α4β7 integrin-dependent adhesion of T cells to MAdCAM-1 is blocked by vedolizumab in patients with chronic refractory pouchitis

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Abstract

Background: The anti-α4β7 integrin antibody vedolizumab is an established therapeutic option for the treatment of inflammatory bowel disease (IBD). It has also been successfully used in patients with chronic antibiotic-refractory pouchitis following proctocolectomy with ileal pouch-anal anastomosis. However, the expression and function of gut-homing markers as well as strategies to predict the response to vedolizumab in pouchitis are understudied so far.

Methods: We used flow cytometry and dynamic adhesion assays to study the expression and function of gut-homing integrins on T cells from patients with pouchitis and controls as well as longitudinally during therapy of pouchitis with vedolizumab. Moreover, we describe clinical effects of vedolizumab in a cohort of patients with pouchitis.

Results: T cells from patients with pouchitis express a specific profile of gut-homing integrins. Integrin α4β7 on T cells from patients with pouchitis mediates adhesion to mucosal addressin cell adhesion molecule (MAdCAM)-1, which can be blocked by vedolizumab in vitro. Vedolizumab efficiently treats pouchitis in a portion of patients and response correlates with dynamic adhesion profiles to MAdCAM-1.

Conclusion: Our data suggest that T cell trafficking seems to be important for the pathogenesis of pouchitis and support the therapeutic use of vedolizumab. Integrin function might serve as a biomarker to predict response to vedolizumab.

Keywords: ileal pouch-anal anastomosis, pouchitis, proctocolectomy, T cells trafficking, vedolizumab

Received: 11 June 2021; revised manuscript accepted: 4 October 2021.

Introduction

An increasing armamentarium of therapeutic options is available for the treatment of inflammatory bowel diseases (IBD) with its main entities Crohn’s disease (CD) and ulcerative colitis (UC).1 However, a subgroup of patients still requires restorative proctocolectomy due to refractory disease or (pre-)malignant conditions. This predominantly concerns patients with UC, in which proctocolectomy is considered a curative therapy. Although the colectomy rates have somewhat decreased in the era of biologics,2 still up to 10% of the patients with UC need to undergo the procedure within 10 years from diagnosis. Particularly, in patients with fulminant disease, colectomy rates continue to reach 30%.3

An ileal pouch-anal anastomosis (IPAA) is usually performed following proctocolectomy to create a reservoir to increase the patients’ quality of life by limiting the number of bowel movements. However, at least 50% of the patients subsequently develop at least one episode of inflammation of the pouch, also called pouchitis.4 Around
15% of the patients with previous UC suffer from chronic pouchitis after proctocolectomy with IPAA, which is characterized by continuous or relapsing signs of inflammation, such as an increased frequency of bowel movements, bloody or mucous rectal discharge and pain.

The pathogenesis of pouchitis is not fully understood, but probably multifactorial. Since the ileal mucosa undergoes morphological changes including an increase of crypt depth and a reduction of villus height that is sometimes referred to as ‘colonic metaplasia’, a recurrence of UC in the ileal pouch has been suggested. Moreover, the microbiome of the previous ileum switches towards a more colon-like phenotype in the ileal pouch after proctocolectomy. Together with the high response rates to antibiotic therapy, this drives the hypothesis that dysbiosis is a key element of pouchitis pathogenesis. Similar to other IBDs, there are also several genetic polymorphisms in susceptibility loci that have been described to associate with an increased risk for the development of pouchitis.

While antibiotics such as ciprofloxacin or metronidazole are the first-line agents for the treatment of acute pouchitis, antibiotic combination therapy and immune-modulating drugs can be considered in chronic pouchitis. Specifically, oral corticosteroids, topical tacrolimus and the anti-TNF-α antibodies infliximab and adalimumab are recommended options in antibiotic-refractory patients, but are not effective in all of them. Yet, novel biologic therapies such as the anti-α4β7 integrin antibody vedolizumab have been introduced for the therapy of IBD in recent years and might therefore be alternatives for the treatment of pouchitis. Vedolizumab blocks the α4β7-dependent extravasation process of circulating gut-homing T lymphocytes to the intestine via mucosal addressin cell adhesion molecule (MAdCAM)-1 expressed on the intestinal endothelium. Since chronic pouchitis is characterized by the infiltration of granulocytes and also lymphocytes to the ileal pouch mucosa, it seems natural to consider vedolizumab in pouchitis. Indeed, several cohort studies suggested that vedolizumab is effective for this indication.

