Patients With Psoriasis Treated With Brodalumab: A Pooled Post Hoc Analysis of a Marker of Liver Inflammation in Individuals With Potential Indicators of Early Nonalcoholic Fatty Liver Disease

Ronald Prussick, MD[1]; Mark Lebwohl, MD[2]; Nadege Gunn, MD[3]; Susan Harris, MS[4]; Jason Vittitow, PhD[4]; Zeev Heimanson, PharmD[4]; Abby Jacobson, MS, PA-C[5]; Robert J. Israel, MD[4]

[1]George Washington University, Washington, DC; [2]Mount Sinai Hospital, New York, NY; [3]Austin Gastroenterology, Austin, TX; [4]Salix Pharmaceuticals, Bridgewater, NJ; [5]Ortho Dermatologics, Bridgewater, NJ

INTRODUCTION

- Nonalcoholic fatty liver disease (NAFLD) is a broad term that includes a range of liver diseases categorized via imaging or histology in patients with intrahepatic fat accumulation without substantial alcohol consumption (eg, nonalcoholic fatty liver; nonalcoholic steatohepatitis)[1]
  - NAFLD is intimately linked to metabolic syndrome and is commonly associated with comorbidities, such as diabetes mellitus, dyslipidemia, and obesity[1,2]
- Interestingly, patients with psoriasis are at increased risk for NAFLD compared with patients without psoriasis[3,4]
  - In one population-based cohort study, patients ≥55 years of age with psoriasis were 70% more likely to have NAFLD after adjusting for confounding risk factors (adjusted odds ratio, 1.7; 95% confidence interval, 1.2–2.5)[4]
  - Published cohort data have suggested that the overall prevalence of NAFLD in adults with psoriasis approaches 50%[5] to 60%[6]
- Although the relationship between psoriasis and NAFLD has not been fully elucidated, chronic low-grade systemic inflammation plays a key role in psoriasis and NAFLD pathophysiologies[7,8]
- Current guidelines from the American Association for the Study of Liver Diseases do not recommend routine screening for NAFLD in high-risk groups in nonhepatology settings[1]
  - Therefore, the possible presence of NAFLD and potential harmful versus beneficial impact of psoriasis medications on the liver in patients with NAFLD should be carefully considered[4]
- Brodalumab is an anti–interleukin (IL)-17 receptor A monoclonal antibody indicated for moderate to severe plaque psoriasis in adults who have failed or lost response on other systemic therapies[9]
  - Binding to this receptor inhibits IL-17–mediated release of pro-inflammatory cytokines and chemokines
- Given the potential role chronic low-grade systemic inflammation may play in the relationship between psoriasis and NAFLD,[7,8] a post hoc exploratory analysis was conducted to examine changes in C-reactive protein (CRP), a systemic marker of chronic inflammation,[10] in patients with psoriasis and early indicators of NAFLD who were treated with brodalumab

OBJECTIVE

- Post hoc analysis to examine changes in CRP levels in patients with psoriasis with an aspartate aminotransferase (AST)-to-alanine aminotransferase (ALT) ratio suggestive of liver fibrosis or who had decreases in liver test parameters while taking brodalumab in clinical trials

METHODS

- Exploratory analysis of data pooled from 4 randomized, double-blind, placebo-controlled trials[11-13]
- Included patients who received ≥1 dose of subcutaneous brodalumab 210 mg every 2 weeks, ustekinumab per the US indicated dosing regimen[14] (in 2 trials[13]), or placebo
- Patients were subgrouped post hoc (ie, not prespecified outcomes) by various indicators to determine liver disease (eg, baseline AST/ALT ratio [≥0.9 suggestive of mild to more advanced fibrosis[15,16]] and maximum postbaseline AST and ALT grade decreases during treatment [based on common terminology criteria for adverse events])
- Findings were summarized using descriptive statistics (eg, mean and standard deviation)

RESULTS

- Overall, 1496 patients received ≥1 dose of brodalumab 210 mg every 2 weeks, 613 patients received ≥1 dose of ustekinumab, and 879 patients received ≥1 dose of placebo in the 4 trials (Table 1)
  - 802 patients in the brodalumab group, 339 in the ustekinumab group, and 474 in the placebo group had an AST/ALT ratio ≥0.9

