Herpes Zoster Events With Anifrolumab in Patients With Active SLE: An Integrated Analysis of Phase 2 and Phase 3 Trials

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Background

- In the phase 2 MUSE and phase 3 TULIP-1 and TULIP-2 trials, treatment with anifrolumab, a monoclonal antibody to type I interferon receptor subunit 1, was associated with clinical benefit for patients with systemic lupus erythematosus (SLE)[1–3]
- In all 3 trials, herpes zoster (HZ) was observed more frequently in patients who received anifrolumab versus placebo
- HZ has also been more frequently reported in patients with SLE receiving several other biologic and nonbiologic immunomodulatory agents (eg, Janus kinase inhibitors, anti-tumor necrosis factor-α agents) compared with placebo[4,5]

Objective

We conducted an integrated analysis to characterize the frequency and nature of HZ events with anifrolumab across the MUSE and TULIP trials

Methods

Trial Design

- MUSE, TULIP-1, and TULIP-2 were randomized, double-blind, 52-week trials that evaluated the efficacy and safety of anifrolumab 300 mg versus placebo (IV, Q4W for 48 weeks) in patients with moderate to severe, seropositive SLE despite standard-of-care treatment[1–3]
- MUSE also included a 1000-mg treatment arm, and TULIP-1 included a 150-mg treatment arm

Assessments and Statistical Analyses

- Data from patients who received anifrolumab 300 mg or placebo in MUSE, TULIP-1, and TULIP-2 were pooled
  - Data from patients in the MUSE 1000-mg treatment arm and the TULIP-1 150-mg treatment arm were each analyzed separately
- The following characteristics of HZ events were summarized by frequency and percentage of patients:
  - All HZ adverse events (AEs); HZ events deemed serious (SAEs)
  - HZ AEs leading to discontinuation of investigational product and by intensity
  - HZ AEs by number of dermatomes and locations (data not available for MUSE)
- Time to first onset of HZ during treatment was presented as a Kaplan–Meier plot
- Reported HZ event rates were based on exposure-adjusted incidence rates (EAIRs), defined as the number of patients with an event divided by the total exposure time among patients in the treatment group
  - EAIRs are reported as events per 100 patient-years and derived by number of patients with an event/[sum of time at risk in days/(365.25×100)]
  - Comparisons between treatment groups (risk difference) and 95% confidence intervals (CIs) were estimated based on the Miettinen and Nurminen method[6]
  - Adjusted difference in cumulative proportions are presented for HZ AEs based on Cochrane–Mantel–Haenszel weighting[7]
  - Subgroup analyses of proportions of patients with HZ were performed on pooled data from the anifrolumab 300 mg and placebo arms of TULIP-1 and TULIP-2 (differences in MUSE data collection prevented pooling)

Results

Patients

- In pooled data from MUSE, TULIP-1, and TULIP-2, 459 patients received ≥1 dose of anifrolumab 300 mg and 466 received ≥1 dose of placebo
- In addition, 93 patients received anifrolumab 150 mg in TULIP-1 and 105 received 1000 mg in MUSE
- HZ events occurred in 4.3% (48/1123) of patients (6.4% [42/657], any anifrolumab dose; 1.3% [6/466], placebo)

Herpes Zoster Events

- 28 patients (6.1%) receiving anifrolumab 300 mg and 6 (1.3%) receiving placebo developed HZ (**Table 1**)
- HZ occurred in 5.4% and 8.6% of patients who received anifrolumab 150 mg (TULIP-1) or 1000 mg (MUSE) compared with 1.6% and 1.0% of patients in the placebo groups

Table 1. Herpes Zoster Events During Treatment With Anifrolumab 300 mg Versus Placebo in Pooled MUSE, TULIP-1, and TULIP-2 Data

	Anifrolumab 300 mg (n=459)		Placebo (n=466)		Difference (anifrolumab 300 mg vs placebo)	
Herpes zoster AEs	n (%)	EAIR (per 100 PY)	n (%)	EAIR (per 100 PY)	EAIR (per 100 PY) risk difference (anifrolumab 300 mg – placebo) (95% CI)	Adjusted difference in cumulative percentage (95% CI)
Any AE	28 (6.1)	6.9	6 (1.3)	1.5	0	0
Any AE with outcome of death	0	0	0	0	0	0
Any SAE	2 (0.4)	0.5	0	0	0.5 (–0.5, 1.7)	0.4 (–1.1, 2.0)
Any DAE	2 (0.4)	0.5	0	0	0.5 (–0.5, 1.7)	0.4 (–1.1, 2.0)
Any AE by maximum reported intensity						
Mild	9 (2.0)	2.2	1 (0.2)	0.3		
Moderate	17 (3.7)	4.1	5 (1.1)	1.2		
Severe	2 (0.4)	0.5	0	0		

