SAT0253 EFFICACY AND SAFETY OF LEFLUNOMIDE THERAPY IN LUPUS NEPHRITIS:A META-ANALYSIS

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Objectives: To evaluate the efficacy and safety of leflunomide in treating lupus nephritis (LN).
Methods: According to the requirements of meta-analysis, a literature search about efficacy and safety of leflunomide therapy in LN was performed among Cochrane clinical controlled trials database, PubMed, BMJ-Clinical Evidence, CNKI, VIP and Wanfang data from the establishment of the database till December 2010.All included RCTs were graded in term of randomization, allocation concealment and blinding and non-RCTs were graded in term of grouping method, blinding, withdrawal and loss of follow-up, baseline comparability, diagnostic criteria and bias control. RevMan 5.0 software was used for meta-analysis.
Results: A total of 828 literatures were included. Five RCTs and 2 non-RCTs were enrolled for meta-analysis.Leflunomide group was treated with leflunomide and glucocorticoid, while control group was given cyclophosphamide and glucocorticoid or placebo. The 24 h urine protein, SCr and SLEDAI scores of leflunomide group were significantly lower than that of cyclophosphamide group. There was no significant difference in C3,positive rate of anti-ds DNA between leflunomide group and cyclophosphamide group. There was no significant difference in infection, herpes zoster,hypertension, palpitations, leukopenia, alopecial, elevation in ALT, memoxenia, rashes, or the incidence of gastrointestinal reactions between the two groups.
Conclusions: Based on the current evidence, the efficacy and safety of leflunomide for treatment of LN are close to cyclophosphamide. Further evidence from RCT studies is needed to elucidate the efficacy and safety of leflunomide for LN.
Disclosure of Interest: None declared
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SAT0254 SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SUBCUTANEOUS AND INTRAVENOUS ANIFROLUMAB IN HEALTHY VOLUNTEERS

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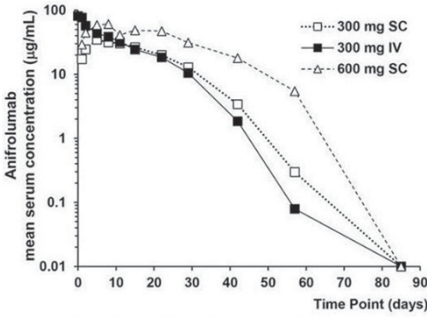
Background: Anifrolumab is a fully human anti–interferon-α receptor monoclonal antibody in Phase III development for systemic lupus erythematosus (SLE). In Phase IIb trials, intravenous (IV) anifrolumab (300 mg every 4 weeks) significantly decreased SLE disease activity with safety and tolerability comparable to placebo.[1]
Objectives: The primary objective of this Phase I, double-blind, randomized, controlled study (NCT02601625) was to characterize the pharmacokinetics (PK), safety, and tolerability of anifrolumab administered subcutaneously (SC) and intravenously to healthy volunteers.
Methods: Thirty male and female adults were assigned to three sequential treatment cohorts of equal size (anifrolumab 300 mg SC injection; anifrolumab 300 mg IV; anifrolumab 600 mg SC by infusion). Individuals were randomized within each cohort to receive a single dose of either anifrolumab (n=6/cohort) or placebo (PBO) (n=4/cohort). Serial blood samples were collected up to Day 85. Serum anifrolumab concentrations were analyzed with a validated assay. PK parameters were estimated by noncompartmental analysis. Immunogenicity of anifrolumab was assessed by measuring serum anti-drug antibodies (ADAs).
Results: Anifrolumab serum concentration-time profiles and primary PK parameters in healthy volunteers are presented in the figure and table, respectively. Anifrolumab serum concentrations were below the limit of detection in all individuals by 85 days post dose. Maximum serum concentrations in the SC cohorts occurred after 4 to 7 days. Exposure to SC anifrolumab increased approximately dose proportionally from 300 mg to 600 mg based on AUC. At the 300-mg dose, anifrolumab exposure after SC administration reached approximately 86% of the IV administration exposure. SC administration of anifrolumab 300 mg and PBO elicited minimal injection-site reactions. Transient injection-site induration occurred in five of six individuals in the anifrolumab 600-mg group and two of four in the PBO group. Transient, mild to moderate injection-site induration and pruritus occurred simultaneously in two of six individuals in the anifrolumab 600-mg group, but not those in the PBO group. Adverse events were reported by 50% (n=9) of anifrolumab-treated and 33% (n=4) of PBO-treated individuals. No serious adverse events were observed. ADAs were detected in only one individual in the anifrolumab 300-mg IV group at the Day-85 assessment.