Table 1. Demographics and Baseline Characteristics (Overall Pooled Population)

Parameter	Brodalumab 210 mg q2w (n=1496)	Ustekinumab (n=613)	Placebo (n=879)
Age, y, mean (SD) Range	45.0 (12.9) 18–75	45.1 (13.1) 18–75	44.6 (12.9) 18–86*
Male, n (%)	1037 (69.3)	417 (68.0)	607 (69.1)
Race, white, n (%)	1351 (90.3)	551 (89.9)	799 (90.9)
Psoriasis duration, y, mean (SD)	18.6 (12.3)	18.5 (12.2)	18.5 (12.0)
PASI score, mean (SD) Range	20.2 (8.0) 12–72	20.0 (8.4) 12–60	20.0 (8.2) 12–66

*2 patients were >75 years of age.
PASI = Psoriasis Area Severity Index; q2w = every 2 weeks; SD = standard deviation.

- For the subgroup of patients with a baseline AST/ALT ratio of ≥0.9 to <1.4, a larger mean numeric decrease from baseline in CRP level was observed for patients treated with brodalumab and ustekinumab compared with placebo after 12 weeks of treatment (Table 2; Figure 1)

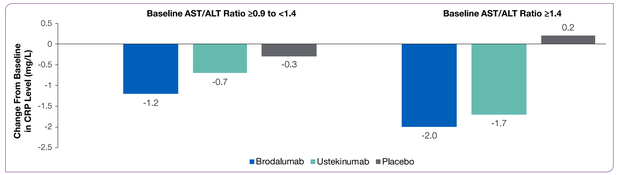
Table 2. CRP Levels in Patients Subgrouped by Baseline AST/ALT Ratio

Assessment	Brodalumab 210 mg q2w	Ustekinumab	Placebo
Baseline AST/ALT ratio of ≥0.9 to <1.4			
Baseline CRP level, mg/L Mean (SD)	n=607 6.4 (11.8)	n=264 4.9 (5.4)	n=361 5.7 (9.2)
Week 12 CRP level, mg/L Mean (SD)	n=599 5.2 (10.9)	n=259 4.2 (5.3)	n=343 5.3 (12.7)
Change from baseline at Week 12 CRP level, mg/L Mean (SD)	n=587 -1.2 (13.1)	n=255 -0.7 (5.4)	n=341 -0.3 (11.7)
Baseline AST/ALT ratio ≥1.4			
Baseline CRP level, mg/L Mean (SD)	n=178 6.6 (12.6)	n=69 5.6 (9.8)	n=109 6.2 (11.9)
Week 12 CRP level, mg/L Mean (SD)	n=176 4.6 (9.1)	n=64 4.1 (9.6)	n=103 6.5 (9.6)
Change from baseline at Week 12 CRP level, mg/L Mean (SD)	n=174 -2.0 (11.6)	n=63 -1.7 (7.4)	n=102 +0.2 (11.8)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; q2w = every 2 weeks; SD = standard deviation.

- Similarly, for patients with an AST/ALT ratio of ≥1.4, a larger mean numeric decrease from baseline in CRP level was observed for patients treated with brodalumab or ustekinumab compared with placebo after 12 weeks of treatment (Table 2; Figure 1)

Figure 1. Change From Baseline in CRP Levels at Week 12, by Baseline Liver Function Parameter AST/ALT Ratio



ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein.

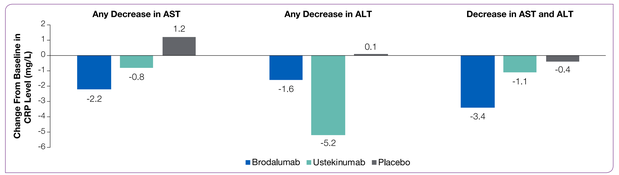
- During 12 weeks of treatment, a larger numeric decrease from baseline in CRP levels was observed in patients with any decrease in AST grade, ALT grade, or both in brodalumab and ustekinumab groups versus placebo (Table 3; Figure 2)

Table 3. CRP Levels in Patients With Any Decrease in AST Grade, ALT Grade, or Both During 12 Months of Treatment