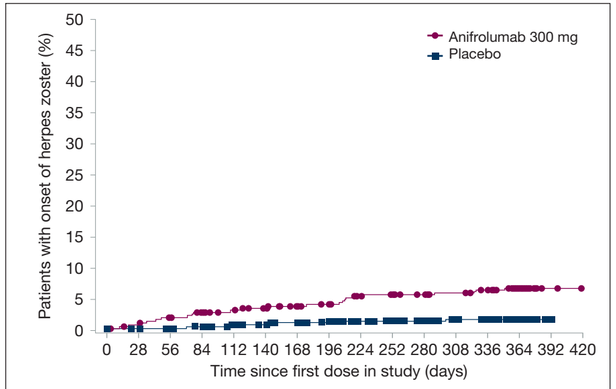
AE, adverse event; CI, confidence interval; DAE, adverse event leading to discontinuation of investigational product; EAIR, exposure-adjusted incidence rate; PY, patient-years; SAE, serious adverse event.
EAIR was reported per 100 PY and defined as the number of patients with the specific event divided by the total exposure time in years and then multiplied by 100. The exposure time was defined as the time from the date of first administration of investigational product to the date of first event, death, end of treatment plus 28 days, or end of study, whichever came first.

- HZ events were of mild or moderate intensity in 44/48 patients and of severe intensity in 4 patients (anifrolumab 300 mg, n=2; 1000 mg, n=2)
- Serious HZ AEs occurred in 3 patients (anifrolumab 300 mg, n=2; 1000 mg, n=1)
  - One patient (anifrolumab 300 mg) also had an SAE of transverse myelitis
- All anifrolumab-treated patients and 4 of 6 placebo-treated patients who had a HZ event received antiviral treatment, and all cases resolved
- 44 of 48 patients with HZ AEs continued in the study; all HZ AEs leading to discontinuation were nonserious (anifrolumab 150 mg, n=1; 300 mg, n=2; 1000 mg, n=1)
- 5 cases involved ≥3 dermatomes (anifrolumab 150 mg, n=1; anifrolumab 300 mg, n=3; placebo, n=1)

Time to First Onset of Herpes Zoster

- Time to first onset of HZ was slightly shorter in the anifrolumab 300-mg versus the placebo group (**Figure 1**)
  - There was no difference between the anifrolumab 300 mg and placebo groups in HZ event duration

Figure 1. Time to First Onset of Herpes Zoster During Treatment With Anifrolumab 300 mg Versus Placebo in Pooled MUSE, TULIP-1, and TULIP-2 Data



If a patient had no herpes zoster events during treatment, the time to first onset was censored at the date of last administration of investigational product plus 24 days.

Figure 2. Adjusted Difference in Cumulative Proportions of Patients With Herpes Zoster Events in Subgroups of Patients Treated With Anifrolumab 300 mg Versus Placebo in Pooled TULIP-1 and TULIP-2 Data

