Faecal Calprotectin and C-Reactive Protein Levels Are Correlated With Long Term Clinical and Endoscopic Outcomes: Analysis of the OASIS Open Label Extension Trial of Etrasimod for Ulcerative Colitis

Andres Yarur,† Michael Chioroan,‡ Jinkun Zhang,§ Walter Reinsch,¶ Séverine Vermeire,** Julian Panes,†† Laurent Peyrin-Biroulet,‡‡ Bruce E. Sands,† Christopher H. Cabell,¶ Snehul U. Naik,§ William J. Sandborn‡

†Medical College of Wisconsin, Milwaukee, WI, USA; ‡Virginia Mason Medical Center, Seattle, WA, USA; §Arena Pharmaceuticals, Inc., San Diego, CA, USA; ¶Medical University of Vienna, Vienna, Austria; **University Hospitals Leuven, Leuven, Flanders, Belgium; ††Hospital Clinic of Barcelona, D-EBE, P. Carlos, Barcelona, Spain; Department of Gastroenterology, Gastroenterology and Hepatology, University Hospital of Lausanne, Lausanne, Switzerland; ‡‡Vanderbos Haslam–Nancy, France; §Icahn School of Medicine at Mount Sinai, New York, NY, USA; ††University of California San Diego, La Jolla, CA, USA

Introduction

• Surrogate biomarkers of disease activity in ulcerative colitis are used to assess responses to treatment.

- Etrastimod (APD334) is a small, oral, selective sphingosine 1-phosphate receptor modulator with efficacy in patients with moderately to severely active ulcerative colitis (UC) in the pivotal, double-blind (DB), placebo-controlled, multicentre phase 2 OASIS study (NCT02447392) and the open-label extension (OLE) study (NCT02353645).

- The biomarkers faecal calprotectin (FC) and C-reactive protein (CRP) previously were shown to be useful in evaluating efficacy in the OASIS DB study.

- In the present post hoc analysis of the OLE, we evaluated the utility of FC and CRP as surrogate biomarkers for assessing sustained efficacy in patients with UC receiving etrasimod.

Methods

Study Design

- During the DB study, adult patients who met the inclusion criteria of a modified Mayo Clinic Score (mMCS) of 4 with endoscopic subscore ≤2, and rectal bleeding subscore ≤1 were treated once daily with etrasimod 1 mg, etrasimod 2 mg, or placebo.

- Patients who completed the DB study were eligible to enrol in the OLE and receive etrasimod 2 mg once daily for up to 52 weeks.

Figure 1. Study Design

Figure 2. FC and CRP Levels Over Time by DB Treatment Group

Statistical Analyses

- Analyses were performed using the elasmtic modified intention-to-treat population, which included patients who received etrasimod 2 mg throughout the OLE period and who had all required assessments.

- Comparisons between FC and CRP levels versus baseline (pre-specified) and between patients who achieved remission and those who did not (post hoc) by study week were made using a Wisconsin rank-sum test (2-sided P values).

- Comparisons between patients with normalization of FC and CRP versus baseline (post hoc) used a paired Student t test on response (response = 0, yes; 1, no).

- Analysis of correlation between mMCS, endoscopic subscore, CRP, and FC was performed using the Spearman’s rank coefficient.

Results

Patient Disposition and Characteristics

- 118 patients (84% of DB completers) entered the OLE study. 112 patients (99%) of the OASIS (etrasimod safety population) received etrasimod 2 mg at any point during the OLE.

- 105 patients (evaluable cohort) received etrasimod 2 mg throughout the OLE.

- 92/112 (82.1%) patients in the etrasimod safety population completed the OLE.

- Mean (standard deviation [SD]) drug exposure was 45 (9) and 80 (14) months in the DB study and 33 (9) and 12 (1) months in the OLE study.

- Patients within the etrasimod safety population had the following demographic and baseline characteristics:

  - Mean (SD) age of 43.7 (13.3) years at the start of the DB study and 60.7 years at the start of the OLE.
  - 60% of patients were male, and 93% were white.
  - Mean (SD) duration of UC of 8.9 (6.1) years at the start of the DB study with a mean (SD) mMCS of 4.2 (4.4) at the start of the OLE.
  - Median (range) values for FC and CRP of 850.5 (30–22,716) mg/L and 4.5 (0.2–119.0) mg/L, respectively, at the start of the OLE.

- At EOT, 70% of patients overall had a clinical response, 35% were in clinical remission, and 45% had endoscopic improvement.

