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Risankizumab Concentration but not IL-22 Levels are Associated With Clinical and Biochemical Remission in Patients With Crohn's Disease

Risankizumab (RZB) is a monoclonal antibody that targets the p19 subunit of interleukin (IL)-23.[1] The ADVANCE and MOTIVATE randomized controlled trials (RCTs)[2] demonstrated that intravenous (IV) RZB compared with placebo led to higher rates of clinical remission and endoscopic response at week 12 in patients with active Crohn's disease (CD).[2] The phase III FORTIFY RCT showed that subcutaneous (SC) RZB was significantly more effective than placebo for achieving clinical remission and endoscopic response as maintenance therapy in patients with moderate-to-severe active CD.[3]

Therapeutic drug monitoring has been extensively studied in inflammatory bowel disease (IBD) with anti-tumor necrosis factor.[4,5] However, there is limited data regarding the role of therapeutic drug monitoring in patients with IBD treated with RZB. Exposure–response analyses showed that the IV induction dose of 600 mg had similar efficacy with the 1200 mg dose for all investigated outcomes, achieving a near maximal response and a plateau of efficacy.[6] Regarding the maintenance phase, quartile analysis of average RZB concentrations between week 40 and week 48 demonstrated a trend of higher response in the higher range of exposure for most of the evaluated outcomes including endoscopic remission. Regarding immunogenicity, it seems that anti-drug antibodies against RZB are rare.[7]

This study aimed to investigate the association of maintenance serum RZB concentration with clinical and biochemical remission and whether IL-22 levels predict response to RZB.

Materials and Methods

Study Design and Outcomes

This single-center prospective study included consecutive patients with CD receiving compassionate-use RZB between July 2019 and July 2020. All patients were treated with an induction IV regimen of RZB 600 mg given at weeks 0, 4, and 8, followed by a maintenance SC regimen of 360 mg every 8 weeks. Compassionate use of RZB was only available after failure of all approved biologic therapies. Patients with other dosing regimens of RZB were excluded from the study. Other exclusion criteria were age <18 years, perianal fistulizing CD without luminal disease, ulcerative colitis, presence of an ostomy, IBD unclassified, and prior use of an anti-IL-23 inhibitor. For all patients, RZB concentrations, IL-22 levels, C-reactive protein (CRP), and fecal calprotectin (FC) were assessed just before a SC injection during a routine visit at the infusion center. Due to compassionate use, each injection every 8 weeks was performed at the infusion center. The investigated outcome was clinical and biochemical remission defined as a CD activity index <150 associated with CRP <5 mg/L and FC <250 μg/g of stool. Clinical and biochemical activity was evaluated blindly in respect to RZB concentration and IL-22 levels. The measurement of RZB concentration and IL-22 levels and statistical analysis are described in the Supplementary Appendix. The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. Written informed consent was obtained from all patients included in the study. The study was approved by the Commission Nationale Informatique et Liberté (CNIL) (Number: 1849323).

Results

Study Population

The study population consisted of 28 patients with CD (mean age: 44 years; sex ratio, male/female: 1.3) (Supplementary Table 1). At inclusion, the median albumin, FC, and CRP levels were 36.9 g/L, 721 μg/g of stools, and 9.8 mg/L, respectively. Mean ($\pm$ standard deviation [SD]) duration of follow-up was 18 $\pm$ 12 months. Twenty patients (71.6%) were in clinical and biochemical remission at the time of the first SC RZB injection. Forty-four of the 95 RZB samples (46%) were from patients in clinical and biochemical remission.

Association of RZB Concentrations With Clinical and Biochemical Remission

Patients in clinical and biochemical remission at the time of SC RZB injection had higher mean ($\pm$SD) RZB concentrations than patients without clinical and biochemical remission (21.6 $\pm$ 13.3 vs 7.4 $\pm$ 6.4 μg/mL, respectively; $P = .001$). Biochemical and clinical remission rates were significantly greater in the higher

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compared with the lower RZB quartiles ($P = .010$) (Figure 1*A*). The rate of clinical and biochemical remission was 4.2%, 29%, 71%, and 79% for the four quartiles of RZB concentration. Receiver operating characteristic (ROC) curve analysis (Figure 1*B*) (area under the ROC curve [AUC], 0.93; $P < .001$) identified a RZB concentration threshold of 11.5 μg/mL to be significantly associated with clinical and biochemical remission (sensitivity [SN], 81.8%; specificity [SP], 80.3%; positive predictive value [PPV], 78.2%; negative predictive value [NPV], 83.6%; accuracy, 81%). No anti-drug antibodies to RZB were found in any of the samples. Furthermore, the progression-free survival curves of lack of clinical and biochemical remission were significantly higher in the group of patients with RZB concentration >11.5 μg/mL compared with patients with RZB concentration $\leq 11.5 \mu$g/mL ($P = .02$) (Figure 1*C*).

