Glucocorticoid biomarkers of steroid response and disease activity in Vogt-Koyanagi-Harada disease

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Introduction

- Earlier immunomodulatory treatment is associated with better visual outcomes in refractory VKH patients.
- The evaluation of disease activity may be a challenge due to the known presence of subclinical activity in some clinically inactive VKH patients.
- The mechanisms of glucocorticoid (GC) are mediated by the GC receptor (GR) with two classical transcriptional isoforms: alpha isoform (GRα) and beta isoform (GRβ).
- GR-isofoms have been implicated in the mechanism of GC-refractoriness in other inflammatory diseases.

Objective

- To investigate the role of GR isoforms and MKP1 -a GC inducible gene- in peripheral blood mononuclear cells (PBMC) as a biomarker of GC-refractoriness and disease activity, in patients with VKH.

Patients & Methods

- Prospective cohort study of adult VKH subjects, with no other auto-immune disorders, cancer, pregnancy or systemic anti-inflammatory drugs within 1 month.
- Definition of GC-Refractoriness: Reactivation with an equivalent dose of prednisolone of 10 mg or more, during the first cycle of steroid treatment.
- Definition of reactivation: Anterior chamber cells and/or vitreous haze > 1+ or presence of subretinal fluid/serous retinal detachment or findings compatible with active inflammation on ancillary testing (FFA, OCT, ICG).
- Treatment scheme: Prednisone 1mg/kg/day until controlling inflammation. Azathioprine was added if GC-refractoriness or GR-related side effects.
- After isolation using a Ficoll gradient protocol, PBMCs were cultured in complete RPMI + 10% Fetal Bovine Serum for 3 days.
- PBMCs were stimulated with Dexamethasone 1µM the last 6 days of culture.
- PBMCs of healthy donors (HD) were isolated and stimulated with CD3/CD28 (5 µg/ml), LPS (10 ng/ml) and PHA (5 µg/ml) for 24 hrs.
- Biomarkers: Quantitative RT-PCR was used to evaluate mRNA levels of GRα, GRβ, and MKP-1.

Results

Patients & Methods (cont’d)

- The cohort was divided in inactive and active patients. Data are presented as the mean ± standard deviation (Mann Whitney test, *p=0.005).
- A comparison with the data regarding active and inactive VKH patients is included.
- Data are presented as the mean ± standard deviation (Mann Whitney test, *p=0.05).
- Role of inflammation in the expression of MKP-1 in healthy donors.

Conclusion

- The evaluation of the expression of GR isoforms and MKP1 as potential biomarkers of treatment response and disease activity can contribute to the early identification of GC-refractoriness and subclincial inflammation in VKH patients.

References


Table 1. Demographics and clinical characteristics of VKH patients (n=20)

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<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>n=20</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>35 ± 10.7</td>
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<tr>
<td>VKH diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable</td>
<td>6 (30)</td>
<td></td>
</tr>
<tr>
<td>Incomplete</td>
<td>10 (50)</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>4 (20)</td>
<td></td>
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<tr>
<td>Clinical inflammation, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Active</td>
<td>7 (35%)</td>
<td></td>
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<tr>
<td>Inactive</td>
<td>13 (65%)</td>
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<tr>
<td>Treatment response, n (%)</td>
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<td></td>
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<tr>
<td>GC-sensitive</td>
<td>10 (50%)</td>
<td></td>
</tr>
<tr>
<td>GC-refractory</td>
<td>9 (45%)</td>
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<tr>
<td>Unknown*</td>
<td>1 (5%)</td>
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