STPM363

Application of Model-Based Meta-Analysis to Set Benchmarks for New Treatments of Systemic Lupus Erythematosus

Kosalaram Goteti[1], Ramon Garcia[2], William Gillespe[2], Jonathan French[2], Lena Klopp-Schulze[3], Ying Li[1], Cristina Vazquez Mateo[1], Sanjeev Roy[4], Oliver Guenther[3], Lisa Benincosa[1], Karthik Venkatakrishnan[1]

[1]EMD Serono Research and Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA, Darmstadt Germany)

[2]Metrum Research Group, Tarriffville, CT, US

[3]Merck KGaA, Darmstadt, Germany

[4]Ares Trading S.A., Eysins, Switzerland (an affiliate of Merck KGaA, Darmstadt, Germany)

INTRODUCTION

- ❑ Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple organ systems and is unpredictable in disease course, with fluctuating disease activity including flares.
- ❑In the past 60 years, there have been only two drugs developed that have been approved by the Food and Drug Administration (FDA) for treatment of SLE, anifrolumab and belimumab.
- ❑ In the development of SLE treatment it is important to assess a compound's efficacy by comparing it to benchmark drug treatments of SLE.
- ❑ When evaluating the efficacy of an SLE treatment in a clinical trial, several composite instruments have been used to assess SLE disease activity such as: Systemic Lupus Erythematosus Responder Index (SRI) and BILAG-based Composite Lupus Assessment (BICLA).
- ❑**The overall objective of this model based meta-analysis (MBMA) was to:**
  - ❑ perform a literature review of randomized clinical trials of drugs for SLE and curate the data identified in this review in a manner suitable for MBMA (2000-2021),
  - ❑ develop a MBMA disease trajectory model (DTM) with treatment effects for SLE composite scores using summary-level data, and
  - ❑ use the MBMA DTM to make predictions of SLE composite scores at treatment duration milestones for the FDA approved treatments of SLE, anifrolumab and belimumab.

METHODS

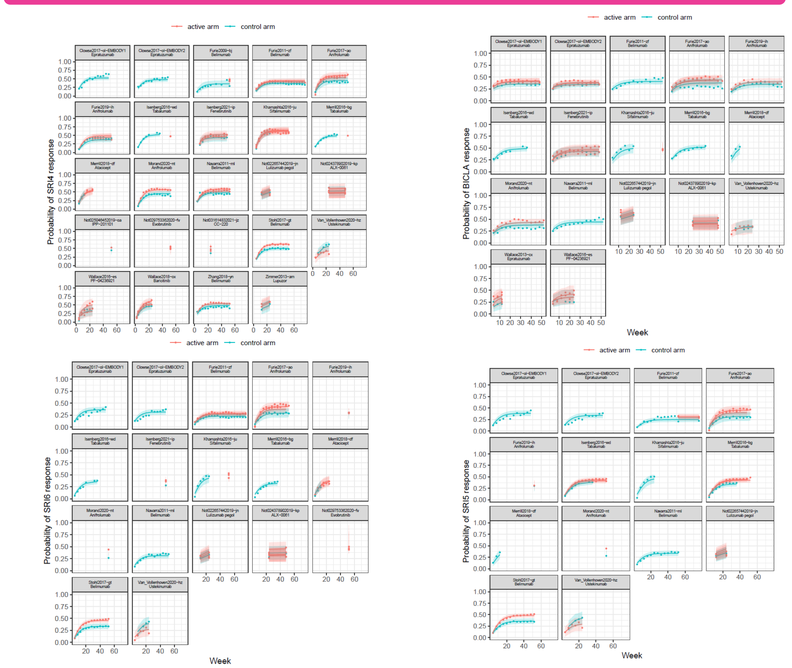
- ❑SLE trials were searched using PubMed and www.clinicaltrials.gov using treatment name, SLE and clinical trial as search criteria (2000-2021).
- ❑The extracted information of each manuscript consists of 4 data structures:
  - ❑study - descriptors common to all treatment interventions within a study,
  - ❑intervention - descriptors of drug regimen of treatments within a study (administration, frequency, dose, compound, etc),
  - ❑unit - Baseline descriptors unique to treatment intervention (disease severity, SLE functioning, demographics, etc),
  - ❑outcomes - post-baseline SLE efficacy data. Extraction of data from plots in publications was performed using Webplot Digitizer.
- ❑The final curated dataset consisted of 25 studies and 81 treatment arms. (Table 1)
- ❑ A previously developed SLE latent variable model (*K Goteti et al ACOP Annual Meeting 2021,* PIB-011) of placebo arm (placebo + standard of care treatments) patients from multiple studies was used to describe aggregate SLE endpoints (SRI-4, SRI-5, SRI-6, and BICLA) over time for the various SLE placebo and treatment arms in a Bayesian MBMA framework.
- ❑ Continuous dose-effect relationships using an Emax model were included for anifrolumab, belimumab, CC-220 (Iberdomide), epratuzumab, lulizumab pegol, and sifalimumab while the remaining drug, dose, route, and frequency combinations were modelled as discrete dose effects.
- ❑ Model variations were explored and compared using the expected log posterior density (ELPD) criterion and were evaluated using residual diagnostics and visual predictive checks (VPCs).
- ❑All modeling was done in CmdStanR.