However, studies on the expression and function of gut homing markers such as α4β7 integrin in chronic pouchitis as well as strategies to predict the success of vedolizumab are completely lacking so far. Here, we analysed the expression of integrins on T cells from patients with chronic pouchitis and assessed their dynamic adhesion to MAdCAM-1. We report the efficacy of vedolizumab in a cohort of patients with chronic pouchitis and show that response to vedolizumab seems to associate with integrin function, which might be used to predict outcomes.

Methods

Patients and samples

We collected peripheral blood from adult patients with chronic antibiotic-refractory pouchitis (as evidenced by clinical, endoscopic and histologic assessment) following proctocolectomy with IPAA for UC (n = 17), from patients with active UC (n = 10) and from healthy controls (n = 9); 65% of the patients with pouchitis and 40% of the patients with active UC had previously received anti-TNF therapy. The patients were recruited at the IBD Outpatient Clinic of the Department of Medicine 1 of the University Hospital Erlangen. From 10/2015 to 08/2021, eleven patients with chronic pouchitis were treated with vedolizumab at our centre. In some of them, we also collected blood samples directly before the initiation of therapy with vedolizumab and after 6 weeks of treatment in addition to prospective assessment of symptoms and clinical condition. Blood was obtained following informed written consent and according to the approval of the Ethics Committee of the Friedrich-Alexander-University Erlangen-Nürnberg.

Clinical, endoscopic and histologic assessments were performed as part of routine clinical care according to the criteria of the pouchitis disease activity index (PDAI). Vedolizumab therapy was applied according to standard clinical protocols. The reporting of this study conforms to the STROBE statement. The STROBE checklist is available as Supplementary Table (Suppl. Table 1).

Table 1 summarizes the donors’ baseline characteristics.

Flow cytometry

For the analysis of α4β1, α4β7, αLβ2 and αMβ2 expression on CD3+, CD4+ and CD8+ T cells from the peripheral blood, peripheral blood mononuclear cells (PBMCs) were isolated by
standard density gradient centrifugation with Lymphocyte Separation Medium (Anprotec). Subsequently, they were stained with antibodies against CD3 (VioGreen, REA613; Miltenyi), CD4 (FITC, VIT4; Miltenyi), CD8 (PerCP/Cy5.5, RPA-T8; Biolegend), Integrin α4 (VioBlue, MZ18-24A9; Miltenyi), Integrin β7 (PE, FIB27; Biolegend), Integrin β1 (Alexa Fluor® 647, TS2/16; Biolegend), Integrin α2 (PE-Vio770, REA188; Miltenyi), Integrin αL (PE/Cy7, H1111; Biolegend), Integrin αM (PE, ICRF44; Biolegend) and Integrin β2 (APC, TS1/18; Biolegend) and fixed with the FoxP3/Transcription Factor Staining Buffer Set (eBioscience). Flow cytometry was performed on LSR Fortessa (BD) and MACSQuant (Miltenyi Biotec) instruments. FlowJoTM v10.6 software (BD Life Sciences) was used for analysis of the flow cytometry data and gating on integrins was performed using FMOs or corresponding isotype controls.