Subgroup		Placebo n/N (%)	Anifrolumab 300 mg n/N (%)	Treatment difference (95% CI)	Treatment difference (95% CI)
Overall		5/366 (1.4)	23/360 (6.4)		5.0 (1.9, 8.1)
SLEDAI-2K (screening)	<10	2/106 (1.9)	3/109 (2.8)		0.9 (–5.3, 7.0)
	≥10	3/260 (1.2)	20/251 (8.0)		6.8 (2.7, 10.9)
OCS dosage	<10 mg/day	2/180 (1.1)	12/190 (6.3)		5.4 (0.5, 10.3)
	≥10 mg/day	3/185 (1.6)	12/190 (6.3)		4.7 (–0.0, 9.4)
Type I IFNGS status	Test-high	4/301 (1.3)	19/298 (6.4)		5.0 (1.6, 8.6)
	Test-low	1/64 (1.6)	4/62 (6.5)		4.9 (–5.2, 15.0)
Sex	Male	0/25	3/27 (11.0)		11.0 (–8.7, 30.8)
	Female	5/340 (1.5)	20/333 (6.0)		4.5 (1.3, 7.7)
Age	≥18–65 years	5/358 (1.4)	23/344 (6.7)		5.3 (2.1, 8.5)
	≥65 years	0/7	0/16		0
BMI	≤28 kg/m²	3/223 (1.3)	13/205 (6.3)		5.0 (0.7, 9.3)
	>28 kg/m²	2/142 (1.4)	10/155 (6.5)		5.0 (–0.4, 10.5)
Race	White	4/243 (1.6)	13/235 (5.6)		3.9 (–0.0, 7.9)
	Black/African American	1/48 (1.8)	0/46		–1.8 (–12.9, 9.4)
	Asian	0/35	4/41 (9.8)		9.8 (–5.0, 24.6)
	Other	0/31	4/30 (12.6)		12.6 (–5.4, 30.5)
Region	USA/Canada	3/139 (2.1)	9/139 (6.5)		4.3 (–1.6, 10.2)
	Europe	2/122 (1.6)	5/115 (4.4)		2.8 (–3.2, 8.9)
	Latin America	0/57	4/59 (6.7)		6.7 (–3.6, 17.0)
	Asia Pacific	0/32	4/38 (10.7)		10.7 (–5.7, 26.5)
	Rest of world	0/15	1/9 (15.3)		15.3 (–22.8, 53.3)
ADA	Negative	5/330 (1.5)	21/335 (6.3)		4.8 (1.5, 8.0)
	Positive (at any time)	0/35	2/25 (10.4)		10.4 (–8.5, 29.4)
Immuno-suppressant	Any use	3/176 (1.7)	17/173 (9.8)		8.1 (2.6, 13.7)
	No use	2/189 (1.1)	6/187 (3.2)		2.2 (–1.8, 6.2)

ADA, antidrug antibody; BMI, body mass index; CI, confidence interval; IFNGS, interferon gene signature; OCS, oral corticosteroid.

Herpes Zoster Events by Subgroup

- In subgroup analyses of pooled data available from TULIP-1 and TULIP-2, HZ events were more frequent in patients treated with anifrolumab 300 mg receiving immunosuppressants (9.8%, n=17) than without immunosuppressants (3.2%, n=6) (**Figure 2**)
- No clear trends were otherwise observed in HZ cases by demographics, baseline disease characteristics, or SLE-related medication use (**Figure 2**)

Conclusions

- In the MUSE and TULIP trials, there was an increased risk of HZ with anifrolumab versus placebo
- HZ event characteristics, including duration and severity, were comparable between treatment groups, and most HZ events were mild or moderate, were cutaneous, and resolved without discontinuation of investigational product

References

1. Furie R, et al. *Arthritis Rheumatol*. 2017;69:376–86.
2. Furie R, et al. *Lancet Rheumatol*. 2019;1:E208–19.
3. Morand EF, et al. *N Engl J Med*. 2020;382:211–21.
4. Kennedy P, et al. *J Neurovirol*. 2020;26:482–95.
5. Marra F, et al. *Open Forum Infect Dis*. 2016;3:ofw205.
6. Liu GF, et al. *Stat Med*. 2006;25:1275–86.
7. Chuang-Stein C, et al. *Pharm Stat*. 2011;10:3–7.

Disclosures

JTM has received grant/research support from BMS and GSK, and consultancy fees from AstraZeneca, AbbVie, Amgen, Aurinia, BMS, EMD Serono, GSK, Remegen, Janssen, Provention and UCB. **KK** has received consultancy fees from AstraZeneca. **RF** has received grant/research support and consultancy fees from AstraZeneca. **KW** has received grant/research support from BMS and Pfizer, and consultancy fees from Pfizer, AbbVie, Union Chimique Belge, Eli Lilly, Galapagos, GSK, Roche, and Gilead. **PP** is a shareholder and employee of AstraZeneca. **LP**, **GA**, and **RT** are employees of AstraZeneca.

Acknowledgments

The authors would like to thank the investigators, research staff, health care providers, patients, and caregivers who contributed to this study. Editorial support was provided by Angela Cimmino, PharmD, of JK Associates, Inc., a Fishawack Health Company. This support was funded by AstraZeneca.

Presented at the American College of Rheumatology (ACR) Annual Meeting, ACR Convergence 2020 (All Virtual), November 5–9, 2020