Variables Associated With Clinical and Biochemical Remission

Based on univariate and multivariate Cox regression analysis, RZB concentration was the only variable associated with clinical and biochemical remission (hazard ratio [HR], 1.36; 95% confidence interval [CI], 1.05-1.35; $P = .001$). Conversely, baseline albumin and CRP, as well as patient characteristics, were not significantly associated with clinical and biochemical remission (Supplementary Table 2).

Association of IL-22 Levels With Clinical and Biochemical Remission

IL-22 levels were comparable between patients with and without clinical and biochemical remission (median, 10.4 pg/mL; interquartile range [IQR], 4.2–17.2 pg/mL vs 8.6 pg/mL; IQR, 4.3–16.2 pg/mL, respectively; $P = .73$). No correlation was found between RZB concentrations and IL-22 levels ($P = .06$) (Figure 1*D*). Furthermore, the ROC curve analysis of IL-22 levels was not predictive of clinical and biochemical remission with an AUC of 0.549 (95% CI, 0.468–0.628; $P = .54$, data not shown).

Discussion

Our study, using data from real-life clinical practice, is the first to show a positive association between serum trough RZB concentrations and clinical and biochemical

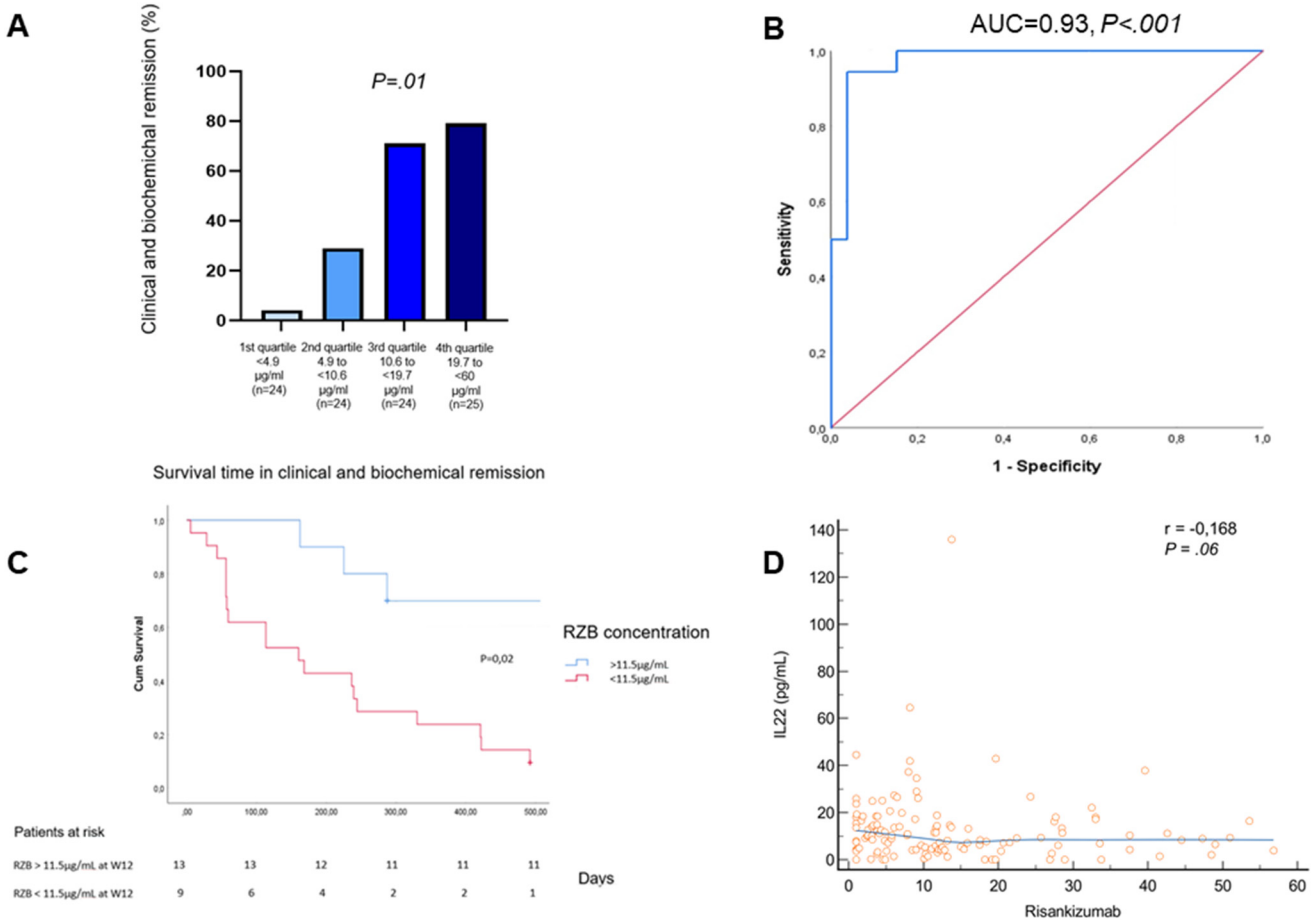

Figure 1. RZB concentration but not IL-22 levels are associated with clinical and biochemical remission in patients with Crohn's disease. (*A*) Quartile analysis of RZB maintenance concentration associated with clinical and biochemical remission. (*B*) Receiver operating characteristic curve analysis of RZB maintenance concentration to predict clinical and biochemical remission. (*C*) Time to loss of clinical and biochemical remission. (*D*) Correlation between IL-22 levels and RZB concentrations. IL, Interleukin; RZB, risankizumab.

response in patients with CD. This is in line with data from exposure-outcome relationship studies referring to other biologics targeting IL-23, such as ustekinumab.[8–11] Furthermore, a RZB maintenance trough concentration of 11.5 μg/mL predicted clinical and biochemical remission with a high SN, SP, PPV, NPV, and accuracy. In fact, RZB concentration was the only variable independently associated with this stringent outcome. Besides IL-23, RZB can modulate intestinal inflammation through other cytokines, including IL-22.