RESEARCH LETTER

Anti-Integrin αvβ6 Antibody Titer as a Predictive Biomarker of Future Treatment Escalation in Patients With Ulcerative Colitis

We have recently reported the use of the anti-integrin αvβ6 antibody to be a biomarker for disease activity and diagnosis of ulcerative colitis (UC).[1] The diagnostic value of this antibody was replicated in a Japanese pediatric population[2] and in Swedish,[3] North American,[4] and Italian[5] adult cohorts. However, little is known about the clinical importance of the anti-integrin αvβ6 antibody for UC treatment as a biomarker for monitoring activity[1,3,5] and predicting the outcome of UC.[4] Herein, we examined whether the anti-integrin αvβ6 antibody titer could be correlated with clinical profiles, including clinical characteristics, disease activity, treatment agents, and outcomes in patients with UC.

Sixty-four patients with UC who permitted the measurement of the anti-integrin αvβ6 antibody at Kyoto University Hospital between January 2017 and November 2018 were enrolled in this retrospective, observational, single-center study. All enrolled patients provided written informed consent. Definitions of clinical profiles and outcomes and methods for measuring the anti-integrin αvβ6 antibody titer and performing statistical analysis are described in the supplemental methods.

Patients' baseline characteristics are presented in Table A1. First, we investigated the association between the anti-integrin αvβ6 antibody titer and clinical profiles at the time of sample collection. Antibody titers in patients with UC did not correlate with clinical characteristics and were comparable between patients with and without immunosuppressant treatment (Figure A). Although serum C-reactive protein levels did not correlate with the antibody titer, the erythrocyte sedimentation rate and partial Mayo score were associated with the antibody titer (Figure B). Additionally, patients with Mayo endoscopic subscore (MES) 3 had significantly higher anti-integrin αvβ6 antibody titers than did those with endoscopic remission (Figure B). Since mucosal healing is currently one of the most important long-term achievable treatment targets in patients with UC,[6] we performed the receiver operating characteristic curve analysis. The analysis showed the discriminating potential of the anti-integrin αvβ6 antibody titer in the diagnosis of MES 0 (area under the curve: 0.780 ± 0.152); the optimized cut-off value of the antibody titer was 1.900 (Figure C). The sensitivity, specificity, positive, and negative predictive values for predicting MES 0 were 88.9%, 61.9%, 33.3%, and 96.3%, respectively.

Second, we assessed the anti-integrin αvβ6 antibody titer as a biomarker for predicting the outcome of UC in 59 patients after excluding 5 patients who underwent colectomy at the sample collection. After a mean follow-up period of 47.4 ± 12.7 months, 18 patients (30.5%) underwent treatment escalation. At the last visit, 19 patients (32.2%) were treated with only 5-aminosalicylic acid or sulfasalazine. Seven patients (11.9%) maintained thiopurines. Infliximab, adalimumab, golimumab, vedolizumab, and ustekinumab were administered in 17 (28.8%), 4 (6.8%), 2 (3.4%), 2 (3.4%), and 2 (3.4%) patients, respectively. Two patients (3.4%) underwent total colectomy, and 4 (6.8%) received no treatment. The anti-integrin αvβ6 antibody titers were not significantly different between the treatment agents at the last visit. However, anti-integrin αvβ6 antibody titers were significantly higher in patients who underwent treatment escalation than that in participants who did not (Figure D). Regarding the prediction of treatment escalation, the area under the curve for the anti-integrin αvβ6 antibody titer was 0.6763 ± 0.145; the optimized cut-off value of the antibody titer was 1.901 (Figure E). When the enrolled patients were grouped into the high-titer and low-titer groups on the basis of the calculated cut-off value, cumulative treatment escalation-free survival was significantly higher in the low-titer group than that in the high-titer group (Figure F). The Cox proportional hazards model demonstrated that the anti-integrin αvβ6 antibody titer was an independent predictor of treatment escalation (Table A2). Additionally, anti-integrin αvβ6 antibody titers were associated with composite adverse outcomes (Figure A1 and Table A3).