Assessment	Brodalumab 210 mg q2w	Ustekinumab	Placebo
Patients with any AST decrease			
Baseline CRP level, mg/L Mean (SD)	n=62 6.7 (8.6)	n=20 2.6 (2.3)	n=26 6.4 (9.9)
Week 12 CRP level, mg/L Mean (SD)	n=58 4.1 (5.5)	n=19 1.6 (1.9)	n=25 7.3 (13.1)
Change from baseline at Week 12 CRP level, mg/L Mean (SD)	n=57 -2.2 (6.0)	n=19 -0.8 (2.1)	n=25 +1.2 (13.6)
Patients with any ALT decrease			
Baseline CRP level, mg/L Mean (SD)	n=61 6.4 (7.8)	n=25 9.3 (34.6)	n=30 5.5 (9.6)
Week 12 CRP level, mg/L Mean (SD)	n=58 4.7 (6.4)	n=22 5.0 (15.2)	n=31 5.5 (8.6)
Change from baseline at Week 12 CRP level, mg/L Mean (SD)	n=58 -1.6 (6.0)	n=22 -5.2 (21.8)	n=30 +0.1 (5.6)
Patients with both AST and ALT decrease			
Baseline CRP level, mg/L Mean (SD)	n=23 6.7 (9.0)	n=9 2.1 (1.9)	n=6 3.4 (3.3)
Week 12 CRP level, mg/L Mean (SD)	n=22 3.3 (5.0)	n=9 1.0 (1.1)	n=6 3.1 (3.5)
Change from baseline at Week 12 CRP level, mg/L Mean (SD)	n=22 -3.4 (6.6)	n=9 -1.1 (1.5)	n=6 -0.4 (2.7)

ALT = alanine aminotransferase; AST = aspartate aminotransferase CRP = C-reactive protein; q2w = every 2 weeks; SD = standard deviation.

Figure 2. Change From Baseline in CRP Levels in Patients With Decreases in ALT and/or AST After 12 Weeks of Treatment



ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein.

CONCLUSIONS

- The post hoc observation of a decrease in CRP levels in patients subgrouped by AST and ALT suggests that brodalumab may have activity in reducing liver inflammation and early indicators of NAFLD; further research is warranted

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ACKNOWLEDGMENTS: The studies were sponsored by Amgen/AstraZeneca and post hoc analyses were supported by Ortho Dermatologics. Technical editorial and medical writing support were provided under the direction of the authors by Mary Beth Moncrief, PhD, Synchrony Medical Communications, LLC, West Chester, PA. Funding for this support was provided by Ortho Dermatologics.

DISCLOSURES: RP reports serving on the speakers' bureau for AbbVie Inc., Celgene Corp., Janssen Pharmaceuticals, Inc., and Pfizer Inc.; serving as a consultant for Immunotec Inc.; and receiving research funding from Celgene Corp. and Novartis AG. ML reports being an employee of Mount Sinai, which receives research funds from AbbVie Inc., Bausch Health Companies Inc., Boehringer Ingelheim GmbH, Celgene Corp., Eli Lilly and Company, Incyte Corp., Janssen Pharmaceuticals, Inc./Johnson & Johnson, LEO Pharma Inc., MedImmune, Novartis AG, Pfizer Inc., SCIderm GmbH, UCB, Inc., and Vidac Pharma; and serving as a consultant for Allergan plc, Aqua Pharmaceuticals, Arcutis Pharmaceuticals, Boehringer Ingelheim GmbH, LEO Pharma Inc., Menlo Therapeutics, Promius Pharma, LLC, and Verrica Pharmaceuticals. NG reports serving as a consultant for AbbVie Inc., Dova Pharmaceuticals, Gilead Sciences, Inc., Intercept Pharmaceuticals, Inc., and Salix Pharmaceuticals; and participating in research sponsored by Axcella Health Inc., Bristol-Myers Squibb Company, Cirius Therapeutics, CymaBay Therapeutics, Genfit, Gilead Sciences, Inc., HighTide Therapeutics Inc., Luminist, Madrigal Pharmaceuticals, Inc., NGM Biopharmaceuticals, Inc., Novo Nordisk, Pfizer Inc., Progenity, Inc., and Second Genome, Inc. SH, JV, ZH, and RJI report being employees of Salix Pharmaceuticals or its affiliates. AJ reports being an employee of Ortho Dermatologics.