Correlation of Fecal Calprotectin and C-Reactive Protein Concentrations With Clinical Outcomes and Endoscopic Disease Activity in Patients With Ulcerative Colitis Receiving Induction Therapy With Etrasimod

Andres Yarur,[1*] Vipul Jairath,[2*] Jinkun Zhang,[3] Julián Panés,[4] Michael Chiorean,[5] Laurent Peyrin-Biroulet,[6] Séverine Vermeire,[7] Christopher H. Cabell,[3] Snehal U. Naik,[3] William J. Sandborn[8]

[1]Medical College of Wisconsin, Milwaukee, WI, USA; [2]Western University, London, Ontario, Canada; [3]Arena Pharmaceuticals, Inc., San Diego, CA, USA; [4]Hospital Clinic of Barcelona, IDIBAPS, CIBERehd, Barcelona, Spain; [5]Virginia Mason Medical Center, Seattle, WA, USA; [6]University Hospital of Nancy, Vandœuvre-lès-Nancy, France; [7]University Hospitals Leuven, Leuven, Flanders, Belgium; [8]University of California San Diego, La Jolla, CA, USA; *Co-first author

Introduction

- Surrogate biomarkers of disease activity in ulcerative colitis are needed to assess responses to treatment
- Sphingosine-1-phosphate (S1P) receptor modulators lead to reduced inflammation and induction of clinical remission in patients with ulcerative colitis[1]
- Etrasimod (APD334), a once-daily, oral, selective S1P receptor modulator, showed efficacy in patients with moderately to severely active ulcerative colitis in the randomized, double-blind, placebo-controlled, phase 2 OASIS study[2]
- This post hoc analysis of the phase 2 OASIS study assessed the utility of fecal calprotectin and C-reactive protein as surrogate biomarkers for assessing efficacy in patients receiving etrasimod

Methods

Post hoc Study Design

- Patients enrolled in the phase 2 OASIS study (ClinicalTrials.gov identifier, NCT02447302):
  - were aged 18—80 years
  - had moderate to severe ulcerative colitis (3-component modified Mayo Clinic score [MCS] of 4—9 with endoscopic subscore ≥2 and rectal bleeding score ≥1)
  - had prior inadequate response or loss of response or intolerance to at least one conventional agent, anti-tumor necrosis factor-α (TNF-α) agent, or anti-integrin agent
- Patients were randomized to receive oral etrasimod 1 mg, etrasimod 2 mg, or placebo, all once daily for 12 weeks
- Fecal calprotectin and C-reactive protein were measured at baseline and weeks 4, 8, and 12 from stool and blood samples, respectively
- Clinical and endoscopic outcomes were evaluated at baseline and week 12 using MCS
  - The modified MCS (range 0—9) included endoscopic, rectal bleeding, and stool frequency subscores
  - Remission was defined as an endoscopic subscore ≤1 (with absence of friability), rectal bleeding and stool frequency scores ≤1, and a stool frequency decrease from baseline of ≥1

Statistical Analyses

- The effect of treatment with etrasimod versus placebo at each time point and over the 12 weeks was analyzed with a mixed model for repeat measures of log-transformed biomarker values (1-sided *P* values) with current oral corticosteroid use, prior exposure to TNF-α antagonists, treatment, week, and treatment-by-week interaction as factors and baseline value as a covariate
- Comparisons between those who achieved remission by study week and those who did not were assessed by a Wilcoxon rank-sum test (2-sided *P* values)
- Analysis of correlation between modified MCS, endoscopic subscore, C-reactive protein, and fecal calprotectin was conducted using the Spearman's rank coefficient (2-sided *P* values)