In line with previous reports,[1,3,5] this study indicated that the anti-αvβ6 integrin antibody titer correlated with clinical and endoscopic disease activities in patients with UC, confirming the usefulness of this antibody titer as a monitoring biomarker for UC. Furthermore, this study demonstrated no association between the antibody titer and treatments at the time of sample collection, which has not been assessed in the previous reports.

Notably, we found that the antibody titers were statistically higher in patients undergoing treatment escalation than that in participants without. The anti-integrin αvβ6 antibody titer had a modest value for prognosticating treatment escalation; the optimal cut-off value of 1.901 clearly discriminated between patients with and without treatment escalation using Kaplan-Meyer analysis. The Cox hazard model indicated that the anti-integrin αvβ6 antibody titer was an independent predictor for treatment escalation. Furthermore, higher antibody titers were associated with adverse UC outcomes in this study, as well as in a previous report evaluating recently diagnosed UC.[4] The mean disease

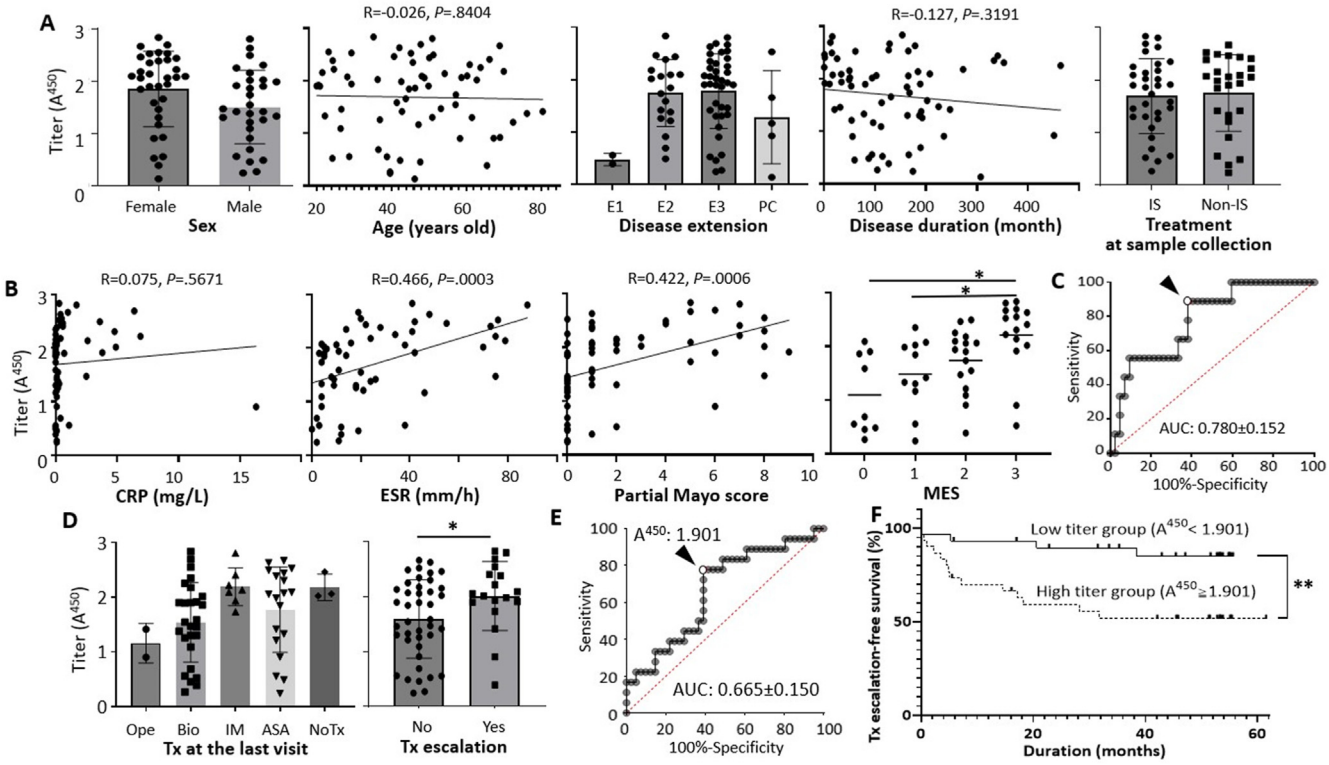

Figure. Anti-$\alpha\beta$6 integrin antibody titers and clinical characteristics, disease activity, treatment agents, and outcomes in patients with ulcerative colitis. (A) The anti-integrin αvβ6 antibody titers are comparable between male and female patients (Student *t*-test) and between different disease extensions (Tukey-Kramer test). The antibody titers do not have a significant association with age or disease duration (linear regression analysis). The anti-integrin αvβ6 antibody titers are similar between the patients with and without immunosuppressant treatment at sample collection (Student *t*-test). (B) Linear regression analysis reveals that the antibody titers are associated with the ESR and partial Mayo score but not with the serum CRP levels at sample collection. Patients with MES 0 or 1 have significantly lower titers than those with MES 3 (Tukey-Kramer test). (C) The ROC curve is generated to evaluate the use of the anti-integrin αvβ6 antibody titer to diagnose MES 0. The optimized cut-off value is calculated by the Youden index and indicated by an arrowhead. (D) The anti-integrin αvβ6 antibody titers at sample collection are comparable between the different treatment agents at the last visit (Tukey-Kramer test). Patients with treatment escalation have significantly higher titers than those without (Student *t*-test). (E) The ROC curve is generated to evaluate the use of the anti-integrin αvβ6 antibody titer for predicting treatment escalation. The optimized cut-off value is calculated by the Youden index and indicated by an arrowhead. (F) On