Biomarker Analyses

- Overall, patients in the mITT evaluable cohort had a median decrease in FC of 601.1 mg/kg (P < 0.001) at EOT compared with DB baseline (Figure 2A).

- For each treatment group, CRP trended toward a decrease from baseline (Figure 2B).

- FC and CRP levels were in remission at EOT (Figure 2B).

- Figure 3. Correlation Analysis of Clinical and Endoscopic Disease Activity, FC Level, and CRP Level at EOT

Table 1. Correlation Analysis of Clinical and Endoscopic Disease Activity, FC Level, and CRP Level at EOT

<table>
<thead>
<tr>
<th>Variables Compared</th>
<th>DB Study</th>
<th>OASIS</th>
<th>Placebo</th>
<th>Remission Status at EOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>mMCS vs FC</td>
<td>Spearman coefficient</td>
<td>n = 20</td>
<td>n = 79</td>
<td>P = 0.019</td>
</tr>
<tr>
<td>CRP vs FC</td>
<td>Spearman coefficient</td>
<td>n = 20</td>
<td>n = 68</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>CRP vs mMCS</td>
<td>Spearman coefficient</td>
<td>n = 20</td>
<td>n = 68</td>
<td>P = 0.001</td>
</tr>
</tbody>
</table>

Conclusions

- Patients with UC who received etrasimod 2 mg throughout the OLE exhibited statistically significant decreases in FC throughout the study. FC levels are highly correlated with long-term clinical and endoscopic outcomes.

- FC and (to a lesser extent) CRP were useful biomarkers associated with response to therapy in patients with UC treated with etrasimod in this study.

Acknowledgements

The study and analyses were supported by Arena Pharmaceuticals, Inc. (Redondo Beach, CA, USA). Medical writing support was provided by Simon Healthcare (Philadelphia, PA, USA) and supported by Arena Pharmaceuticals, Inc.

Presented at European Crohn’s and Colitis Organisation (ECCO), February 12–15, 2020, Vienna, Austria

References


Disclosures

- All authors were employees of Arena Pharmaceuticals, Inc. (Redondo Beach, CA, USA) and are shareholders of the company.

- A.M. was vice president of Global Development, Arena Pharmaceuticals, Inc., San Diego, CA, USA. I.V. was president and chief executive officer of Arena Pharmaceuticals, Inc., San Diego, CA, USA, and a shareholder of the company.

- S.E. has served as an expert or consultant for AbbVie, Janssen, Janssen Biotech, Inc., Celgene, Amgen, Genentech, Celgene, plasterstone, venturel, and Biogen, and received consulting fees, travel grants, and reimbursement for meeting expenses from these companies.

- W.H. received consulting fees from Abbott Laboratories, Boehringer Ingelheim, Celgene, Galapagos, Gilead, Janssen, and Pfizer.

- J.C. has received consulting fees from AbbVie, Janssen, Janssen Biotech, Inc., Celgene, Amgen, Genentech, Celgene, plasterstone, venturel, and Biogen, and received consulting fees, travel grants, and reimbursement for meeting expenses from these companies.

- J.Z. received consulting fees from AbbVie, Janssen, Janssen Biotech, Inc., Celgene, Amgen, Genentech, Celgene, plasterstone, venturel, and Biogen, and received consulting fees, travel grants, and reimbursement for meeting expenses from these companies.

- J.C. was employed by Genentech and Celgene during the conduct of this study.

- L.P.B. has served as a consultant or advisor to: AbbVie, Celgene, Galapagos, Gilead, Janssen, Janssen Biotech, Inc., Merck, Merck Sharp & Dohme, Novartis, Pfizer, UCB, and Viromed. J.P. has served as a consultant or advisor to: Janssen, Janssen Biotech, Inc., Celgene, Amgen, Genentech, Celgene, plasterstone, venturel, and Biogen. W.J.S. has received research grants from Targeted Therapeutics, Inc., and serves on the scientific advisory board for: Protagonist Pharmaceuticals, Inc., Cytogen Corp., and Allunion therapeutics, Inc. W.J.S. was a regular speaker or consultant for: Abbott Laboratories, Boehringer Ingelheim, Celgene, Galapagos, Gilead, Janssen, Janssen Biotech, Inc., Celgene, plasterstone, venturel, and Biogen. J.P. was a consultant for: AbbVie, Celgene, Genentech, Janssen, Janssen Biotech, Inc., Merck, Merck Sharp & Dohme, Novartis, Pfizer, UCB, and Viromed.