**Dynamic adhesion assays**

CD4+ T cells were isolated from PBMCs with immunomagnetic beads (Miltenyi Biotec) according to the manufacturer’s instructions. CD4+ T cells were fluorescently labelled with carboxyfluorescein succinimidyl ester (CFSE; Life Technologies). Labelled cells were resuspended at 1.5 million cells/ml in RPMI 1640 medium (Thermo Fisher) with 1% penicillin/streptomycin (Biochrom) and 10% FCS (Pan Biotech) and incubated with or without the anti-α4β7 integrin antibody vedolizumab (10 µg/ml, Takeda) in vitro. Finally, cells were harvested and resuspended in adhesion buffer (pH 7.4; 150 mM NaCl, 10 mM HEPES, 1 mM CaCl2, 1 mM MgCl2, 1 mM
Miniature borosilicate capillaries (Vitrocom) were coated with Fc chimera of rhMAdCAM-1 (R&D Systems) at a concentration of 5 µg/ml in 150 mM NaCl with 10 mM HEPES for 1 h at 37°C. Unspecific binding sites were blocked with 10% foetal bovine serum (FBS) or 5% bovine serum albumin (BSA) in phosphate-buffered saline (PBS) for 1 h at 37°C. Capillaries were then connected to plastic tubing, which was inserted in a peristaltic pump (Baoding Shencheng Precision Pump Company). The flow rate of the pump was set to 10 µl/min and cells were perfused through the capillaries. Time-lapse confocal microscopy was used to quantify the dynamic adhesion to MAdCAM-1 for a 3-min-period. The three sequential images from the beginning and the end of the sequence were overlaid using ImageJ (NIH) allowing the quantification of adherent cells before and after the adhesion period. The difference was calculated to obtain the dynamic adhesion during the 3-min-period.

**Statistical analysis**

Statistical analyses were performed using GraphPad Prism (GraphPad Software, Inc.) and results are shown as mean with standard error of the mean (SEM). Shapiro–Wilk test was used to test for normal distribution. When comparing two groups, statistical differences were tested using Student’s t-test for data with normal distribution. When comparing more than two groups, statistical differences were tested using one-way ANOVA with Tukey’s multiple comparison for data with a normal distribution or Kruskal–Wallis test with Dunn’s multiple comparison for data without a normal distribution. Differences with an α value of \( p < 0.05 \) were defined as statistically significant. Significance levels are indicated by asterisks (\( *p < 0.05 \), \( **p < 0.01 \), \( ***p < 0.001 \)).

**Results**

**Circulating T cells from patients with chronic pouchitis express a specific profile of gut-homing integrins**

Since the expression of \( \alpha 4 \beta 7 \) integrin and other integrins involved in gut homing had not been explored in chronic pouchitis so far, we performed flow cytometry of circulating T cells from patients with chronic pouchitis (naïve for anti-\( \alpha 4 \beta 7 \) therapy), UC and healthy controls.

The expression of \( \alpha 4 \beta 7 \) on overall CD3\(^+\) T cells as well as on the CD4\(^+\) and the CD8\(^+\) T cell subsets was similar in patients with pouchitis compared to controls, but slightly lower on CD4\(^+\) T cells compared to UC (Figure 1(a)). This indicated that target cells for vedolizumab circulate in the peripheral blood of patients with chronic refractory pouchitis. Interestingly, the expression of \( \alpha 4 \beta 1 \), an integrin heterodimer interacting with endothelial vascular cell adhesion molecule (VCAM)-1 and previously implicated into the homing process to the ileum,\(^{33}\) was increased on CD8\(^+\) T cells from patients with pouchitis (Figure 1(b)). Integrin \( \alpha L\beta 2 \), which binds to intercellular cell adhesion molecule (ICAM)-1 on the endothelium, was similar in patients with pouchitis compared with UC and healthy controls (Figure 1(c)) and the expression of \( \alpha M\beta 2 \) integrin, which also ligates to ICAM-1, was numerically, but not significantly higher on CD3\(^+\) and CD4\(^+\) T cells in pouchitis compared with UC patients and controls (Figure 1(d)).

Together, these observations showed that T cells in the peripheral blood of patients with pouchitis express a specific profile of integrins, indicating that gut homing might be an important event in pouchitis.

**\( \alpha 4 \beta 7 \) integrin on CD4\(^+\) T cells from patients with pouchitis mediates adhesion to MAdCAM-1**

Having shown that \( \alpha 4 \beta 7 \)-expressing T cells as potential targets of vedolizumab circulate in the peripheral blood of patients with pouchitis, we aimed to explore the function of \( \alpha 4 \beta 7 \) in the context of pouchitis.

