Objectives:

Direct and indirect. C4BP are known to be reduced by warfarin treatment (2) as well as by aPL. Its main isoform is bound to protein S in the circulation. Levels of both protein S and C4BP are known to be reduced by warfarin treatment (2) as well as by aPL, directly and indirectly.

Background:

Complement plays a role in the Antiphospholipid Syndrome (APS). C4b Binding Protein (C4BP) is a complement inhibitor with anticoagulant function (1). It belongs to the same protein family as β2GPI, the main antigen in APS. Its main isoform is bound to protein S in the circulation. Levels of both protein S and C4BP are known to be reduced by warfarin treatment (2) as well as by aPL, directly and indirectly.

Objectives:

To investigate the levels of C4BP in primary (p) and secondary (s) APS, also considering warfarin treatment.

Methods:

The total amount of C4BP (C4BP) was measured by using magnetic carbonyloxylated microspheres which were coupled with a monoclonal antibody against the α-chain of human-C4BP to capture the antigen. To detect C4BP the same antibody was used, biotinylated. The binding of biotinylated antibodies was detected by streptavidin-phycocerythrin and data were collected using a MAGPIX Multiplex Reader. Using independent t-test, we compared C4BP in 118 SLE patients with repeated positivity for Antiphospholipid antibodies (aPL) (39/118 on warfarin), 291 aPL negative SLE patients (16/291 on warfarin), 67 pAPS (33/67 on warfarin), and 322 controls (none on warfarin). We then performed an interaction and a mediation analysis (3) in the SLE group to study the impact of warfarin on C4BP levels: since warfarin is mostly prescribed to aPL+ patients, it is considered a mediator in the reducing effect of aPL on C4BP. Therefore we compared individuals exposed and non-exposed to the presence of aPL with or without the mediator warfarin and calculated the percentage of reduction in C4BP that could be attributed to aPL or warfarin.

Results:

Overall C4BP is 20% reduced in aPL+ patients (fig 1), independently of SLE, past thrombotic events and nephritis. Warfarin treated patients have lower levels of C4BP (fig 2). According to mediation analysis 11% of C4BP reduction is due to aPL and 9% to warfarin.

Conclusion:

Both aPL and warfarin decrease levels of C4BP, a complement and coagulation regulator. Reduction of this complement inhibitor could contribute to complement activation and thrombosis in APS. Our results raise new questions regarding the effects of warfarin treatment on complement and coagulation in APS.

References:


Disclaimer:

AV is employed at the Swedish Medical Products Agency; the views expressed in this paper are the personal views of the authors and not necessarily the views of the Government Agency.

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Disclosure of Interests:

None declared.

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EVALUATION OF A PATIENT COMPLETED DISEASE FLARE QUESTIONNAIRE IN PSORIATIC DISEASE

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Background:

Psoriatic Disease (PsD) is a chronic inflammatory disease of the skin, nails, joints, and entheses. A number of composite disease activity measures have been developed though there is yet consensus as to which to use in the clinic and in clinical trials. A patient completed disease flare questionnaire, covering multiple domains of disease impact, has been developed but has yet to be fully validated.

Objectives:

To validate the FLARE questionnaire in PsD.

Methods:

The 10 question FLARE instrument was administered to 141 patients in an observational study of treatment change in PsD over 6 months follow up. Disease activity was measured by the PASDAS and the gold standard of flare...
was based on patient opinion. ROC curve was constructed to examine the optimal cut-off for disease flare. Agreement between the FLARE instrument and patient opinion was assessed by Cohen’s kappa. Test-retest was assessed in 28 patients with stable disease who underwent repeat assessment within 2 weeks and evaluated by intra-class correlation coefficient (ICC).

**Results:** The FLARE questionnaire was administered at 367 patient encounters. ROC analysis indicated that the optimal cut-off for a flare of disease was 4 (sensitivity 82%, specificity 76%; area under curve 0.85: figure). Mean PASDAS scores were 2.7 and 6.3 for no-flare (4) and flare (≥4) respectively (p < 0.0001). For those patients who had a flare, the frequency of response to each question was given in the table. Agreement between patient opinion and questionnaire was 0.57, and between patient opinion and physician (based on treatment escalation) 0.43. ICC for the questionnaire was 0.87 (95% CI 0.72 – 0.94).

**Conclusion:** In PsD a flare represents escalation of symptoms and signs across multiple domains, as measured by the FLARE instrument; a score of 4 or more has external validity both in terms of composite disease activity and overall patient opinion of the state of their condition.

