Impact of HLA-B27 Status on Clinical Outcomes Among Patients With Ankylosing Spondylitis Treated With Secukinumab

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BACKGROUND

- Ankylosing spondylitis (AS) is strongly associated with the genetic marker HLA-B27
- In patients with AS, negative HLA-B27 status is a predictor of worse response to tumor necrosis factor inhibitors[1]
- Approximately 80% to 90% of Caucasian patients with AS express HLA-B27 compared with < 8% of the Caucasian population; these trends are similar in Chinese patients
- Secukinumab, a fully human monoclonal antibody that selectively neutralizes interleukin 17A, has shown long-lasting efficacy and safety in the treatment of AS[2,3]
- The impact of HLA-B27 status on the clinical efficacy of secukinumab in the treatment of AS in racially diverse populations is not well understood

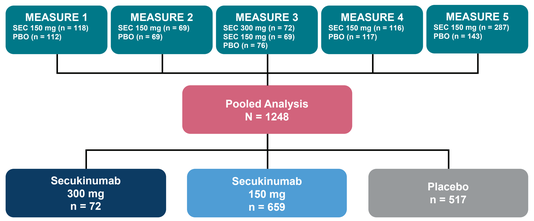
OBJECTIVE

- To analyze the impact of HLA-B27 status on clinical outcomes at Week 16 in patients with AS treated with secukinumab vs placebo pooled from the MEASURE 1-5 studies (NCT01358175, NCT01649375, NCT02008916, NCT02159053, and NCT02896127)[2,4-6]

METHODS

- Patients with AS were pooled from the randomized, double-blind, placebo-controlled, phase 3 MEASURE 1-5 trials and stratified by HLA-B27 status (**Figure 1**)
- All trials included patients who received secukinumab 150 mg every 4 weeks with or without an initial loading dose (10 mg/kg intravenously [IV] at Weeks 0, 2, and 4 or 150 mg subcutaneously at Weeks 0, 1, 2, and 3) or placebo control[2,4-6]
  - MEASURE 3 included an additional arm of patients receiving secukinumab 300 mg every 4 weeks following the initial IV loading dose[4]
  - Patients from MEASURE 1 and 2 who received secukinumab 75 mg were not included in this pooled analysis
  - A large proportion of patients enrolled in MEASURE 5 was from China[6]
- Efficacy at Week 16 was determined by the proportion of patients achieving 20% or 40% improvement in Assessment of SpondyloArthritis international Society score (ASAS20 and ASAS40, respectively), ASAS5/6, ASAS partial remission, 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50), and Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP) of < 2.1 or < 1.3
- All outcomes were compared within HLA-B27 strata between patients receiving secukinumab and those receiving placebo using logistic regression at Week 16 with nonresponder imputation for missing data
- All analyses were for hypothesis generation, without adjustment for multiple comparisons

Figure 1. Study Design



PBO, placebo; SEC, secukinumab.

RESULTS

Patient Population and Baseline Characteristics

- This pooled analysis included 1248 patients from the MEASURE 1-5 trials, including 1043 (83.6%) who were HLA-B27+ and 205 (16.4%) who were HLA-B27−
- Some imbalances in baseline characteristics were evident across treatment groups, particularly for age, sex, CRP levels, and previous tumor necrosis factor inhibitor experience (**Table 1**)
  - HLA-B27+ patients were younger and more frequently male than HLA-B27− patients (**Table 1**)

Table 1. Pooled Baseline Patient Characteristics Stratified by HLA-B27 Status

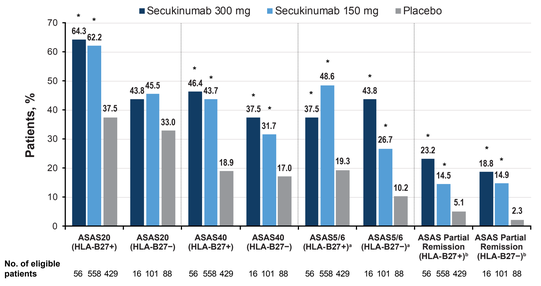
Characteristic	Secukinumab 300 mg (n = 72)		Secukinumab 150 mg (n = 659)		Placebo (n = 517)	
HLA-B27 Status	HLA-B27+ (n = 56)	HLA-B27− (n = 16)	HLA-B27+ (n = 558)	HLA-B27− (n = 101)	HLA-B27+ (n = 429)	HLA-B27− (n = 88)
Age, mean (SD), years	40.9 (11.9)	47.8 (9.9)	38.1 (11.7)	43.6 (10.3)	38.9 (12.2)	46.1 (12.5)
Male, n (%)	40 (71.4)	8 (50.0)	435 (78.0)	51 (50.5)	329 (76.7)	41 (46.6)
Race, n (%)						
White	46 (82.1)	9 (56.3)	292 (52.3)	64 (63.4)	268 (62.5)	66 (75.0)
Asian	1 (1.8)	1 (6.3)	241 (43.2)	19 (18.8)	145 (33.8)	7 (8.0)
BMI, mean (SD), kg/m^2	27.4 (5.2)	29.2 (4.4)	25.9 (5.7)	26.9 (5.9)	25.9 (4.8)	27.7 (5.9)
Current smoker at baseline, n (%)	17 (30.4)	4 (25.0)	187 (33.5)	22 (21.8)	142 (33.1)	29 (33.0)
Patient global assessment (VAS 0-100), mean (SD)	71.4 (16.4)	78.0 (16.3)	69.2 (16.2)	71.4 (17.3)	69.9 (16.3)	72.1 (15.1)
Total back pain (VAS 0-100), mean (SD)	72.8 (14.5)	77.8 (17.0)	70.4 (16.0)	71.3 (15.1)	71.0 (15.5)	73.6 (14.7)
BASDAI, mean (SD)	6.8 (1.4)	7.2 (1.4)	6.8 (1.4)	6.9 (1.5)	6.8 (1.4)	7.0 (1.2)
ASDAS-CRP, mean (SD)	3.6 (0.9)	3.8 (0.8)	3.8 (0.9)	3.6 (0.9)	3.8 (0.9)	3.6 (0.7)
CRP, mean (SD), mg/L	10.9 (13.6)	10.3 (12.0)	17.6 (27.1)	16.6 (34.0)	16.6 (22.3)	9.8 (12.6)
Time since AS diagnosis, mean (SD), years	5.5 (7.2)	5.9 (8.5)	6.9 (7.9)	4.4 (6.1)	7.1 (8.4)	3.9 (4.6)
Previous TNFi use, n (%)	13 (23.2)	6 (37.5)	141 (25.3)	30 (29.7)	102 (23.8)	35 (39.8)

