The future perspectives in the treatment of SLE & Sjögren’s

Background: Lupus nephritis (LN) is one of the most common severe clinical manifestations of systemic lupus erythematosus (SLE), occurring in 21%–48% of SLE patients.[1] The kidney is the major organ affected in SLE, with persistent inflammation leading to progressive loss of renal function and chronic kidney disease (CKD). The decline in kidney function levels in accumulation of multiple circulating uremic toxins negatively affect multiple organ systems, causing increased cardiovascular and kidney damage, among other effects.[2] Given the clear link to kidney function, uremic toxins may serve as biomarkers of kidney damage and of treatment response. Anifrolumab, a monoclonal antibody that targets the type I interferon (IFN) receptor subunit 1, is approved for moderate to severe SLE treatment.[3]

Objective: To identify novel biomarkers of treatment response and provide insights into the mechanism of action of anifrolumab in LN.

Methods: In the 52-week phase 2 clinical trial TULIP-LN (NCT02547922), 147 patients with active LN were randomized 1:1:1 to receive intravenous anifrolumab every 4 weeks at standard SLE dosing (basic regimen [BR], 300mg), intensified dosing (intensified regimen [IR], 900mg for the first 3 doses, 300mg thereafter), or placebo in addition to standard therapy.[4] Serum samples were obtained from 140 of these patients at baseline (BL) and Weeks 12, 24, and 52. Serum metabolites were analyzed using an unbiased liquid chromatography–mass spectrometry-based approach. Metabolites that were differentially modulated in the anifrolumab IR vs placebo group were identified using a mixed effects model evaluating the interaction of metabolite levels and treatment, adjusted for patients’ IFN gene signature (IFNGS) status (high/low) and 24-hour urine protein–creatinine ratio (UPCR ≥3 or ≤3). Relationships between BL metabolite level and clinical characteristics of kidney damage were assessed by Spearman’s correlation. Association of BL metabolite levels with complete renal response were evaluated by logistic regression, adjusted for IFNGS and UPCR status.

Results: Our unbiased metabolomic approach identified 2 metabolites significantly impacted by anifrolumab treatment compared with placebo (Figure 1). Cytosine (Cyt) and indoxyl sulfate (IS) levels were significantly reduced following anifrolumab IR treatment compared with placebo, while an intermediate, non-significant reduction was observed longitudinally with anifrolumab BR. At baseline, Cyt and IS serum levels were positively correlated with serum creatinine and negatively correlated with estimated glomerular filtration rate. Baseline IS levels were also associated with complete renal response at Week 52. Compared to the trend observed in nonresponders, IS levels in responders were reduced from BL to Week 52. A trend in reduction of multiple uremic toxins not limited to IS was detected with anifrolumab treatment compared with placebo. An increase in creatinine clearance with anifrolumab treatment was observed longitudinally, suggesting improvements in kidney function following anifrolumab treatment. Over-all, our results contribute to a deeper understanding of how inhibition of type I IFN affects renal disease in LN.

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REFERENCES:
Background: Telitacicept (TACI-Fc fusion protein) is a novel BlyS (B-lymphocyte stimulator)/APRIL (a proliferation-inducing ligand) dual inhibitor, which has been approved in 2021 in China for the treatment of patients with active systemic lupus erythematosus (SLE)[1].

Objectives: Assess the efficacy and safety of telitacicept in SLE patients in a double-blind, randomized, placebo-controlled, phase 3 trial.

Methods: In this study, 335 active SLE patients who were receiving stable standard therapy with positive ANA/anti-dsDNA and a SELENA-SLEDAI score ≥8 were randomized 1:1 to receive telitacicept 160 mg (N=167) or placebo (N=168) subcutaneously weekly for 52 weeks. The primary endpoint was the response rate of SLE responder index 4 (SRI4) at Week 52. Key secondary endpoints included: SELENA-SLEDAI, PGA, immunological biomarkers including C3, C4, IgM, IgG, IgA and CD19+ B cells. Safety was assessed during the study.

Results: Baseline demographics and disease characteristics were comparable between the two groups. The primary endpoint at Week 52 was met, with significantly greater proportions of patients in telitacicept 160 mg group vs placebo group achieving SRI4 response (Table 1). SRI4 response was sustained in telitacicept 160 mg group up to Week 52 (Figure 1A). Significantly greater proportions of subjects in telitacicept 160 mg group had improvement in SELENA-SLEDAI and PGA (Table 1 & Figure 1B, 1C). Rapid and sustained increase of C3 and C4 (Figure 1G, 1H), and reduction of IgM, IgG, IgA and CD19+ B cells (Figure 1D, 1E, 1F, 1I) were observed following telitacicept treatment. Incidences of TEAEs and infections were comparable between the two groups. Most of TEAEs were mild to moderate in severity. A greater proportion of patients receiving placebo had SAEs and serious infections compared with telitacicept 160 mg. (Table 1).

Conclusion: This phase 3 trial met the primary endpoint. Telitacicept 160 mg showed good clinical benefits and a favorable safety profile in SLE patients.

REFERENCE:

Acknowledgements: The patients and their families who participated in this clinical trial.


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Table 1. Key efficacy and safety data.

<table>
<thead>
<tr>
<th>Efficacy, FAS</th>
<th>Placebo (N=168)</th>
<th>Telitacicept 160 mg (N=167)</th>
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<tbody>
<tr>
<td>Primary endpoint</td>
<td></td>
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<tr>
<td>SRI-4 Response at Week 52 (MII), n(%)</td>
<td>64(38.1%)</td>
<td>138(82.6%)</td>
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<tr>
<td>SRI-4 Response at Week 52 (NRI), n(%)</td>
<td>55(32.7%)</td>
<td>112(67.1%)</td>
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<tr>
<td>SRI-4 Response at Week 52 (LOCF), n(%)</td>
<td>63(37.5%)</td>
<td>138(82.6%)</td>
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<tr>
<td>Secondary endpoints</td>
<td></td>
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<tr>
<td>≥4-point reduction in SELENA-SLEDAI at Week 52, n(%)</td>
<td>68(40.5%)</td>
<td>117(70.1%)</td>
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<tr>
<td>≥0.3-point reduction in PGA at Week 52, n(%)</td>
<td>94(58%)</td>
<td>141(84.4%)</td>
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<tr>
<td>SAE, n(%)</td>
<td>10.6±8.9</td>
<td>1.0±6.4</td>
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SAE Placebo Telitacicept 160 mg

TEAE, n(%) | 14(8.6%) | 103(61.6%) |

IgG, n(%) | 64(38.1%) | 138(82.6%) |

Infections and infestations | 8(E) | 12(7.2%) |

Urinary tract infection, n(%) | 26(15.5%) | 19(11.4%) |

Nasopharyngitis, n(%) | 11(6.5%) | 4(2.4%) |

Herpes zoster, n(%) | 6(3.6%) | 8(4.8%) |

Gastroenteritis, n(%) | 6(3.6%) | 3(1.8%) |

Serious infections | 5(3.0%) | 2(1.2%) |

*P<0.001 vs. Placebo. *Missing data were imputed by multiple imputation. **AEs with an incidence of ≥3% in any group were listed. FAS, full analysis set. SRI, SLE responder index. MI, missing data were imputed by multiple imputation. NRI, missing data were imputed as non-re- sponse. LOCF, missing data were imputed by last observation carry forward method. PGA, physician's global assessment. SFI, SLE flare index. SS, safety set. TEAE, treatment-emergent adverse event. SAE, serious adverse event. SOC, system organ class.