Anifrolumab Serum PK Parameters

	Anifrolumab		
	300 mg SC (N=6)	300 mg IV (N=6)	600 mg SC (N=6)
C_{max} (μg/mL)			
Mean ± SD	36.2±11.6	82.4±13.2	63.9±20.5
CV (%)	32.1	16.0	32.0
AUC (day.μg/mL)			
Mean ± SD	785±331	907±175	1,828±680[a]
CV (%)	42.1	19.3	37.2
t_{max} (day)			
Median	4.13	0.03	7.00
Minimum–maximum	4.02–7.00	0.03?1.03	3.96?8.95

[a]N=5 because 1 individual was lost to follow-up at 1 month post dose. AUC = area under serum concentration-time curve from time zero extrapolated to infinity; C_{max} = observed maximum serum concentration; CV = coefficient of variation; t_{max} = time to reach maximum serum concentration.

Serum Concentration–Time Profiles



Mean data below limits of detection are plotted as 1/2 of the lower limits of quantification (0.02 μg/mL).

Conclusions: Exposure of anifrolumab 300 mg SC was approximately 86% of IV administration, with single SC administrations of anifrolumab being generally well-tolerated in healthy volunteers.
References:
[1] Furie R, et al. Arthritis Rheumatol. 2017;69:376–86.
Disclosure of Interest: R. Tummala Employee of: AstraZeneca, T. Rouse Employee of: AstraZeneca, A. Berglind Shareholder of: AstraZeneca, BMS, Employee of: AstraZeneca, L. Santiago Shareholder of: AstraZeneca, Employee of: MedImmune
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SAT0255 A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, ASCENDING-DOSE, SAFETY STUDY OF CC-220 IN SUBJECTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: CC-220 is a CUL4CRBN E3 ubiquitin ligase modulator that binds to cereblon and leads to potent and deep reduction of the transcription factors Ikaros (IKZF1) and Aiolos (IKZF3), which are overexpressed in the peripheral blood of Systemic Lupus Erythematosus (SLE) subjects. This study evaluated the safety, and tolerability of CC-220 in subjects with SLE. Exploratory efficacy assessments were included.
Methods: Subjects with history of SLE ≥6 months and a baseline of hybrid SELENA-SLEDAI (hSS) score ≥4 were randomized to 1 of 4 escalating doses of CC-220 or matching placebo (PBO). The 4 active treatments were CC-220 0.3 mg QOD, 0.3 mg QD, 0.3 mg alternating with 0.6 mg QD, and 0.6 mg QD; subjects were randomized 4:1 active to PBO in each group for 12 weeks of treatment, followed by 12 weeks of observational follow-up and/or long-term extension. Stable doses of corticosteroids (≤10 mg prednisone or equivalent daily), non-steroidal anti-inflammatory drugs, and antimalarials were permitted. Safety assessments included clinical evaluation of adverse events (AEs), laboratory parameters, electrocardiograms, physical examinations, and overall tolerability. Exploratory efficacy assessments included hSS, Cutaneous Lupus Area and Severity Index (CLASI) skin scores, Physician Global Assessment (PGA), swollen joint counts (SJC), and tender joint counts (TJC).
Results: A total of 42 adult subjects were randomized; 39 subjects were female (93%); Mean age was 47.2 years; 64% were White and 31% were Black or African-American. Mean SLE duration was 9.4 years, with a mean baseline hSS score of 6.6, CLASI activity score of 9.8, and PGA score of 1.3. Seventy-nine percent of subjects completed the study; 9 of 42 subjects discontinued, of which 6 subjects discontinued due to an adverse event (AE): 1 in the placebo group and 5 in the 2 highest CC-220 groups combined. No discontinuations were due to lack of efficacy. Four subjects had serious AEs (highest CC-220 doses: n=2 [pneumonia]; PBO: n=2). Three subjects had neutropenia (grade 3: n=2; grade 1: n=1); 2 subjects in the highest CC-220 dose group had dermatitis, and 1 subject in the 0.3 mg QD and 1 in the 0.6 mg QD dose groups had urticaria. Mean reductions in the CLASI activity score at day 85 ranged from 4.3 to 7.8 in the CC-220 treatment groups compared to an increase of 0.4 in the placebo group. More subjects receiving CC-220 had a ≥4-point reduction in hSS score vs PBO by Day 85 (22.2%>50.0% vs 12.5%).
Conclusions: CC-220 was generally well tolerated in this SLE population over 12 weeks of treatment, with neutropenia and dermatitis observed at the highest doses studied. Treatment with CC-220 resulted in a trend toward greater improvement