AS, ankylosing spondylitis; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score with C-reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; TNFi, tumor necrosis factor inhibitor; VAS, visual analog scale.

Efficacy

- Regardless of HLA-B27 status, patients receiving any dose of secukinumab were significantly more likely to report ASAS40, ASAS5/6, and ASAS partial remission than those receiving placebo (P < .05 for all comparisons; **Figure 2**)
- HLA-B27+ patients receiving any dose of secukinumab were significantly more likely to achieve ASAS20 than those receiving placebo (P < .05; **Figure 2**), whereas HLA-B27− patients experienced a lower response rate that did not reach statistical significance vs placebo
  - For ASAS partial remission, a high-threshold measure of clinical improvement with lower placebo response than ASAS20 or ASAS40, response rates were more balanced between HLA-B27+ vs HLA-B27− patients

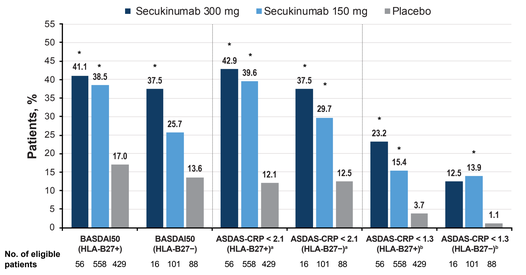
Figure 2. Percentages of Patients With AS Achieving ASAS Responses at Week 16, Stratified by HLA-B27 Status (nonresponder imputation)



AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis international Society.
Logistic regression analysis used treatment and tumor necrosis factor α inhibitor status as factors and baseline weight as a covariate.
* P < .05 compared with placebo.
ᵃ 20% improvement in ≥ 5 ASAS domains.
ᵇ Score of ≤ 2 in the patient global, pain, and function domains.

- Regardless of HLA-B27 status, patients receiving any dose of secukinumab were significantly more likely to achieve ASDAS-CRP of < 2.1 than those receiving placebo (P < .05 for all comparisons; **Figure 3**)
- HLA-B27+ patients receiving any dose of secukinumab were significantly more likely to achieve BASDAI50 than those receiving placebo; among HLA-B27− patients, only those receiving secukinumab 300 mg were more likely to achieve BASDAI50 vs placebo (P < .05 for all comparisons; **Figure 3**)
  - BASDAI50 response rates among HLA-B27− patients receiving secukinumab 150 mg did not reach statistical significance vs placebo
- HLA-B27+ patients receiving any dose of secukinumab were significantly more likely to achieve ASDAS-CRP of < 1.3 than those receiving placebo; among HLA-B27− patients, only those receiving secukinumab 150 mg were more likely to achieve ASDAS-CRP of < 1.3 vs placebo (P < .05 for all comparisons; **Figure 3**)
  - ASDAS-CRP < 1.3 response rates among HLA-B27− patients receiving secukinumab 300 mg did not reach statistical significance vs placebo

Figure 3. Percentages of Patients With AS Achieving BASDAI50 and ASDAS-CRP Responses at Week 16, Stratified by HLA-B27 Status (nonresponder imputation)



AS, ankylosing spondylitis; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score with C-reactive protein; BASDAI Bath Ankylosing Spondylitis Disease Activity Index.
Logistic regression analysis used treatment and tumor necrosis factor α inhibitor status as factors and baseline weight as a covariate.
* P < .05 compared with placebo.
ᵃ All patients had ASDAS-CRP of > 2.1 at baseline.
ᵇ All patients had ASDAS-CRP of > 1.3 at baseline.

CONCLUSIONS

- In a large pooled population of patients with AS including patients from China, secukinumab was effective regardless of HLA-B27 status in most, but not all, outcome measures of efficacy; HLA-B27 may be a predictor of response
- HLA-B27+ patients experienced numerically increased therapeutic benefit compared with HLA-B27− patients

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DISCLOSURES

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