Results

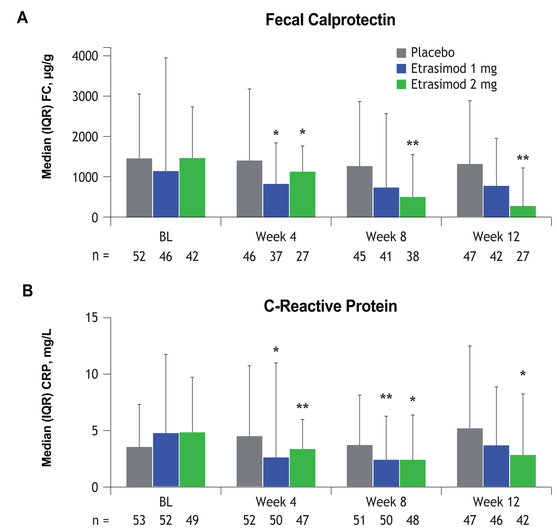
Table 1. Baseline Patient Demographics and Disease Characteristics

	Placebo (n = 54)	Etrasimod 1 mg (n = 52)	Etrasimod 2 mg (n = 50)
Age, mean ± SD, years	44.8 ± 14.9	43.2 ± 12.2	40.4 ± 12.4
Sex: male, n (%)	32 (59.3)	30 (57.7)	27 (54.0)
Race: white, n (%)	51 (94.4)	48 (92.3)	49 (98.0)
Weight, mean ± SD, kg	75.8 ± 16.2	73.7 ± 13.4	70.4 ± 16.7
Duration of UC, mean ± SD, years	8.6 ± 7.2	7.0 ± 6.1	6.2 ± 4.7
Disease location, n (%)[a]			
Proctosigmoiditis	34 (63.0)	34 (65.4)	30 (60.0)
Pancolitis	23 (42.6)	20 (38.5)	14 (28.0)
Current oral corticosteroid use, n (%)[b]	16 (29.6)	13 (25.0)	18 (36.0)
Duration of oral corticosteroid use, median (range), weeks[c]	31.4 (1.1—1304.4)	26.1 (1.6—260.9)	25.7 (2.1—432.4)
Total MCS, mean ± SD	8.7 ± 1.7	8.8 ± 1.4	8.9 ± 1.5
Modified MCS, mean ± SD	6.5 ± 1.5	6.5 ± 1.2	6.6 ± 1.2
CRP, median (range), mg/L	3.63 (0.31—59.10)	4.85 (0.21—245.00)	4.92 (0.29—76.90)
Fecal calprotectin, median (range), μg/g	1429 (67—16,226)	1210 (30—24,190)	1449 (71—21,559)

CRP, C-reactive protein; MCS, Mayo Clinic score; SD, standard deviation; UC, ulcerative colitis.
[a]Some patients reported disease localization of both proctosigmoiditis and pancolitis: placebo, n = 8; etrasimod 1 mg, n = 11; etrasimod 2 mg, n = 9. [b]Prednisone at a stable dose of ≤10 mg/day, budesonide at a stable dose of ≤9 mg/day, or equivalent steroid. [c]Includes prior and concomitant treatment.

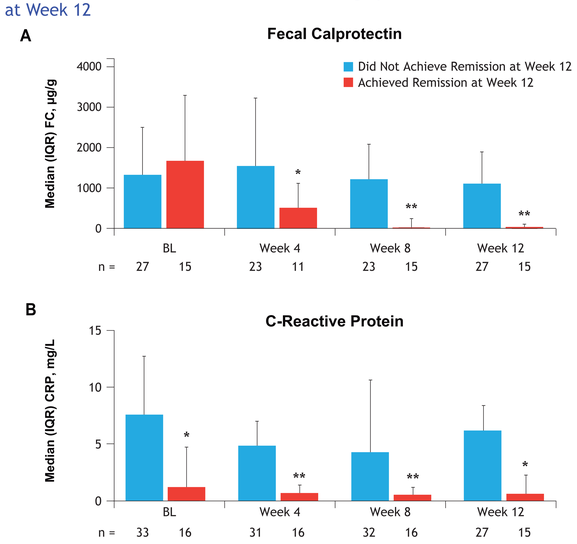
- Patients who received etrasimod 2 mg had significant decreases in fecal calprotectin and C-reactive protein compared with placebo across the study (geometric ratio of fecal calprotectin and C-reactive protein over placebo: 0.42 [*P* < 0.001] and 0.70 [*P* = 0.01], respectively)
  - Patients who received etrasimod 1 mg had a significant decrease in C-reactive protein compared with placebo across the study (geometric ratio: 0.72 [*P* = 0.02]), and a decrease in fecal calprotectin versus placebo that did not reach statistical significance (geometric ratio: 0.71 [*P* = 0.08])
- Decreases in fecal calprotectin and C-reactive protein levels in patients who received etrasimod 2 mg versus placebo were first observed at week 4 and were sustained through week 12 (**Figure 1**)
- Patients who received etrasimod 2 mg and achieved remission at week 12 had significantly lower levels of fecal calprotectin at weeks 4, 8, and 12 compared with patients who did not achieve remission (**Figure 2A**)
  - Week 12 median fecal calprotectin for patients who achieved remission versus those who did not achieve remission: 62.0 versus 1129 μg/g (*P* < 0.001)
- Patients who received etrasimod 2 mg and achieved remission at week 12 had significantly lower levels of C-reactive protein at all time points compared with patients who did not achieve remission, including at baseline (**Figure 2B**)