RESULTS

Table I: Drug regimens for different SLE treatments in literature review (2000-2021)

Amount (unit)	Route of Administration	Frequency	Study n (%)	Treatment Arm n (%)	Enrolled Patients n (%)
Treatment: ALX-0061					
75 (mg)	subcutaneous	Q4W	1 (4)	1 (2)	64 (1)
150 (mg)	subcutaneous	Q2W	1 (4)	1 (2)	62 (1)
150 (mg)	subcutaneous	Q4W	1 (4)	1 (2)	62 (1)
225 (mg)	subcutaneous	Q2W	1 (4)	1 (2)	62 (1)
Treatment: Anifrolumab					
150 (mg)	IV	Q4W	1 (4)	1 (2)	93 (1)
300 (mg)	IV	Q4W	3 (12)	3 (5)	459 (6)
1000 (mg)	IV	Q4W	1 (4)	1 (2)	104 (1)
Treatment: Ataciept					
75 (mg)	subcutaneous	QW	1 (4)	1 (2)	102 (1)
150 (mg)	subcutaneous	QW	1 (4)	1 (2)	104 (1)
Treatment: Baricitinib					
2 (mg)	oral	QD	1 (4)	1 (2)	105 (1)
4 (mg)	oral	QD	1 (4)	1 (2)	104 (1)
Treatment: Belimumab					
1 (mg/kg)	IV	Q2Wx3+Q4W	3 (12)	3 (5)	673 (8)
4 (mg/kg)	IV	Q2Wx3+Q4W	1 (4)	1 (2)	111 (1)
10 (mg/kg)	IV	Q2Wx3+Q4W	4 (16)	4 (7)	1145 (14)
200 (mg)	subcutaneous	QW	1 (4)	1 (2)	556 (7)
Treatment: CC-220					
0.15 (mg)	oral	QD	1 (4)	1 (2)	42 (1)
0.3 (mg)	oral	QD	1 (4)	1 (2)	82 (1)
0.45 (mg)	oral	QD	1 (4)	1 (2)	81 (1)
Treatment: Epratuzumab					
100 (mg)	IV	Q2W	1 (4)	1 (2)	39 (0)
400 (mg)	IV	Q2W	1 (4)	1 (2)	38 (0)
600 (mg)	IV	QW	3 (12)	3 (5)	568 (7)
1200 (mg)	IV	Q2W	3 (12)	3 (5)	563 (7)
1800 (mg)	IV	Q2W	1 (4)	1 (2)	38 (0)
Treatment: Evobrutinib					
25 (mg)	oral	QD	1 (4)	1 (2)	118 (1)
50 (mg)	oral	BID	1 (4)	1 (2)	117 (1)
75 (mg)	oral	QD	1 (4)	1 (2)	117 (1)
Treatment: Fenebrutinib					
150 (mg)	oral	QD	1 (4)	1 (2)	87 (1)
200 (mg)	oral	BID	1 (4)	1 (2)	88 (1)
Treatment: IPP-201101					
200 (mcg)	subcutaneous	Q4W	1 (4)	1 (2)	101 (1)
Treatment: Lulizumab pegol					
1.25 (mg)	subcutaneous	Q2W	1 (4)	1 (2)	70 (1)
5 (mg)	subcutaneous	Q2W	1 (4)	1 (2)	68 (1)
12.5 (mg)	subcutaneous	Q2W	1 (4)	1 (2)	68 (1)
12.5 (mg)	subcutaneous	QW	1 (4)	1 (2)	69 (1)
Treatment: Lupuzor					
200 (mg)	subcutaneous	Q2W	1 (4)	1 (2)	51 (1)
200 (mg)	subcutaneous	Q4W	1 (4)	1 (2)	49 (1)
Treatment: PF-04236921					
10 (mg)	subcutaneous	Q6Wx3	1 (4)	1 (2)	45 (1)
50 (mg)	subcutaneous	Q6Wx3	1 (4)	1 (2)	47 (1)
Treatment: Sifalimumab					
200 (mg)	IV	Q2Wx3+Q4W	1 (4)	1 (2)	108 (1)
600 (mg)	IV	Q2Wx3+Q4W	1 (4)	1 (2)	108 (1)
1200 (mg)	IV	Q2Wx3+Q4W	1 (4)	1 (2)	107 (1)
Treatment: Tabalumab					
120 (mg)	subcutaneous	Q2W	2 (8)	2 (4)	753 (9)
120 (mg)	subcutaneous	Q4W	2 (8)	2 (4)	754 (9)
Treatment: Ustekinumab					
6-90 (mg/kg-mg)	IV-SC	once-Q8W	1 (4)	1 (2)	60 (1)

