Table 1. Spearman Rho Correlation between timed function tests and MMT8, FZ-1, patient and physician VAS

<table>
<thead>
<tr>
<th>Δ MMT8</th>
<th>Δ FI-2</th>
<th>Δ Hip flexion right</th>
<th>Δ Hip flexion left</th>
<th>Δ Neck flexion</th>
<th>Δ Shoulder flexion right</th>
<th>Δ Shoulder flexion left</th>
<th>Δ Shoulder abduction right</th>
<th>Δ Shoulder abduction left</th>
<th>Δ Step test right</th>
<th>Δ Step test left</th>
<th>Δ Heel rise</th>
<th>Δ Toe rise</th>
<th>Δ Physician VAS</th>
<th>Δ Patient VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.382</td>
<td>0.337</td>
<td>0.398</td>
<td>0.413</td>
<td>0.590</td>
<td>0.300</td>
<td>0.222</td>
<td>0.236</td>
<td>0.236</td>
<td>0.744**</td>
<td>0.489</td>
<td>0.294</td>
<td>0.446</td>
<td>-0.506**</td>
<td>-0.597**</td>
</tr>
</tbody>
</table>

For correlations: *p < 0.05; **p < 0.01; ***p < 0.001

Conclusion: Timed function tests correlated well with MMT 8 and parameters with FI-2. Thus these tests are good alternatives in assessing disease activity and response assessment in inflammatory myositis.

References:

Disclosure of Interests: None declared

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SAT0315

INHIBITION OF MICROSOMAL PROSTAGLANDIN E SYNTHASE-1 (mPGES-1) BY GS-248 REDUCES PROSTAGLANDIN E2 BIOSYNTHESIS WHILE INCREASING PROSTACYCLIN IN HUMAN SUBJECTS

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Background: Microsomal prostaglandin E synthase-1 (mPGES-1) catalyzes the formation prostaglandin (PG) E₂ from cyclooxygenase derived PGH₂. Inhibition of mPGES-1 leads to reduction of pro-inflammatory PGE₂, while in vessels there is a concomitant increase of vasoprotective prostacyclin (PGI₂) via shunting of PGH₂ to PGI₂. The prostaglandin profile following mPGES-1 inhibition, explains the anti-inflammatory effects and also opens for the possibility of treating inflammatory diseases with concomitant vasculopathies. GS-248 is a potent and selective inhibitor of mPGES-1 exhibiting sub-nanomolar IC₅₀ in human whole blood ex vivo.

Objectives: To evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of GS-248.

Methods: Healthy males and females (age 18–73 years) were included in the study. Six cohorts were administered single oral doses of 1-300mg GS-248 (n=36) or placebo (n=12), three cohorts were administered once daily doses of 20-180mg GS-248 (n=18) or placebo (n=12) over ten days. In addition, 8 subjects were treated in a separate cohort with 200mg celecoxib bid for ten days. Blood samples were drawn for measurement of GS-248 exposure and production of PGE₂ after LPS incubation ex vivo. The content of PGE₂ and PGI₂ metabolites was measured in urine. All analyses were performed by LC-MS/MS.

Results: GS-248 was safe and well tolerated at all tested dose levels. Maximum plasma concentration was achieved 1 - 2.5 hours after dosing, and half-life was about 10 hours. Induced PGE₂ formation ex vivo, catalyzed by mPGES-1, was completely inhibited for 24 hours after a single low dose (40mg) of GS-248. In urine, GS-248 dose-dependently reduced the excretion of PGE₂ metabolite by more than 50% whereas the excretion of metabolite increased more than twice the baseline levels. In the celecoxib cohort urinary metabolites of both PGE₂ and PGI₂ were reduced with approx 50%.

Conclusion: GS-248 at investigated oral doses was safe and well tolerated. There was a sustained inhibition of LPS induced PGE₂ formation in whole blood. In urine, there was a metabolite shift showing reduced PGE₂ and increased PGI₂, while celecoxib reduced both PGE₂ and PGI₂ metabolites. This suggests that selective inhibition of mPGES-1 results in systemic shunting of PGH₂ to PGI₂ formation, leading to anti-inflammatory and vasodilatory effects, while preventing platelet activation. The results warrant further evaluation of GS-248 in inflammatory conditions with vasculopathies such as Digital Ulcers and Raynaud’s Phenomenon in Systemic Sclerosis.

References:


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SAT0316

ANTI-PM/SCL ANTIBODIES IN SYSTEMIC SCLEROSIS: CLINICAL ASSOCIATIONS IN THE RESCLE COHORT

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Background: Anti-PM/Scl antibodies are associated to systemic sclerosis (SSc) but are not specific to SSc. The true prevalence of anti-PM/Scl antibodies in SSc is unknown, ranging from 2.5% to 12.5%. An association between anti-PM/Scl antibodies with muscular involvement, pulmonary fibrosis, calcinosis, and a relatively benign prognosis have been described.

Objectives: To compare the clinical manifestations and prognosis of SSc patients according the presence of anti-PM/Scl antibodies in the cohort of RESCLE (Spanish Scleroderma Registry).

Methods: From the Spanish Scleroderma Study Group database, we selected patients in whom anti-PM/Scl antibodies had been tested. We compared demographic features, clinical manifestations, laboratory characteristics, and survival data between patients according the anti-PM/Scl antibodies status.

Results: 72 out of 947 (7%) patients tested positive for anti-PM/Scl antibodies. As presenting SSc manifestations, patients with anti-PM/Scl antibodies had higher prevalence of puffy fingers (11% versus 2%; p=0.002) and arthralgias (11% versus...
versus 4%; p=0.03), and lower prevalence of Raynaud’s phenomenon (65% versus 82%; p=0.002). Regarding cumulative manifestations, myositis (51% versus 15%; p<0.001), arthritis (43% versus 22%; p=0.001), and interstitial lung disease (ILD) (60% versus 45%; p=0.014) were more prevalent in patients with anti-PM/Scl antibodies. In fact, those patients with anti-Pm/Scl antibodies presented with FVC (77.4% ± 23.1% versus 85.8% ± 23.1%; p=0.006) and more severe ILD defined as FVC <70% (41% versus 24%; p=0.004). Death rate was similar in patients with and without PM/Scl antibodies (18% versus 17%; p=0.871). We did not find differences in terms of death rate nor in the causes of death (SSc and non-SSc-related) according to the anti-PM/Scl antibodies profile. The 5- and 10-years survival rates of patients with anti-PM/Scl antibodies were 91% and 82% respectively, without differences with those without these antibodies (93% and 85%, respectively).

Conclusion: In Spanish SSc patients, the presence of anti-PM/Scl antibodies confer a distinctive clinical profile. However, anti-PM/Scl antibodies do not play a role in the prognosis of these patients.

References:


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