Table 1. CLASI-50 Response Rates by Subgroups at Week 24

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo (n=83)</th>
<th>0.15 mg QD vs Placebo</th>
<th>0.3 mg QD vs Placebo</th>
<th>0.45 mg QD vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/m (%)</td>
<td>Str Diff in % (95% CI)</td>
<td>P value</td>
<td>n/m (%)</td>
</tr>
<tr>
<td>All pts</td>
<td>37/83 (44.6)</td>
<td>19/42 (45.2)</td>
<td>0.4 (-17.3, 18.5)</td>
<td>0.999</td>
</tr>
<tr>
<td>CCLE-A p&lt;8</td>
<td>10/20 (50.0)</td>
<td>8/13 (61.5)</td>
<td>15.9 (-17.42, 45.45)</td>
<td>0.399</td>
</tr>
<tr>
<td>CCLE</td>
<td>23/50 (46.0)</td>
<td>15/30 (50.0)</td>
<td>4.8 (-17.22, 26.31)</td>
<td>0.368</td>
</tr>
<tr>
<td>SCLC</td>
<td>9/17 (52.9)</td>
<td>5/9 (55.6)</td>
<td>2.6 (-33.04, 36.33)</td>
<td>0.029</td>
</tr>
<tr>
<td>CCLE</td>
<td>5/18 (27.8)</td>
<td>7/14 (50.0)</td>
<td>22.2 (-10.51, 50.00)</td>
<td></td>
</tr>
</tbody>
</table>

Δ, treatment difference of adjusted means; CCLE, chronic cutaneous lupus erythematosus; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index activity score; IFN, interferon; SCLC, subacute cutaneous lupus erythematosus.

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Background: Hydroxychloroquine (HCQ) is commonly used for the treatment of various autoimmune diseases. The medication is generally well-tolerated. However, long-term use after 5 years may increase the risk of retinopathy. One study in 2014 has demonstrated the risk can be as high as 75%. Optical Coherence Tomography (OCT) has become a major modality in screening retinopathy.

Objectives: To evaluate the prevalence of retinal toxicity among patients using hydroxychloroquine and to determine various risk factors associated with hydroxychloroquine-associated retinal toxicity.

Methods: We performed a retrospective chart review on a cohort of adult patients with long-term use (≥ 5 years cumulative) of HCQ between January 1st, 2011 to December 31st, 2018 from the Kaiser Permanente San Bernardino County and Riverside medical center areas in Southern California, USA. Patients were excluded if they had previously been diagnosed with retinopathy prior to hydroxychloroquine use, were deceased, or had incomplete OCT exam. Our primary endpoint was the prevalence of patients who developed retinal toxicity detected by OCT, and later confirmed by retinal specialists. Potential risk factors associated with increased risk of retinopathy by approximately 5 to 19 folds. Similarly, weight-based dosage, duration of use and cumulative dose. Duration of therapy for 10 years or more increased risk of retinopathy by approximately 5 times. Patients who have cumulative dose of 2000 grams or more had greater than 15 times higher risk of developing retinopathy. Duration of use for 10 years or more (odd ratio 4.32, 95% CI 1.99 – 12.49), age (odd ratio 1.04; 95% CI 1.01 – 1.08), cumulative dose of more than 1500 grams (odd ratio 7.4; 95% CI 1.40 – 39.04) and atherosclerosis of the aorta (odd ratio 2.59; 95% CI, 124 – 5.41) correlated with higher risk of retinal toxicity.

Results: Among 676 patients exposed to more than 5 years of HCQ, the overall prevalence of retinal toxicity was 6.8%, and ranged from 2.5% to 22.2% depending on the age, weight-based dosage, duration of use and cumulative dose. Duration of therapy for 10 years or more increased risk of retinopathy by approximately 5 to 19 folds. Similarly, weight-based dosage of 7 mg/kg/day or greater was associated with increased risk of retinopathy by approximately 5 times. Patients with cumulative dose of 2000 grams or more had greater than 15 times higher risk of developing retinopathy. Duration of use for 10 years or more (odd ratio 4.32, 95% CI 1.99 – 12.49), age (odd ratio 1.04; 95% CI 1.01 – 1.08), cumulative dose of more than 1500 grams (odd ratio 7.4; 95% CI 1.40 – 39.04) and atherosclerosis of the aorta (odd ratio 2.59; 95% CI, 124 – 5.41) correlated with higher risk of retinal toxicity.