[1] Several studies have identified IL-22 and IL-17, both cytokines downstream of IL-23, as predictors of response to IL-23 inhibition. Consequently, this biomarker could predict and/or assess response to IL-23 inhibition.[12] However, a RCT showed that baseline serum IL-22 levels before the initiation of RZB treatment were not predictive of clinical remission at week 12.[2] In the same line, our study showed that IL-22 levels during maintenance RZB treatment were not predictive of clinical and biochemical remission in patients with CD.

Our study has some limitations. First, the sample size was rather small. In addition, no endoscopic data were available for analysis. However, we analyzed clinical and biochemical remission, including 2 objective markers of inflammation. Moreover, our study included patients with CD with prior failure to multiple biologic therapies and cannot be generalized to bio-naive patients.

In conclusion, this pilot study showed that RZB concentrations, in contrast to IL-22 levels, are associated with clinical and biochemical remission in patients with CD. A RZB maintenance concentration threshold of 11.5 μg/mL may predict clinical and biochemical remission in patients with CD and is also associated with significantly higher progression-free survival. However, larger prospective studies are needed to confirm these findings.

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2024.03.039.

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Conflicts of interest

These authors disclose the following: Xavier Roblin served as a speaker, a consultant, and/or an advisory board member for MSD, Pfizer, Janssen, Takeda, Abbvie, Amgen, Biogen, Galapagos, Roche, Theradiag, and Celltrion. Konstantinos Papamichael received lecture/speaker fees from Mitsubishi Tanabe Pharma, Physicians Education Resource LLC, and Grifols; scientific advisory board fees from ProciseDx Inc and Scipher Medicine Corporation; and serves as a consultant for Prometheus Laboratories Inc. Adam S. Cheifetz served as a consultant and or advisory board member for Janssen, Abbvie, Protagonist, Spherix, Artizan (SAB), Food is Good, Clario, Pfizer, Fresenius Kabi, Artugen, Procise, Prometheus (SAB), Equillium, Samsung, Arena, Grifols, Bacainn, BMS, and Takeda. Stephane Paul served as a speaker, a consultant, and/or an advisory board member for MSD, Abbvie, Pfizer, Theradiag, Takeda. The remaining authors disclose no conflicts.