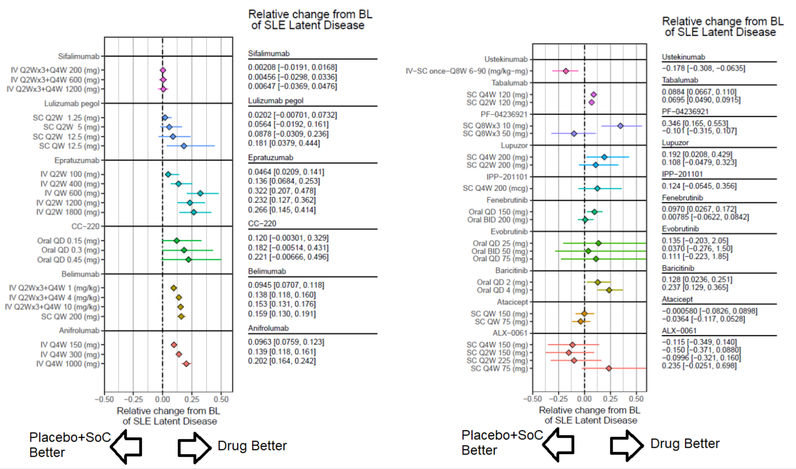
Figure 1: Visual Predictive Checks for SLE endpoints



RESULTS

- ❑ The literature review identified 25 different studies, 81 different treatment arms, and a total of 16 different drugs of SLE, with the most common being belimumab, anifrolumab, and epratuzumab (Table I).
- ❑ The most common endpoints reported were SRI-4, SRI-6, BICLA, and SRI-5. Other efficacy outcomes, such as Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) and Lupus Low Disease Activity State (LLDAS), were not widely reported so they were not included as outcomes in model development due to data limitations.
- ❑ After exploring model variations, a model with relative change treatment effect and without any treatment effects on the rate parameter provided adequate fit according to ELPD.
- ❑ Residual diagnostics of this model were not reflective of any model deficiencies, and VPCs showed alignment between the observed and simulated data; therefore, this model was selected as the final predictive MBMA DTM. (Figure 1)
- ❑ Model estimates indicate that for a treatment arm receiving anifrolumab (mg) IV Q4W treatment, the effect at 50% of Emax is achieved at a dose of 259 mg (95% CI = (71, 544)) and for a treatment arm receiving belimumab IV (mg/kg) Q2Wx3+Q4W treatment, the effect at 50%of Emax is achieved at a dose of 0.79 mg/kg (95% CI = (0.33,1.5)). (Figure 2)

Figure 2: Treatment effect estimates using MBMA SLE DTM



CONCLUSION

- ❑ A literature review of randomized clinical trials of drugs for SLE was performed where summary-level data of longitudinal efficacy data, dose regimens, and baseline disease severity was collected for each treatment arm.
- ❑ This summary data was used to develop a latent MBMA DTM for the SLE longitudinal efficacy data of SRI and BICLA SLE outcomes.
- ❑ The model included a continuous Emax dose effect for the FDA approved SLE treatments anifrolumab and belimumab.
- ❑ The final MBMA DTM can be used to predict response rates of SRI and BICLA so they can be used as benchmarks for new treatments of SLE.