Conclusion: The overall prevalence of retinopathy was 6.8%. Regular OCT screening, especially in patients with hydroxychloroquine use for more than 10 years, daily intake > 7mg/kg, or cumulative dose > 1500 grams is important in detecting hydroxychloroquine-associated retinal toxicity.

Fig 1. CLASI-50 Percent Change from Baseline by CI. Subtype for All Patients and Patients with High Baseline Expression of M04 or Type I IFN Gene Signature.
Methods: Pre-treatment whole blood samples were collected in TEMPUS tubes from subjects undergoing first RTX treatment within BILAG-BR. IFN-Scores were derived using a custom Tagman array as previously described [1]. Clinical response was defined as improvement in BILAG-2004 disease activity, with a maximum of one domain showing persistent BILAG-2004 grade B disease, and no new BILAG grade A or B disease flares at 6 months. The mucocutaneous domain of BILAG was then analysed separately.

Results: 147 patients were studied, of whom 90 had follow up data available. Baseline BILAG-2004 grade A/B disease activity predominantly affected the mucocutaneous domain in 74/147 (50.3%), musculoskeletal in 61/147 (41.5%), and renal domain 66/147 (37.4%). At 6 months 59/90 (65.6%) achieved an overall treatment response. Responders showed significantly higher mean IFN-Score-B compared with non-responders (-1.8 vs -2.4, p = 0.04). Among those with active grade A/B BILAG-2004 mucocutaneous disease at baseline, 38/50 (76%) showed improvement within this domain at 6 months. However, among overall non-responders, 77/109 (22.8%) had new or residual BILAG-A mucocutaneous disease at 6 months post RTX, indicating it to be a substantial component of overall treatment failure. In contrast, persistent grade A musculoskeletal disease was seen in 9.7% of non-responders. BILAG-A mucocutaneous disease is characterised by severe manifestations including extensive rashes covering > 18% of body surface area, severe bullous lupus or paucicellular and disabling deep mucosal ulceration. Neither IFN-Score-A nor IFN-Score-B were significantly associated with the severity of mucocutaneous disease at baseline. However, individuals with persistent or new BILAG-A mucocutaneous disease at six months following RTX displayed significantly lower baseline IFN-Score-B than those with improving or residual less severe disease (-3.0 vs -2.1, p = 0.04) after RTX.

Conclusion: Low IFN score-B status identified an endotype of severe mucocutaneous SLE which was resistant to RTX therapy in the BILAG-BR cohort. We previously showed that high IFN-Score-B independently predicts overall therapeutic response to rituximab. Further work will aim to refine IFN status as overall and organ specific biomarkers in SLE.

REFERENCES:

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OP0134

NOVEL INTERFERON GENE EXPRESSION SCORES PREDICT REFRACTORY SEVERE CUTANEOUS DISEASE FOLLOWING RITUXIMAB THERAPY IN SLE


Background: We developed and validated two continuous interferon-stimulated gene (ISG) expression scores (IFN-Score-A and IFN-Score-B) that predict clinical outcomes in SLE. IFN-Score-A includes ISGs typically present in a global interferon signature while IFN-Score-B includes additional ISGs potentially responsive to multiple IFN subtypes [1]. We have previously shown that these scores associate with treatment response following rituximab (RTX) therapy within the British Isles Lupus Assessment Group (BILAG) Biologics Register (BILAG-BR), a UK wide study of patients treated with RTX for active SLE following cyclophosphamide and/ or mycophenolate mofetil treatment failure. Specifically, multivariable analysis showed higher baseline IFN-Score-B independently predicted BILAG response at 6 months post treatment [2]. We also showed that response of cutaneous lupus to RTX can be poor even when other organs respond well, and that interferons are enriched in the skin of patients with SLE where dysregulated keratinocytes are a source of IFNs [3]. MASTERPLANS is a consortium aimed at identifying therapeutic biomarkers in SLE.

OBJECTIVES: To investigate how IFN-Score-A and -B associated with skin disease and response to RTX.

OP0135

SAFETY AND EFFICACY OF SUBCUTANEOUS BELIMUMAB AND INTRAVENOUS RITUXIMAB COMBINATION IN PATIENTS WITH PRIMARY SJÖGREN’S SYNDROME: A PHASE 2, RANDOMISED, PLACEBO-CONTROLLED 68-WEEK STUDY

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