Therapeutic vaccination in tuberculosis
Phase I/II Randomized Clinical Trial of the H56:IC31 vaccine and adjunctive Cyclooxygenase-2-inhibitor treatment


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Disclosure Statement

I have no conflicts of interest to declare that are relevant to the research and content that I will present.
Host-Directed-Therapies (HDT) in Tuberculosis

✓ The MDR/XDR-TB epidemic calls for new therapeutic approaches
✓ Two strategies may facilitate clearance of TB disease: strengthening of immune responses eradicating the pathogen and reduced hyperinflammation.
✓ Immune modulating ‘Target-organ-saving’ strategies may prevent tissue damage in long-lasting and advanced TB
✓ HDT may have implications for the efficacy of post-exposure TB vaccines
✓ HDT has potential as adjuvant to shorten standard and MDR-TB treatment regimens
✓ Approved drugs as cyclooxygenase inhibitors or therapeutic vaccines can act as HDT
HYPOTHESIS

**Hypothesis 1** – COX-2i (Etoricoxib) given during the first 84 days of standard TB treatment improves naturally Mtbc-specific immunity in patients with active TB disease

**Hypothesis 2** - H56:IC31 vaccine given in 2 doses elicits vaccine specific immunity in patients with active TB disease

**Hypothesis 3** - COX-2i (Etoricoxib) boosts H56:IC31 vaccine-induced responses in patients with active TB disease
Study design – phase I/II open-label RCT (TBCOX2)

Randomisation ratio 2:2:1
- Etoricoxib
- H56:IC31
- Controls

Randomisation ratio 1:2
- Etoricoxib + H56:IC31
- Controls

Sampling days:
0 84 98 140 154 182 238

- H56:IC31 5 µg i.m.
- Etoricoxib p.o
- Standard TB treatment p.o
The TB vaccine H56:IC31

H56:IC31 vaccine candidate designed to boost BCG and introduce ESAT-6 specific immunity.

H56: fusion protein of 3 antigens expressed at different stages of Mtb infection. T helper type 1 cell stimulating adjuvant, IC31® (Valneva).

**H56 fusion protein:**
- **Ag85B:** An immunodominant antigen secreted in the acute phase of infection
- **ESAT-6:** virulence-ass. antigen highly expressed throughout all stages of infection
- **Rv2660c:** A stress-induced antigen, expression strongly associated with latent TB

**IC31® adjuvant:** A 2-component adjuvant comprised of an oligodeoxynucleotide ODN1a and a polypeptide KLK, signalling through TLR9

Study Flow chart

222 patients assessed for eligibility
Nov 2015 - Jan 2019

51 patients enrolled and randomized

171 patients not enrolled (Site 1/Site 2: 161/10)
- Breach of inclusion/exclusion criteria: 106/3
- Declined to participate: n=23/4
- Other reasons: n=32/3

All randomized patients, N=51

- Etanercept n=13
- H56:IC31 n=14
- Control n=12

2 incorrect enrolment

Safety analyses set (SAS), N=47

- Etanercept n=13
- H56:IC31 n=12
- Control n=12

2 SAE
1 protocol deviation

Full analysis set (FAS), N=40

- Etanercept n=10
- H56:IC31 n=12
- Control n=10

1 voluntary discontinuation
1 moved abroad

Patients completed study Day 238, N=34

- Etanercept n=9
- H56:IC31 n=10
- Control n=9

1 moved abroad

- Etanercept n=8
- H56:IC31 n=10
- Control n=9

1 voluntary discontinuation
1 moved abroad

1 SAE
1 pregnancy

1 SAE
1 Safety

1 pregnancy
1 moved abroad
Immune effects of COX-2i (etoricoxib) in TB
H56:IC31 vaccine is immunogenic in TB patients
Ag85B responses in vaccinated TB patients
Polyfunctional T cells responses to H56:IC31 vaccine in TB patients

CD4 T-cells responsive to H56:I31
- Poly-cytokine IFNγ⁺IL2⁺TNFα⁺
- Duo-cytokine: IL2⁺TNFα⁺
- Duo-cytokine: IFNγ⁺IL2⁺
- Duo-cytokine: IFNγ⁺TNFα⁺
H56:IC31 antibody responses in TB patients

Table 4. H56:IC31-vaccine serum conversion

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion of converters N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoricoxib (N= 10)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>H56:IC31 vaccine (N= 12)</td>
<td>9 (75%)</td>
</tr>
<tr>
<td>Control (N= 10)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Etoricoxib and H56:IC31 vaccine (N= 8)</td>
<td>6 (75%)</td>
</tr>
</tbody>
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Conversion was defined by >2 fold increase in anti-H56 IgG level from day 84 to any time point between day 98 and 238.
COX-2i (etoricoxib) reduces H56:IC31 vaccine T cell responses
Summary

- Overall Safety in this phase I/II RCT was good
- We observed 3 Serious Averse Events in the COX-2i-groups
- No Serious Averse Events were related to the H56:IC31 vaccine.
- The H56:IC31 vaccine induced robust expansion of polyfunctional T-cells
- Seroconversion occurred in a higher proportion in H56:IC31-group
- Adjuvant COX2i reduced T-cell responses to H56:IC31 vaccination.
CONCLUSION

• We report the first-in-human clinical data on therapeutic vaccination with H56:IC31 during active TB disease

• The H56:IC31 vaccine is safe and immunogenic in TB disease, supporting further studies of H56:IC31 as HDT strategy

• COX-2i appears to be safe, but our data do not support COX-2i as HDT
Chronic Infections Research Group (CIRG)

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