Serum autoantibody profiling of primary Sjögren’s syndrome patients reveals novel biomarkers associated with the disease, disease activity, and clinical response to VAY736

Introduction

- Overexpression of B cell activating factor (BAFF) in salivary glands contributes to the pathogenesis of primary Sjögren’s syndrome (pSS) through autoimmune (AA) production.
- Treatment of pSS patients with VAY736, an anti-BAFF receptor mAb, appears promising and was associated with a depletion of circulating B cells and a positive therapeutic effect [1].
- In addition to the classical anti-SS-A/Ro and anti-SS-B/La, a broader set of AABs may reflect B cell disturbances in pSS and could serve as markers during clinical development of novel pSS therapeutics.

Objectives

- The study was undertaken to explore novel AABs in pSS and their associations with the disease, disease activity, and clinical response to VAY736.

Methods

- A discovery screen was designed comprising 1,596 antigens, which are directly relevant to pSS-associated processes (Fig. 2).
- Human protein antigens were selected from the Protagen xMAP® protein library of 8,000 recombinant proteins.
- Proteins are expressed in E.coli and purified using His-Tag protein purification.
- Antigens include diagnostic antigens as well as cytokines, chemokines, salivary gland proteins, proteins involved in apoptosis.

Fig. 2: Overview of antigens included in this study

- IgG antibodies were measured using the bead-based Luminex® xMAP® platform SeroTag® (Fig. 3).
- High-Throughput technology with human proteins as analytes
- Serum-based, minimal sample volume (~ 5µl) required
- Stable antibodies (IgG-all isoforms)
- Standardized and easy sample handling and logistics
- Luminex platform widely used and accepted by FDA, EMA

Fig. 3: Schematic SeroTag workflow of bead-based assays

Results

- Compared to HC, pSS patients had increased IgG AAB levels to 36 antigens, including the known SSA and SSB (p<0.05).
- Examples are shown in Fig. 4.
- No reduction in AAB levels was observed in response to VAY736 at week 12.

Conclusions

The genes encoding novel antigens are involved in apoptotic, anti-viral, metabolic, inflammatory, blood coagulation and B-cell processes, suggesting a possible link to the disease pathology. Further large-scale studies are needed to confirm the value of these markers.

References


Fig. 4: Box and Whisker plots showing novel autoantibodies in HC and pSS

Fig. 5: Autoantibodies correlating with clinical outcome scores

- 51 serum AAB levels correlated with salivary BAFF levels, but not BAFF serum levels (p<0.05, |r|>0.55).

Fig. 6: Autoantibodies correlating with salivary BAFF levels

- No reduction in AABs was observed in response to VAY736 at week 12.

Table 1: Statistical approach

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<th>Identification of AABs associated with pSS</th>
<th>Statistical approach</th>
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<td>AAB levels in HC and pSS patients at baseline</td>
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<td>pSS at baseline and week 12, as well as relative changes</td>
<td>Parameters: AAB levels in pSS patients at baseline and week 12, as well as relative changes Tests: Pearson correlation with clinical and lab scores</td>
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Table 2: Clinical and lab scores

- ESSDAI and ESSPRI
- Short Form-36 mental and physical
- Multidimensional Fatigue Inventory and fatigue sub-scores
- Patient’s and physician’s Visual Analog Scores
- Ocular Staining Score
- Salivary flow rate
- B cell count
- Serum and salivary BAFF

Fig. 1: Study design

- Serum samples were collected from pSS patients pre- and post-VAY736 administration, and from age and gender-matched HCs (Fig. 3). Statistical analysis was conducted as detailed in Table 1.