Safety and preliminary evidence of efficacy in a phase I clinical trial of autologous tolerising dendritic cells exposed to citrullinated peptides (Rheumavax) in patients with rheumatoid arthritis

Ranjeny Thomas, Shayna Street, Nishta Ramnoruth, Helen Pahau, Soi Law, Marion E. G. Brundik, Claire Hyde, Brendan O’Sullivan, Christine Capini, Al Tran, Jennifer Ng, Sanjoy Paul. Diamantina Institute, Princess Alexandra Hospital, University of Queensland and School of Population Health, University of Queensland, Brisbane, Australia

Disclosures: none
Funding: NHMRC, ARC, Arthritis Qld, PAH Fund, Qld Smart State, Ausindustry

Theoretical background: generating regulatory T cells to suppress RA

- Dendritic cells (DC) bring antigens from tissues to draining lymph nodes, educating T cells. PAMPs activate DC NF-κB, promoting T cell activation
- DC generated in presence of NF-κB inhibitor Bay11-7082 (irreversible classical and alternate NF-κB pathway inhibitor) exposed to antigen suppress primed immune responses.

Peptides

Citrullinated peptide sequences
- VETGIDGOVI
- WYNCICHAAN
- LTQCIGSVLR
- QYMCIADQAGGLR

Human native protein
- Vimentin 447-455
- Fibrinogen β chain 433-441
- Fibrinogen α chain 717-725
- Collagen type II 1237-1249

Proof of concept phase I clinical trial of Rheumavax
Proof of concept phase I clinical trial Rheumavax: study design

Aims
- Demonstrate safety of Rheumavax
- Obtain evidence of mechanism
- Phase I clinical data to describe effects in man

Primary outcomes
- Safety
- Tolerance

Secondary outcomes
- Efficacy
- Swollen joints, tender joints, CRP and DAS

Groups
- Rheumavax 1 million x 1
- Rheumavax 5 million x 1. Control (no placebo)

Major inclusions
- HLA-SE+ ACPA+ RA any duration
- Treated by a rheumatologist
- Max prednisone 10mg

Major exclusions
- Malignancy
- Allergy (history and RAST test)
- Serious infection last 28 days

Dose
<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Age (SEM)</th>
<th>% Female</th>
<th>% RF+</th>
<th>Mean disease duration (SEM)</th>
<th>Concomitant treatment</th>
<th>Mean DAS (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (11)</td>
<td>58 (3)</td>
<td>54</td>
<td>91</td>
<td>2.3 yr (0.8)</td>
<td>MTX+LEF MTX+SSZ HCQ MTX+TNFi</td>
<td>2.9 (0.4)</td>
</tr>
<tr>
<td>1 million DC (9)</td>
<td>57 (3)</td>
<td>55</td>
<td>78</td>
<td>3.4 yr (0.9)</td>
<td>MTX+LEF MTX+SSZ+HCQ MTX+TNFi</td>
<td>2.9 (0.5)</td>
</tr>
<tr>
<td>5 million DC (9)</td>
<td>56 (3.4)</td>
<td>89</td>
<td>100</td>
<td>2.9 yr (1)</td>
<td>MTX MTX+SSZ+MTX HCQ+MTX SSZ+HCQ</td>
<td>2.5 (0.4)</td>
</tr>
</tbody>
</table>

Rheumavax: Baseline demographics

Indoleamine 2,3, dioxygenase (IDO)
- Enzyme catalyzing degradation of tryptophan to kynurenine
- Expression upregulated by inflammation, IFN-γ
- Increased IDO activity in RA serum (kyn:trp), No effect TNFi
- In humans chronic IDO associated with ageing, depression, insulin resistance, iNOS activity
- Trp starvation promotes T cell apoptosis and Treg function, blocking IDO improves some models of autoimmunity eg CIA
- BUT in the K/BxN mouse model of RA, blocking IDO improved disease by blocking B cell autoreactivity

Rheumavax: adverse events

Predicted toxicities
- Acute disease flare
- Anaphylaxis, allergy
- Injection site reaction or draining lymphadenopathy
- Hypoglycemia

Adverse events low dose: grade 1 (of 4)
- 1 low neutrophils
- 1 low lymphocytes
- 1 discovered lipoma
- 1 elevated alk phos

High dose: grade 1 (of 4)
- 2 headache
- 3 low Hb
- 2 low lymphocytes
- 2 low WCC
- 1 raised AST
- 1 raised ALT
- 1 transient hypoglycemia
**Rheumavax: DAS 4v over 6 months**

**Rheumavax: joint counts and systemic measures over 1 month**

**Rheumavax: Change in IDO related to change in regulatory populations in blood**

**Rheumavax: Regulation over time**

**Conclusions**

- Within the context of SE+ ACPA+ treated, early RA, cit-peptide exposed tolerising autologous DC:
- Well tolerated without major AE or flares
- Preliminary evidence of additional disease control to patients with active disease
- Systemic effects on insulin sensitivity, immune tolerance including reduction in IDO activity
- Proof-of-concept: tolerising immuno-therapy using cit-peptides
- Potential for further development of strategies targeting DC and cit-peptide in specific HLA-DR groups
- Tolerance biomarkers suggest improvement in immune "hyper-regulation"