**References:**  

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**Table 1: FLARE item response for those in flare vs not in flare**

<table>
<thead>
<tr>
<th>Item</th>
<th>FLARE instrument score ≤4</th>
<th>FLARE instrument score ≥4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening itch</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Worsening skin area</td>
<td>35 (19)</td>
<td>108 (58)</td>
</tr>
<tr>
<td>Increasing joint pain</td>
<td>27 (15)</td>
<td>91 (49)</td>
</tr>
<tr>
<td>Increasing number of tender joints</td>
<td>34 (19)</td>
<td>161 (86)</td>
</tr>
<tr>
<td>Decrease in ability to perform activities</td>
<td>20 (11)</td>
<td>142 (76)</td>
</tr>
<tr>
<td>Worsening in ability to move easily</td>
<td>8 (4)</td>
<td>126 (67)</td>
</tr>
<tr>
<td>Increase in frustration</td>
<td>14 (8)</td>
<td>142 (76)</td>
</tr>
<tr>
<td>Worsening in depression</td>
<td>8 (4)</td>
<td>90 (48)</td>
</tr>
<tr>
<td>Worsening in feeling of tiredness all the time</td>
<td>37 (21)</td>
<td>148 (79)</td>
</tr>
<tr>
<td>Worsening in the number or combination of symptoms</td>
<td>7 (4)</td>
<td>134 (72)</td>
</tr>
</tbody>
</table>

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**Figure. ROC analysis of FLARE questionnaire**

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**AB1242**  
A NOVEL BIOMARKER OF MMP-CLEAVED PROLARGIN IS ELEVATED IN PATIENTS WITH PSORIATIC ARTHRITIS COMPARED TO OTHER FIBRO-INFLAMMATORY DISEASES

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**Background:** Psoriatic Arthritis (PsA) is a chronic inflammatory disease, characterized by involvement of skin, axial and peripheral skeleton. Prolargin is a class II small leucine-rich proteoglycan found to be expressed in connective tissues of patients with PsA, and previously suggested to be remodelled upon treatment. Fragments of prolargin could quantitatively tissue turnover in individuals with PsA and reflect pathological tissue changes in these patients.

**Objectives:** This study aimed at developing an immunoassay targeting a neo-epitope of prolargin cleaved by matrix metalloproteinases (MMPs), named PROM, and measure PROM levels in serum from two cohorts of patients affected by PsA and healthy controls.

**Methods:** Development of a novel immunoassay targeting a specific MMP-generated neo-epitope fragment of prolargin (PROM) together with technical validation was performed, and then evaluated in serum from two independent cohorts. The technical validation included inter- and intra-variation, linearity, spiking recovery, stability and specificity. Specificity was tested using an elongated peptide, a truncated peptide and a non-sense peptide. The Discovery Cohort consists of 13 healthy individuals and 11 PsA patients, mean age 58, 60.3% female and 100% Caucasian. The Validation Cohort included 35 healthy individuals and 112 PsA patients with low disease activity included in a 24-week randomized, double-blind, placebo-controlled trial of 3g n-3 polysaturated fatty acids (PUFA), a cohort of patients diagnosed with PsA by the CASPAR criteria. These patients had a mean age of 50.8, 57.8% female and 100% Caucasian. Clinical variables and serum samples were collected at baseline and after 24 weeks of follow-up. An unpaired t-test was used for evaluation of healthy individuals and patients affected by PsA, while a paired t-test was used for evaluation of treatment at baseline and after 24 weeks.

**Results:** A technically robust and specific assay was developed. The inter- and intra-assay variation of PROM was determined as 14% and 4% respectively. PROM showed a good dilution recovery, spiking recovery, and storage freezing-stability stability (All, 100%±20%). PROM showed to be specific towards the targeted sequence, and did not show any reactivity towards the truncated peptide, elongated peptide or non-sense peptide. In the Discovery Cohort, serum levels of PROM were increased in patients with PsA compared to healthy individuals (p=0.032, Figure 1A). This increase was confirmed by the Validation Cohort, where PsA patients were significantly increased compared to healthy individuals at baseline (p=0.002, Figure 1B). After 24 weeks, the levels of PROM were unchanged in the n-3 PUFA treated group.

**Figure 1.**

**Conclusion:** The novel biomarker PROM, reflecting connective tissue remodelling, is elevated in PsA patients compared to healthy controls in two independent cohorts. No significant association was found for PROM in a low disease activity group of PsA patients treated with n-3 PUFA.

**References:** None