the basis of the optimized cut-off value for detecting treatment escalation, enrolled patients were grouped into the low-titer and high-titer groups. Cumulative treatment escalation-free survival rates in the low-titer and high-titer groups are 93.1% and 69.8% at 1 year and 89.4% and 51.6% at 3 years, respectively. Cumulative treatment escalation-free survival is significantly higher in the low-titer group than that in the high-titer group (log-rank test). *: $P < .05$, **: $P < .01$. E1, proctitis; E2, left-sided; E3, pancolitis; PC, post-colectomy; Tx, treatment; IS, immunosuppressant; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MES, Mayo endoscopic subscore; AUC, area under the curve; Ope, operation; Bio, biologics; IM, immunomodulators; ASA, aminosalicylic acids; ROC, receiver operating characteristic.

duration of 133.2 months in the present study suggests that the anti-integrin αvβ6 antibody titer could prognosticate a clinical course in not only patients with recent onset of UC but also in those with long-standing UC.

This study has some limitations. It was a single-center, retrospective study with a small sample size. Thus, large-scale, multicenter, prospective studies are warranted to validate the predictive value of the anti-integrin αvβ6 antibody titer. Moreover, disease activity at sample collection varied. Hence, further investigations that only enroll patients with either remission or active UC are necessary.

In summary, this study's findings suggest that the anti-integrin αvβ6 antibody titer correlated with disease activity and future treatment escalation in patients with UC. Given its high specificity in UC diagnosis,[1–5] the anti-integrin αvβ6 antibody could have a unique advantage compared with other biomarkers that have a limitation as a nonspecific response to systemic and/or intestinal inflammation other than UC.

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Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2024.10.022.

References

1. Kuwada T, et al. Gastroenterology 2021;160:2383–2394.e21.
2. Muramoto Y, et al. Gastroenterology 2022;163:1094–1097.e14.
3. Rydell N, et al. J Clin Med 2022;11:1881.
4. Livanos AE, et al. Gastroenterology 2023;164:619–629.
5. Marafini I, et al. Dig Liver Dis 2024;56:55–60.
6. Turner D, et al. Gastroenterology 2021;160:1570–1583.

Abbreviations used in this paper: **MES, Mayo endoscopic subscore; UC, ulcerative colitis**

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Ethical Statement:
This study followed the Declaration of Helsinki and was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (protocol number: R1004).

Data Transparency Statement:
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Reporting Guidelines:
STROBE.