To this end, we used dynamic adhesion assays, in which we perfused CD4\(^+\) T cells from the peripheral blood through glass capillaries coated with MAdCAM-1 as the main ligand of \( \alpha 4 \beta 7 \). As previously demonstrated and expected,\(^{34}\) CD4\(^+\) T cells from donors with UC adhered to MAdCAM-1 and vedolizumab was able to substantially reduce dynamic adhesion. When using cells from patients with pouchitis, we observed a similar level of adhesion to MAdCAM-1. Again, vedolizumab led to a dramatic reduction of adhering cells that was numerically even higher than in UC (Figure 2).
Vedolizumab is efficient for the treatment of pouchitis

Eleven patients with chronic antibiotic-refractory pouchitis were treated with vedolizumab at our centre between 10/2015 and 08/2021. Full PDAI (pouchitis disease activity index) data were available from eight of them. The mean PDAI at baseline was 10.6. After a mean follow-up of 10
months it significantly dropped to 6.8. At this point, 50% of the patients had reached remission (as defined by a PDAI score of <7). Seven patients were under continuous therapy with vedolizumab after 1 year of follow-up. In these patients, the clinical subscore of the PDAI after 1 year of treatment was significantly reduced compared to before therapy (Figure 3; Table 2).

α4β7 integrin function correlates to response to vedolizumab in chronic pouchitis
Non-response to biologics is a key problem in the management of IBDs and individualized treatment approaches based on biomarkers have been proposed to optimize response and remission rates. We had earlier described that response to vedolizumab therapy in UC correlates with increased adhesion of CD4+ T cells to MAdCAM-1 at baseline and high in vitro efficacy of the antibody at baseline.

We sequentially collected peripheral blood from four patients with chronic pouchitis directly before the initiation of vedolizumab therapy and after 6 weeks of treatment.

Interestingly, when quantifying dynamic adhesion of CD4+ T cells to MAdCAM-1 at baseline, we found considerable differences in the number of adhering cells between those individuals (Figure 4). Moreover, while in vitro exposure of the cells with vedolizumab led to a clear reduction of adhesion in three of them, vedolizumab had no effect...
Figure 3. Clinical outcomes of treatment with vedolizumab in pouchitis. [a] PDAI score of patients with pouchitis before and under treatment with vedolizumab (left panel, mean follow-up 10 months), fraction of patients with pouchitis achieving remission under therapy with vedolizumab (middle panel, mean follow-up 10 months) and clinical subscore of the PDAI in patients continuing vedolizumab therapy for 1 year at induction and after 1 year (right panel). [b] Representative endoscopic findings in patients with pouchitis before and during vedolizumab therapy. [c] Representative histological findings in patients with pouchitis before and during vedolizumab therapy. n = 7–8.
PDAI, pouchitis disease activity index; VDZ, vedolizumab.
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on dynamic adhesion of cells from one patient. Strikingly, we observed a response to vedolizumab in the three patients with high inhibition of adhesion by vedolizumab in vitro, while the patient with lowest baseline adhesion and absent in vitro inhibition of adhesion did not respond to vedolizumab.

Together, these findings suggested that adhesion of peripheral blood CD4+ T cells to MAdCAM-1 in vitro as well as the effect of vedolizumab on dynamic adhesion correlate with the success of vedolizumab therapy and might therefore be used to predict clinical outcomes in chronic pouchitis.

Discussion
The α4β7 integrin-MAdCAM-1 pathway is considered a virtually exclusive mechanism to direct trafficking of gut-homing T lymphocytes to the intestine. The expression of α4β7 on T cells with a gut homing phenotype had been described almost 30 years ago and could later be linked to the production of retinoic acid by specialized dendritic cells in the gut-associated lymphoid tissue. Together with the functional role of α4β7 as a ligand mediating firm adhesion to MAdCAM-1 and the expression of MAdCAM-1 on high endothelial venules of the intestinal tract, this leads to a trafficking system with imprinting of the capacity to home to the target tissue on lymphocytes primed in the gut.

Since lymphocyte infiltration is a hallmark of IBDs such as CD and UC, it was obvious to investigate the applicability of strategies blocking α4β7. Following promising results in a preclinical model and early clinical studies, large phase III trials demonstrated efficacy and safety of the anti-α4β7 integrin antibody vedolizumab and led to the approval of the drug. Since then, vedolizumab is successfully used to treat CD and UC and has also been shown to block α4β7 in vivo.

