SKIN

RESEARCH LETTER

Brodalumab in The Treatment of Moderate-To-Severe Psoriasis in Patients Refractory to Anti-Interleukin-17A Therapies: Evaluation of Secondary Endpoints

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ABSTRACT

Background: Brodalumab is an interleukin-17 receptor A antagonist approved for the treatment of moderate-to-severe plaque psoriasis. Our prior publication reported significant disease improvement with brodalumab in psoriasis patients who had previously failed treatment with an anti-IL-17A agent.

Methods: We conducted an Institutional Review Board (IRB)-approved open-label study of a total of 39 subjects enrolled at 3 sites with moderate-to-severe psoriasis. All patients previously failed treatment with an IL-17A agent. Subjects received brodalumab 210 mg via subcutaneous injection at weeks 0, 1, and 2, followed by 210 mg every 2 weeks, up to week 16. Subjects were evaluated monthly for improvement in PASI and sPGA.

Results: Of the baseline comorbidities assessed, the only statistically significant difference between responders and non-responders was the presence of higher weight/BMI in non-responders in the AO dataset; this trend disappeared in the NRI dataset. Of the patients that dropped out of the trial early, 3 of the 5 had PASI improvements of $\geq$60%. A rapid onset to disease improvement was seen in the trial.

Conclusion: These results indicate that brodalumab may be a good treatment choice for psoriasis patients, including those with severe disease and/or underlying comorbidities.

Brodalumab is an interleukin-17 receptor A antagonist approved for the treatment of moderate-to-severe plaque psoriasis. In our previous publication, we reported that the majority of patients who had previously had significant improvement with brodalumab. As-observed (AO) results showed Psoriasis Area and Severity Index (PASI)-75, PASI-90, and PASI-100 scores in 76%, 50%, and 32% of patients, respectively, at week 16. Using a non-responder imputation (NRI), PASI-75, PASI-90, and PASI-100 scores were seen in 67%, 44%, and 28% of patients[1].

Although the majority of these patients improved on brodalumab treatment, we sought to investigate factors that differed between the patients who had treatment success with brodalumab and those who did not, as well as other secondary endpoints.

An Institutional Review Board (IRB)-approved open-label study was conducted on a total of 39 subjects enrolled at 3 sites with moderate-to-severe psoriasis. All investigators were Risk Evaluation and Mitigation (REMS) certified. Subjects received brodalumab 210 mg via subcutaneous injection of prefilled syringes at weeks 0, 1, and 2, followed by 210 mg every 2 weeks, up to week 16. All patients previously failed treatment with an IL-17A agent, defined as treatment with either secukinumab or ixekizumab for $\geq$ 3 months without achieving PASI-75 response, or a 50% loss of original improvement.

Endpoints of this extension study included evaluation of baseline characteristics and comorbidities of responders vs non-responders, including weight, body mass index (BMI), smoking status, baseline PASI and static Physician's Global Assessment (sPGA) scores, and body sites involved. Other endpoints included the extent of improvement in non-responders, characterization of the patients who discontinued early from the trial, time to improvement in PASI scores, and the proportion of patients achieving a $\geq$2-point reduction in sPGA at Week 16. For the purposes of these endpoints, "responders" were defined as patients who met sPGA 0 or 1 (clear or almost clear) or PASI-75 at week 16.

Of the baseline characteristics (tables 1, 2), the only statistically significant difference between responders and non-responders was the presence of higher weight/BMI in non-responders, seen in the AO dataset. This trend disappears in the NRI dataset. This is consistent with the known efficacy of brodalumab for obese patients- in its phase III trials, the efficacy of brodalumab did not differ between nonobese vs obese patients (BMI $\geq$30 kg/m^2)^2. There was also a non-statistically significant trend toward more severe disease in the non-responders.

A total of 5 patients discontinued participation in the trial. The most common reason for early discontinuation was lack of efficacy. Percent improvement in PASI scores at early termination were 81% (week 4), and 60%, 35%, 4%, and 61% (week 12). The BMI of the patients who discontinued participation ranged from 20.9 to 29.8.

For those patients who were non-responders at week 16, we observed a partial response (PASI-50) in 50% (AO)/30.8% (NRI).

A rapid onset of disease improvement was observed. By week 4, 53.8% and 23.1% of patients achieved PASI-50 and PASI-75, respectively; increasing to 88.2% and 76.5% at week 16 (AO). A $\geq$2-grade improvement in sPGA at week 16 was achieved by 61.5% of patients (both AO, NRI).

In conclusion, the only statistically significant difference between responders and non-responders was the presence of higher weight/BMI in the AO dataset; this effect disappeared in the NRI dataset. These data suggest that brodalumab may be a good treatment option for psoriasis patients who have failed other biologics, including the anti-IL-17A class, regardless of their underlying disease severity or comorbidities.