Figure 1. (A) Fecal Calprotectin and (B) C-Reactive Protein Levels Over Time by Treatment



BL, baseline; CRP, C-reactive protein; FC, fecal calprotectin; IQR, interquartile range.
P values versus placebo: *$P \leq 0.05$, **$P \leq 0.01$.

Figure 2. (A) Fecal Calprotectin and (B) C-Reactive Protein Levels Over Time in Patients Treated With Etrasimod 2 mg by Clinical Remission Status at Week 12



BL, baseline; CRP, C-reactive protein; FC, fecal calprotectin; IQR, interquartile range.
P values compare patients who achieved remission versus patients who did not achieve remission: *$P \leq 0.005$, **$P \leq 0.0001$.

Table 2. Correlation Analysis of Clinical and Endoscopic Disease Activity, Fecal Calprotectin, and C-Reactive Protein at Week 12

	Placebo	Etrasimod 1 mg	Etrasimod 2 mg
Modified MCS vs FC Spearman coefficient	n = 47 0.46 *P* = 0.001	n = 42 0.40 *P* = 0.009	n = 37 0.71 *P* < 0.001
Endoscopic subscore vs FC Spearman coefficient	n = 47 0.32 *P* = 0.030	n = 42 0.29 *P* = 0.067	n = 37 0.70 *P* < 0.001
Modified MCS vs CRP Spearman coefficient	n = 47 0.45 *P* = 0.002	n = 46 0.42 *P* = 0.003	n = 42 0.55 *P* < 0.001
Endoscopic subscore vs CRP Spearman coefficient	n = 47 0.40 *P* = 0.005	n = 46 0.36 *P* = 0.014	n = 42 0.44 *P* = 0.003
CRP vs FC Spearman coefficient	n = 46 0.35 *P* = 0.016	n = 42 0.30 *P* = 0.050	n = 34 0.61 *P* = 0.001

CRP, C-reactive protein; FC, fecal calprotectin; MCS, Mayo Clinic score.

- In the etrasimod 2-mg group, strong correlations (>0.5) were observed between modified MCS and fecal calprotectin, between endoscopic outcomes and fecal calprotectin, and between modified MCS and C-reactive protein; moderate correlations (0.3 to ≤0.5 were observed between endoscopic outcomes and C-reactive protein (**Table 2**)
  - In the etrasimod 2-mg group, there was a strong correlation between C-reactive protein and fecal calprotectin

Conclusions

- **Patients who received etrasimod 2 mg exhibited significant decreases in both fecal calprotectin and C-reactive protein versus placebo**
- **Fecal calprotectin and C-reactive protein were reliable biomarkers of clinical and endoscopic response in patients with ulcerative colitis enrolled in the OASIS trial**

References

1. Peyrin-Biroulet L, et al. *Autoimmun Rev*. 2017;16:495. 2. Sandborn WJ, et al. *Am J Gastroenterol*. 2018;113:S327.

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