Although further therapeutic options have entered the market recently, adequate disease control is still not reached in all IBD patients. Thus, in UC, restorative proctocolectomy with IPAA is considered as ultima ratio therapy to treat patients with refractory disease course and is also recommended, if endoscopically non-resectable non-polypoid dysplasia develops. Although this surgical approach is a definitive therapy for UC, complications may arise from the ileal pouch including pouchitis. A substantial part of the patients develops chronic pouchitis that is refractory to antibiotic treatment and therefore requires immune-modulating therapy.

Not far to seek, vedolizumab has also been used in this setting and several studies reported convincing efficacy and safety. The expression of MAdCAM-1 in the mucosa of patients with pouchitis has already been described and a very recent study was the first to characterize the expression of α4β7 in the pouch mucosa and the peripheral blood. Similar to our data, in which

| Table 2. Outcomes of vedolizumab therapy. |
|-----------------------------------------|
| Patient | PDAI before therapy | PDAI under therapy |
|         | CS | ES | HS | Total | Week | CS | ES | HS | Total |
| 1       | 3  | 5  | 2.5| 10.5 | 20   | 1  | 3  | 3  | 7    |
| 2       | 4  | 2  | 6  | 12   | 24   | 3  | 0  | 3  | 6    |
| 3       | 3  | 4  | 6  | 13   | 17   | 4  | 4  | 3  | 11   |
| 4       | 5  | 5  | 1.5| 11.5 | 34   | 5  | 2  | 3  | 10   |
| 5       | 4  | 0  | 3  | 7    | 60   | 2  | 0  | 2  | 4    |
| 6       | 4  | 3  | 3  | 10   | 135  | 3  | 2  | 0  | 5    |
| 7       | 4  | 0  | 3.5| 7.5  | 25   | 4  | 0  | 0  | 4    |
| 8       | 4  | 4  | 5  | 13   | 19   | 3  | 2  | 2  | 7    |

CS, clinical score; ES, endoscopic score; HS, histological score; PDAI, pouchitis disease activity index.
Figure 4. Baseline dynamic adhesion to MAdCAM-1 and response to therapy with vedolizumab. Data from four individual patients with pouchitis treated with vedolizumab. Left panels: Representative details from images showing the dynamic adhesion of CD4+ cells to MAdCAM-1 with and without in vitro treatment with vedolizumab at baseline. Overlays of three differentially coloured sequential images (stationary cells appear white) collected at the end of 3 min clips are shown. Below, absolute baseline adhesion during 3 min and absolute reduction of adhesion by vedolizumab treatment in vitro at week 0 (baseline inhibition) are indicated. Right column: Change in PDAI score during vedolizumab therapy. PDAI, pouchitis disease activity index; VDZ, vedolizumab.
we did not find relevant differences in the expression of \( \alpha 4 \beta 7 \) between patients with pouchitis, UC and healthy controls, the authors did not observe differences between patients following IPAA with and without pouchitis. Going beyond the level of expression, our study is the first to report on the function of \( \alpha 4 \beta 7 \) in pouchitis. We show that \( \alpha 4 \beta 7 \) on CD4+ T lymphocytes from patients with pouchitis functionally mediates adhesion to MAdCAM-1 to an at least similar extent as it is the case in UC. Moreover, in vitro treatment with vedolizumab clearly reduces CD4+ T cell adhesion to MAdCAM-1. Together, these data suggest that gut-homing mechanisms in pouchitis and mechanisms of action of vedolizumab are similar in pouchitis compared with UC.\(^{21,46}\) Interestingly, we found increased expression of the integrins \( \alpha 4 \beta 1 \) and numerically also \( \alpha M \beta 2 \) on peripheral blood T cells from patients with pouchitis. Since the respective endothelial ligands VCAM-1 and ICAM-1 are also expressed in the pouch mucosa,\(^{44}\) this suggests that additional trafficking mechanisms may be involved in the pathogenesis of pouchitis. Moreover, we observed high variation in the expression of \( \alpha M \beta 2 \) integrin, which is interesting in view of recent results from a trial with the ICAM-1 antisense oligonucleotide alicafosren in pouchitis.\(^{47}\)