Abbreviations:

AO: As-observed
PASI: Psoriasis Area and Severity Index
NRI: Non-responder imputation
IRB: Institutional Review Board
REMS: Risk Evaluation and Mitigation Strategy
sPGA: static Physician's Global Assessment

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Table 1 Baseline characteristics of responders and non-responders, AO dataset

Baseline Characteristics		Week 16 Responder (N=26)	Week 16 Non-Responder (N=8)	Week 16 Missing (N=5)
Age (years)	N	26	8	5
	Mean (SE)	53.2 (3.43)	49.9 (3.98)	38.2 (6.71)
	Median	51.50	50.00	34.00
	Min, Max	19, 91	28, 66	24, 56
	p-value [a]	0.6149		
Weight (lb)	N	26	8	5
	Mean (SE)	191.3 (7.46)	252.1 (31.56)	160.8 (14.61)
	Median	188.0	241.00	158.00
	Min, Max	122, 267	155, 425	118, 208
	p-value [a]	0.0085		
BMI (kg/m^2)	N	26	8	5
	Mean (SE)	28.6 (0.90)	37.4 (3.95)	25.0 (1.50)
	Median	28.55	35.45	25.00
	Min, Max	21, 39	25, 59	21, 30
	p-value [a]	0.0023		
Smoking Status, n(%)	No	17 (65.4%)	5 (62.5%)	4 (80.0%)
	Yes- current	2 (7.7%)	2 (25.0%)	0
	Yes- former	7 (26.9%)	1 (12.5%)	1 (20.0%)
	p-value [b]	1.0000		
PASI at Baseline	N	26	8	5
	Mean (SE)	21.2 (2.61)	19.3 (5.75)	17.6 (7.42)
	Median	18.15	12.20	10.50
	Min, Max	5, 51	7, 55	4, 43
	p-value [a]	0.7447		
sPGA at Baseline, n(%)	3	17 (65.4%)	3 (37.5%)	3 (60.0%)
	4	9 (34.6%)	5 (62.5%)	2 (40.0%)
	p-value [b]	0.2278		
Comorbidities, n(%)	Diabetes Mellitus	6 (23.1%)	3 (37.5%)	0
	p-value [b]	0.6488		
	Hypertension	13 (50.0%)	3 (37.5%)	2 (40.0%)
	p-value [b]	0.6933		
	Hyperlipidemia	9 (34.6%)	3 (37.5%)	0
	p-value [b]	1.0000		
	Psoriatic Arthritis	2 (7.7%)	0	3 (60.0%)
	p-value [b]	1.0000		
	History of Depression	5 (19.2%)	0	0
	p-value [b]	0.3086		
Locations, n(%)	Head	17 (65.4%)	6 (75.0%)	3 (60.0%)
	p-value [b]	1.0000		
	Trunk	21 (80.8%)	6 (75.0%)	4 (80.0%)
	p-value [b]	1.0000		
	Upper Extremities	22 (84.6%)	8 (100.0%)	3 (60.0%)
	p-value [b]	0.5515		
	Lower Extremities	25 (96.2%)	8 (100.0%)	4 (80.0%)
	p-value [b]	1.0000		

[a] p-value is from a t-test comparing Week 16 Responder with Week 16 Non-Responder; [b] p-value is from the Fisher's exact test comparing Week 16 Responder with Week 16 Non-Responder.

Table 2 Baseline characteristics of responders and non-responders, NRI dataset

Baseline Characteristics		Week 16 Responder (N=26)	Week 16 Non- Responder (N=13)
Age (years)	N	26	13
	Mean (SE)	53.2 (3.43)	45.4 (3.76)
	Median	51.50	47.00
	Min, Max	19, 91	24, 66
	p-value [a]	0.1655	
Weight (lb)	N	26	13
	Mean (SE)	191.3 (7.46)	217.0 (23.44)
	Median	188.00	194.00
	Min, Max	122, 267	118, 425
	p-value [a]	0.1963	
BMI (kg/m^2)	N	26	13
	Mean (SE)	28.6 (0.90)	32.7 (2.99)
	Median	28.55	29.80
	Min, Max	21, 39	21, 59
	p-value [a]	0.1019	
Smoking Status, n(%)	No	17 (65.4%)	9 (69.2%)
	Yes- current	2 (7.7%)	2 (15.4%)
	Yes- former	7 (26.9%)	2 (15.4%)
	p-value [b]	1.0000	
PASI at Baseline	N	26	13
	Mean (SE)	21.2 (2.61)	18.7 (4.36)
	Median	18.15	12.00
	Min, Max	5, 51	4, 55
	p-value [a]	0.6016	
sPGA at Baseline, n(%)	3	17 (65.4%)	6 (46.2%)
	4	9 (34.6%)	7 (53.8%)
	p-value [c]	0.2497	
Comorbidities, n(%)	Diabetes Mellitus	6 (23.1%)	3 (23.1%)
	p-value [b]	1.0000	
	Hypertension	13 (50.0%)	5 (38.5%)
	p-value [b]	0.7342	
	Hyperlipidemia	9 (34.6%)	3 (23.1%)
	p-value [b]	0.7144	
	Psoriatic Arthritis	2 (7.7%)	3 (23.1%)
	p-value [b]	0.3102	
	History of Depression	5 (19.2%)	0
	p-value [b]	0.1488	
Locations, n(%)	Head	17 (65.4%)	9 (69.2%)
	p-value [b]	1.0000	
	Trunk	21 (80.8%)	10 (76.9%)
	p-value [b]	1.0000	
	Upper Extremities	22 (84.6%)	11 (84.6%)
	p-value [b]	1.0000	
	Lower Extremities	25 (96.2%)	12 (92.3%)
	p-value [b]	1.0000	

[a] p-value is from a t-test comparing Week 16 Responder with Week 16 Non-Responder; [b] p-value is from the Fisher's exact test comparing Week 16 Responder with Week 16 Non-Responder; [c] p-value is from the Chi-square test comparing Week 16 Responder with Week 16 Non-Responder