Evidence based medicine


The Kinoid Technology

- Self-polysaccharide anti-IFN-alpha antibodies
- Targets multiple epitopes
- Neutralization of 13 IFN-alpha subtypes
- Specific to IFN-alpha vs cross-neutralization IFN-beta, -gamma
- No blocking anti-Ab antibodies (ADA)
- Broad and sustained efficacy

Phase I-II study of IFN-alpha Kinoid in SLE

**Demographics**

<table>
<thead>
<tr>
<th></th>
<th>18MCG</th>
<th>30MCG</th>
<th>60MCG</th>
<th>120MCG</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Age (Mean, Years)</td>
<td>36</td>
<td>31.7</td>
<td>31.7</td>
<td>38.3</td>
<td>33.2</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Asian (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Duration SLE disease (Mean Years)</td>
<td>10</td>
<td>10.3</td>
<td>10.3</td>
<td>10.3</td>
<td>10.3</td>
</tr>
</tbody>
</table>

**Concomitant Mediations**

<table>
<thead>
<tr>
<th></th>
<th>ICSH</th>
<th>LIEBOS</th>
<th>NS</th>
<th>ICSH</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Anti-Malarial (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Methotrexate (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Azathioprine (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Design**

- **Population:**
  - 18-50 years
  - SLE ACR 4/11
  - SLEDAI: 4-10
  - ANA and/or anti-dsDNA positive
  - Corticosteroid ≤20mg/day
  - No BILAG A
- **Objectives:**
  - Safety
  - Immune response
  - Neutralisation of IFN-alpha and SLE dysregulated genes
  - Clinical scores
  - Schedule of administration:
    - 3 injections, 0-7-28 days
    - 4th dose at week 12 in 50% of patients

**Phase I-II study of IFN-alpha Kinoid in SLE**

**Study design & population**

- DB, placebo controlled, 2:1
- Staggered dose increase:
  - Kinoid 30 mcg/dose vs placebo
  - Kinoid 60 mcg/dose vs placebo
  - Kinoid 120 mcg/dose vs placebo
  - Kinoid 240 mcg/dose vs placebo
- Schedule of administration:
  - 3 injections, 0-7-28 days
  - 4th dose at week 12 in 50% of patients

**Pharmacologicals**

- Neovacs: Engagement fees from Neovacs
- Frédéric HOUSSIAU, Bernard LAUWERS: Consultancy fees from Neovacs
- Geraldine GROUARD-VOGEL, Bernard FARGET, Olivier DIHELLIN, Pierre VANDERPAPELIERE: Neovacs employees, Patients held/tailed, Share options and stock
IFN-alpha-Kinoid Phase I-II study in SLE: Safety

- General safety
  - Mild to moderate, transient local or systemic reactions following Kinoid administration
- Serious Adverse Events:
  - One related SAE in patient after 1st 240 mcg dose:
    - SLEDAI= 12 at entry
    - Flare of lupus caused by spontaneous, abrupt stopping of prednisone 15mg, following T° elevation (38° C) 2 days after 1st Kinoid administration.
    - Hospitalization; No viral infection detected; Recovery without sequelae; Withdrawal from study.
  - One unrelated SAE in placebo: lupus nephritis at month 3
- No unexpected or severe infections

IFN-alpha-Kinoid Phase I-II study in SLE: Immunogenicity

IFN-alpha-Kinoid Phase I-II study in SLE: SLEDAI

IFN-alpha-Kinoid Phase I-II study in SLE: Transcriptomic studies

- Methodology
  - PBMC extracted total RNA, at baseline and follow-up visits
  - Hybridization on Genechip HGU133 Plus 2.0 arrays, using standard Affymetrix protocol
  - RMA (Robust Microarray Analysis) normalization of the samples - Genespring
- Controls
  - Pool of healthy volunteers (HV n=46)
  - In vitro stimulation of 9 HV with IFN-alpha2b
  - In vitro stimulation of 9 HV with IFN-alpha mix
- Signatures
  - All SLE dysregulated genes (comparison HV:SLE)
  - All IFN dysregulated genes (comparison HV with & without stimulation)
  - 21 genes selected by Yao et al, 2009, 33 HGU133 Plus 2.0 probes - IFN Score

SLE samples at baseline cluster into IFN signature-positive and -negative patients

SLE samples at baseline cluster into IFN signature-positive and -negative patients

IFN signature positive SLE n = 19
IFN signature negative SLE n=9

<table>
<thead>
<tr>
<th></th>
<th>IFN signature positive SLE n = 19</th>
<th>IFN signature negative SLE n=9</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>dsDNA Ab (U/L)</td>
<td>315.2 ± 185.3</td>
<td>38.6 ± 25.9</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>C3 (mg/L)</td>
<td>786.3 ± 46.7</td>
<td>786.3 ± 46.7</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>C4 (mg/L)</td>
<td>19.5 ± 10.7</td>
<td>19.5 ± 10.7</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>SLEDAI</td>
<td>8.2 ± 0.5</td>
<td>7.3 ± 0.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

SLE patients with positive IFN signature at baseline have biological indices of higher disease activity
SLE patients with positive IFN signature produce 10x more IFN-binding Ab in response to kinoid

Neutralization of IFN

IFN signature +
IFN signature -

*** p < 0.0005

Compared to placebo and IFN signature negative patients, the effects of kinoid therapy on IFN-induced genes are strongly and significantly different at V10 and V11

Analysis of individual effects of the kinoid on the expression of IFN-induced genes is indicative of a trend toward a dose-response effect

There is a significant correlation between the levels of IFN-binding Ab induced by the kinoid and the decrease in the IFN score at V10, and at V11

There is a significant correlation between the decrease in IFN score and the increase in C3 levels. The increase in C3 correlates significantly with IFN Ab titers.

- Safety: IFN-alpha K is Safe
- Immunogenicity: IFN-alpha K induces Anti-IFN-alpha antibodies in 100% of SLE patients

- Biomarkers:
  - IFN-alpha gene signature positive patients are characterized by:
    - Lower serum C3 values, higher anti-dsDNA Ab titers
    - Higher induction of anti-IFN-alpha antibody response
    - IFN-alpha-K neutralizes IFN-alpha (and SLE) signature
    - Neutralization of the IFN-alpha signature correlates with anti-IFN-alpha antibody levels in response to IFN-alpha-K
    - Increase in serum C3 levels correlates with decrease in IFN score, and with anti-IFN-alpha antibody levels
In patients with a positive IFN signature at baseline, ANOVA studies indicate that the expression of 238 out of 1,798 IFN-dependent genes is significantly modified by kinoid therapy (A) and that of 470 out of 1,247 SLE-dependent genes (B) between V0 and V10.

Genes right of the middle line are down-regulated, genes left of the middle line are up-regulated by kinoid therapy. Genes outside the outer lines are 2-fold up- or down-regulated. The genes are colored according to their level of induction after IFN stimulation.