear, particularly taking into account the utility of anti-integrin therapy in the context of currently available biological therapies. In patients with less severe disease, as assessed by clinical and biochemical markers and naïve to anti-TNFα therapy, those with higher circulating concentrations of vedolizumab at induction are more likely to respond to treatment. The severity of disease at baseline is a robust predictor of response to vedolizumab in both UC and CD patients. Thus, while a higher response rate was observed in patients with a baseline Mayo score < 9 and Crohn's disease activity index (CDAI) score ≤ 330 at 6 and 54 weeks [2, 3], others have reported a less favorable outcome in patients with Harvey–Bradshaw index (HBI) score > 10 and/or a Mayo score > 9 at 54 weeks [7]. Additionally, a history of smoking and active perianal disease were inverse predictors for clinical remission during maintenance therapy [8]. Further on, patients with severe systemic and bowel inflammation, as measured by higher concentrations of the nonspecific inflammatory biomarkers C-reactive protein (C-RP), leukocytosis, and fecal calprotectin are less likely to reach a

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A Lamina Propria

Endothelial cell

MAdCAM-1

α4 subunit

β7 subunit

Blood vessel

B Lamina Propria

Endothelial cell

MAdCAM-1

Vedolizumab

α4 subunit

β7 subunit

Blood vessel

C Cells with high levels of α4β7 expression in responders to vedilizumab

naive cells

CD4 T cells
CD4$^+$CD45RA$^+$CCR7$^+$

CD8 T cells
CD8$^+$CD45RA$^+$CCR7$^+$

B cells
CD19$^+$CD20$^+$CD27$^-$CD38$^-$IgD$^+$

CD4 T$_{EM}$ cells
CD4$^+$CD45RA$^-$CCR7$^+$

CD8 T$_{EM}$ cells
CD8$^+$CD45RA$^-$CCR7$^+$

highly differentiated cells

CD4 T$_{EMRA}$ cells
CD4$^+$CD45RA$^+$CCR7$^-$

CD8 T$_{EMRA}$ cells
CD8$^+$CD45RA$^+$CCR7$^-$

NK cells
CD56$^+$CD161$^+$

◄Fig. 1 Role of α4β7 integrin in the regulation of leukocyte trafficking in the intestine and identification of markers predictive of outcome. **a** Interaction between α4β7 and MAdCAM-1 at the endothelial interface in the intestine. **b** Mechanism of action of vedolizumab. **c** Immunephenotype of IBD patients responders to vedolizumab (from ref. [13]) . High expression of α4β7 in peripheral blood mononuclear cell subsets (memory T cells, T_{EMRA}, and NK cells) at baseline predicts response to vedolizumab

clinical response or to maintain remission when treated with vedolizumab [9, 10]. Elevated C-RP at initiation is also associated with a higher probability of vedolizumab discontinuation due to lack or loss of response.

Additional outcome indicators in CD patients appear to be gender, age, and disease duration, with male, younger patients (age < 35 years), and patients with shorter disease duration (< 7 years) having superior response rates. Other factors that predict a favorable outcome are no use of anti-TNF prior to starting vedolizumab [2, 3] since the probability of a favorable clinical response is significantly greater in patients naïve of biological agents and with early response to treatment [7]. In contrast, predictors of lower rates of response to vedolizumab are the need for steroid co-medication to achieve remission or the need for immunosuppressants to maintain remission [11]. Nonetheless, the question of whether to add or continue thiopurines in combination with vedolizumab remains unclear. Finally, there is evidence that pharmacokinetic factors contribute to the clinical response. Higher vedolizumab concentrations at induction are associated with higher clinical remission rates [12]. It has been suggested that low serum albumin concentrations and high body weight might have a negative impact on vedolizumab pharmacokinetics [11].

While all the above data emphasize general factors that might predict the outcome of a favorable clinical response to vedolizumab, it is unclear whether the immunophenotype of IBD patients prior or during the treatment with anti-α4β7 can predict the outcome. In this issue of *Digestive Diseases and Sciences*, Dr. Boken et al. [13] report on one of the first attempt to study α4β7 expressed on peripheral blood mononuclear cells (PMBC) as a predictor of clinical outcome in IBD patients receiving vedolizumab. The study included 26 subjects (15 with CD, 11 with UC or indeterminate colitis). All subjects but three were anti-TNF experienced. Response, defined by endoscopic (HBI score) or clinical criteria, was achieved in 14 subjects. Nonresponse (12 subjects) was determined by failure to wean steroids in six and a lack of endoscopic improvement in the other six subjects. All non-responders had follow-up evaluations between 90 and 180 days after vedolizumab induction that failed to meet criteria for response.

Blood samples were collected before and through the study, and expression of α4β7 on several PMBC subsets was measured by flow cytometry. The authors identified several candidate biomarkers that were linked to clinical outcome (Fig. 1c). In general, pretreatment α4β7 expression on multiple T, B, and NK subsets was higher in responders than non-responders to vedolizumab. More specifically, a significantly higher *per cell* expression of α4β7 on naïve CD4 and CD8 T cells (CD45RA+CCR7+) and B cells (CD19+CD20+CD27−CD38−IgD+) was predictive of a superior response. Patients who responded to vedolizumab also had a higher percentage of α4β7-expressing CD4 and CD8 effector memory T (T_{MEM}) cells, and a subset of highly differentiated effector CD4 and CD8 T cells, called the terminal effector memory (T_{EMRA}) T cells (CD45RA+CCR7−), showed an even more significant difference in percentage of α4β7 expression at baseline between responders and non-responders (Fig. 1c). Furthermore, the percentage of NK cells (CD56+CD161+) expressing α4β7 prior to treatment with vedolizumab was significantly higher in responders compared to non-responders. The authors concluded that the amount of α4β7 expression on T_{EMRA} and NK cells at baseline provided the best discrimination between responders and non-responders to vedolizumab. Moreover, both serum vedolizumab concentrations and α4β7 receptor saturation at trough were associated with response to therapy before and during vedolizumab therapy. Interestingly, serum vedolizumab concentrations declined more rapidly in non-responders than in responders to vedolizumab, indicating that α4β7 receptors in non-responders were less saturated at vedolizumab concentrations that saturated the receptors in responders. Taken together, these findings suggest that non-responders have either a higher rate of T cell turnover from the bone marrow or increased α4β7 turnover, perhaps via differences in integrin internalization and intracellular trafficking.

Should these results inform prescribing practices for vedolizumab in real-world patients? In other words, should the PMBC of patients for whom vedolizumab therapy is planned be tested for expression of α4β7? The answer at this stage is likely negative. Indeed, the study needs to be taken in an appropriate context: First, the cohort is small, with only 26 patients included and the two arms consist of only 14 and 12 subjects; second, since almost all subjects were anti-TNF experienced, the authors' findings might not generalize to TNF-naïve patients; third, no attempt was made to correlate α4β7 expression on leukocyte subsets with validated clinical response biomarkers such as C-RP, leukocytosis, or fecal calprotectin; and fourth, the blood samples were not collected at standard times, which in clinical trials is generally considered a measure of quality of data.

Even though the study needs further validation in larger cohorts, it provides novel insights that could be taken into account to further define the best personalized approach to target inflammation and immune dysfunction in IBD patients.

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