Supplementary Appendix

Therapeutic Drug Monitoring

Risankizumab (RZB) trough concentrations were measured using the iTRACK10 automated system (Theradiag) through chemiluminescence. The lower limit of quantification for the I-TRACK10 was 1 μg/mL. Drug concentrations <1 μg/mL were replaced with 1 μg/mL to facilitate statistical calculations. Evaluation of anti-drug antibodies to RZB was performed in case of undetectable (<1 μg/mL) RZB concentration using a drug sensitive assay (ELISA from Theradiag). Interleukin (IL)-22 levels were measured using the ELLA automated system (Biotechne) via sandwich ELISA with fluorescence detection. These measurements were performed blinded to clinical and biomarker activity.

Statistical Analysis

IL-22 levels and RZB concentrations were compared between groups using the Mann-Whitney *U* test. A correlation between IL-22 levels and RZB concentrations was calculated using the Spearman correlation test. The performance of RZB concentrations and IL-22 levels for predicting clinical and biochemical remission was evaluated using a receiver operating characteristic curve analysis. The ideal threshold associated with clinical and biochemical remission was identified using the Youden index. A quartile analysis of RZB concentrations and clinical and biochemical remission was also performed. A comparison between quartiles was done using linear-by-linear association. Univariate and multivariate Cox regression analysis was performed to identify variables associated with clinical and biochemical remission. For all comparisons, *P*-values $<$ .05 were considered statistically significant. All statistical tests were conducted using the MedCalc software (version 20.214).

Supplementary Table 1. Demographic and Clinical Characteristics of the Patients at the Time of Inclusion

Patients' demographic and clinical characteristics	Total patients	Patients in clinical and biochemical remission at the end of follow up	Patients not in clinical and biochemical remission at the end of follow-up	*P*
N	28	12	16	NS
Ratio M/F	16/12 (1.3)	6/6	10/6	NS
CD location				NS
L1-ileal disease	10	4	6	
L2-colonic disease	8	3	5	
L3-ileocolonic disease	10	5	5	
CD behavior				
B1-non penetrating, no stricturing	8	3	5	
B3-penetrating	14	5	9	
B2-stricturing	8	3	5	
Perianal	5	2	3	
Age at sampling, *years*	44.0 (5)	43.0 (6)	45 (4)	NS
Disease duration, *years*	9.5 (3.5)	10.5 (3.2)	9.1 (4.1)	NS
Past surgical resection	9	4	5	NS
Active smoking	17	7	10	NS
Prior biological therapy	28	12	16	NS
Concomitant immunomodulators	0	0	0	
Baseline CDAI	295 (240-328)	280 (240-320)	305 (240-340)	NS
Albumin, *g/L*	36.9 (31.3-42.0)	38.2 (33.5-42.5)	35.7 (31.1-41.4)	NS
FC, *μg/g*	721.0 (343.0-1031.5)	821.0 (360-1045)	690 (320-950)	NS
CRP, *mg/L*	9.8 (3.4-21.5)	9.6 (3.5-19.4)	9.9 (4.1-21.3)	NS

Note: Data are presented as number, mean (standard deviation), or median (range).
CD, Crohn's disease; CDAI, Crohn's disease activity index; CRP, C-reactive protein; F, female; FC, fecal calprotectin; M, male; N, number; NS, not significant.

Supplementary Table 2. Univariate and Multivariate Cox Regression Analysis to Identify Variables Associated With Clinical and Biochemical Remission

Parameters	Univariate analysis (*P* value)	Multivariate analysis (HR [95% CI]; *P* value)
Age	.83	
Female	.86	
Duration of disease	.51	
L1 vs L2-L3 phenotype	.90	
B1 vs B2-B3 phenotype	.52	
CRP at inclusion	.22	
FC at inclusion	.09	0.99 (0.991–1.002); ***P* = .055**
Albumin at inclusion	.43	
RZB concentration	**.005**	1.36 (1.05–1.35); ***P* = .001**
IL-22 levels	.74	

Note: Boldface *P* values indicate statistical significance ($P < .05$).
CI, Confidence interval; CRP, C-reactive protein; FC, fecal calprotectin; HR, hazard ratio; IL, interleukin; RZB, risankizumab.