The clinical observations on the treatment of patients with pouchitis with vedolizumab in our small cohort are in line with previous reports\(^{23-25}\) and support the notion that functional blockade of \( \alpha 4 \beta 7 \)-mediated adhesion of T cells to MAdCAM-1 also translates to a clinically relevant reduction of inflammation. It is yet important to note that in all of these studies, only a portion of patients entered remission during vedolizumab therapy. Thus, as in CD and UC, individual factors seem to affect the efficacy of the antibody and, consistently, individualized and tailored approaches to solely treat patients with a high probability of response would be desirable. We had previously described that the dynamic adhesion of CD4+ T cells to MAdCAM-1 at baseline\(^{48}\) might be a biomarker to predict the success of vedolizumab therapy in UC. Here, interestingly, we observed very similar profiles in patients with pouchitis that responded to vedolizumab therapy or not. The cut-off identified in our previous study in UC would also have correctly categorized these patients. Although the very low number of patients that could be included in this kind of analysis is a clear limitation to these data, this suggests that similar prediction strategies might apply in pouchitis.

Two main limitations need to be considered, when interpreting the results of our study: (1) We did not have a control group of patients with IPAA, but without pouchitis available. Thus, we cannot clearly differentiate between effects related to the pouch itself and inflammation in the pouch. However, since no obvious changes in integrin expression and function were observed in patients with pouchitis compared to patients with UC and healthy controls, it is quite likely that neither a pouch nor pouchitis induce major changes in intestinal trafficking circuits or the mechanism of action of vedolizumab. (2) The relatively small number of patients with pouchitis analysed as already mentioned above. However, since chronic pouchitis is a rare disease, our patient numbers are still comparable to other studies in the field.\(^{14,49}\)

Collectively, our study suggests that T cell trafficking mechanisms are important in the context of pouchitis and demonstrates that antagonism of \( \alpha 4 \beta 7 \) by vedolizumab in pouchitis has functional effects in vitro and clinical effects in vivo that might be foreseen by associated biomarkers. Further multi-centre studies including more patients are necessary.

**Acknowledgements**

The research of IA, RA, MFN and SZ was supported by the Interdisciplinary Center for Clinical Research (IZKF) and the ELAN program of the University Erlangen-Nuremberg, the Else-Kröner-Fresenius-Stiftung, the Thyssen-Stiftung, the Fritz Bender-Stiftung, the Dr. Robert Pfleger Stiftung, the Litwin IBD Pioneers Initiative of the Crohn’s and Colitis Foundation of America (CCFA), the Kenneth Rainin Foundation, the Ernst Jung-Stiftung for Science and Research, the German Crohn’s and Colitis Foundation (DCCV) and the German Research Foundation (DFG) through individual grants (ZU 377/4-1) and the Collaborative Research Centres TRR241 (TP C04), 643, 796, and 1181. The authors thank Julia Derdau, Julia Marcks, Monique Slawik, Julia Schuster and Dorothee Dziony for excellent technical assistance.

**Author contributions**

M.M., T.M.M., I.S., L.M., L.B. and C.A. performed the experiments and collected and
analysed the clinical data. C.I.G. analysed the histopathological samples. T.M.M., M.F.N. and S.Z. designed the research. E.B., I.A., F.V., R.A. and M.F.N. contributed samples or protocols. M.M., T.M.M., M.F.N. and S.Z. analysed and interpreted the data. M.M., T.M.M. and S.Z. drafted the manuscript; all authors critically read and revised the manuscript for important intellectual content and approved the final version.

Conflict of interest statement
The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.F.N. has served as an advisor for Pentax, Giuliani, MSD, Abbvie, Janssen, Takeda and Boehringer. S.Z. received honoraria from Takeda, Roche and Janssen. M.F.N. and S.Z. received research support from Takeda, Shire (a part of Takeda) and Roche. The other authors declare no conflicts of interest.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: German Research Foundation (DFG, ZU 377/4-1), Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankungen (scholarship to MM).

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Supplemental material
Supplemental material for this article is available online.

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