Selective Activation of Naturally Occurring Regulatory T Cells (Tregs) by the Monoclonal Antibody (mAb) BT-061. Markers of Clinical Activity and Early Phase II Results in Patients with Rheumatoid Arthritis (RA)

Anatoliy Rudnev1, Sukanya Ragavan2, Christina Trollmo2, Vivianne Malmstroem2, Christian Becker3, Helmut Jonuleit3, Vibeke Strand4, Silke Aigner5, Niklas Czeloth2, Benjamin Daelken2, Andre Engel1, Helga Koch1, Gabriele Niemann1, Frank Osterroth1, Christoph Uherek1, Andrea Wartenberg-Demand1, Olga Ershova6, Tatiana Sotnikova6, Alexander Orlov-Morozov7

1Biotest AG, Dreieich, 2Karolinska Institute, Stockholm, 3Johannes-Gutenberg University, Mainz, 4Division of Immunology, Stanford University, Portola Valley, CA, 5Clinical Hospital for Emergency Medical Care, Yaroslavl, 6Botkin Clinical Hospital, Moscow, 7City Clinical Hospital Nr. 23 n.a. Medsantrud, Moscow

Abstract

Naturally occurring Tregs are essential for maintaining normal immune homeostasis in healthy individuals. In patients with autoimmune diseases reduced numbers or functional impairment of Tregs has been observed. A humanized agonistic mAb, BT-061 selectively activates Tregs. It binds to a unique epitope of the CD4 molecule, leading to induction of Treg specific signaling events. While freshly isolated and resting Tregs do not inhibit T cell proliferation, pre-treatment of Tregs with BT-061 leads to suppression of CD4 and CD8 T effector cell proliferation, reduction of pro-inflammatory cytokines and a moderate increase in the anti-inflammatory cytokine TGF-beta.

To further assess the potential of BT-061 to modulate immune responses, in vitro studies with synovial fluid derived mononuclear cells from patients with active RA were performed. Addition of BT-061 at concentrations between 0.01 and 50 micro g/mL to isolated CD4-positive cells derived from the highly inflammatory milieu of RA synovial fluid suppressed proliferation as well as IFN-gamma production following antigen-specific stimulation.

In a Phase I/IIa trial in patients with psoriasis, a single dose of BT-061 resulted in PASI 50/75 responses for up to 90 days at doses of 0.5, 2.5, 10, 20 mg i.v. and 12.5, 25 mg s.c. A Phase IIa, multicenter, randomized placebo-controlled trial with BT-061 monotherapy was performed in 96 patients with active RA and inadequate responses to one or more traditional DMARD despite 3 months or more of treatment. Patients were randomized to 12 treatment groups: from 1.25–100 mg s.c, or 0.5–25 mg i.v, once weekly for 6 weeks: 6 patients received BT-061 and 2 received placebo in each group. Initial data analysis confirmed the clinical activity of BT-061 by ACR20/50/70 responses in a meaningful proportion of patients despite the short duration of therapy. No major safety signals were identified. Final analyses of safety and efficacy data are ongoing and will be presented.

Phase II multiple dose trials with BT-061 are underway to further evaluate the clinical benefit of BT-061 in patients with RA and psoriasis.

Conflict of interest declaration


Contact
Benjamin_Daelken@biotest.de
Tr egs modulate and balance the immune system. Once activated, Tregs differentiate into a unique lineage of the CD4+ T cells, leading to induction of specific antigen-specific responses. While freshly isolated and resting Tregs do not inhibit T cell proliferation, prior treatment of T cells with BT-061 leads to suppression of CD4 and CD8 T effector cell proliferation, reduction of pro-inflammatory cytokines and a moderate decrease in the anti-inflammatory cytokine TGF-beta.

To further assess the potential of BT-061 to modulate immune responses, in vitro studies with synovial fluid derived Tregs were performed. Addition of BT-061 at concentrations between 6.25 and 50 microg/mL to isolated CD4-positive cells derived from the synovial fluid of patients with RA resulted in suppressive effects as well as a shift in the cytokine profile of these Tregs.

Fig 1: Effect of Tregs and mechanism of action of BT-061

• No evidence of ADCC or CDC and non-depleting.
• Selectively activates Tregs but not normal T cells
• Provides an activation signal to naturally occurring regulatory T cells
• Humanized monoclonal IgG1 antibody BT-061:

Study Design (Biotest Study 962)

• Randomized, placebo-controlled, Phase Ia trial
• 96 patients with RA who had a history of DMARD failure
• BT-061 s.c., (62.5–1000 μg) or 362-45 μg (6 μg per group) weekly for 6 weeks
• Primary end point: ACR 20 after 6 weeks of treatment
• Secondary endpoints included ACR 50/70, DAS28 and EULAR criteria, safety, cytokine assessment, lymphocyte phenotyping.

Results

The most effective route was identified to be s.c. Patient demographics for this patient population are shown in Table 1.

Table 1: Patient Demographics

<table>
<thead>
<tr>
<th>BT-061 (n=6)</th>
<th>Placebo (n=14)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Demographics</td>
<td>(mean±sd)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>46.5±10.2</td>
<td>57.8±10.2</td>
</tr>
<tr>
<td>HAQ (mean)</td>
<td>2.00±1.60</td>
<td>1.83±1.60</td>
</tr>
<tr>
<td>Swollen joint count (mean)</td>
<td>10.0±5.0</td>
<td>10.3±5.0</td>
</tr>
<tr>
<td>Tender joint count (mean)</td>
<td>10.3±5.0</td>
<td>9.8±5.0</td>
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</tbody>
</table>

Table 2: ACR20/50/70 Responses (Day 43 ± 1)

<table>
<thead>
<tr>
<th>BT-061 (n=6)</th>
<th>Placebo (n=14)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>ACR 20</td>
<td>3 (50%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>ACR 50</td>
<td>2 (33%)</td>
<td>0</td>
</tr>
<tr>
<td>ACR 70</td>
<td>1 (17%)</td>
<td>0</td>
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Table 3: Adverse Events

<table>
<thead>
<tr>
<th>BT-061 (n=6)</th>
<th>Placebo (n=14)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Patients with any AE (%)</td>
<td>8 (57%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Patients with serious AE (%)</td>
<td>3 (50%)</td>
<td>3 (50%)</td>
</tr>
</tbody>
</table>

Exploratory Analysis of Cytokine Levels

Analysis of cytokines was undertaken at each study visit before treatment with BT-061 or placebo by multiplex assay, and ELISA on synovial fluid. IL-1alpha, IL-1beta, IL-6, IL-8, IL-10. These were measured as single doses. Both TGF-beta and IFN-gamma were measured as single doses.

No secretion of IL-1alpha or IL-1beta. No T cell proliferation, no secretion of IL-2, IL-4, IL-10. IFN-gamma secretion was also reduced and there was no increase in pro-inflammatory cytokine secretion.

Safety

No death of any patients occurred at any dose level. BT-061 was generally well tolerated. Serious AEs were reported in 2 patients (33%) of those treated with BT-061 (both s.c.) and in 1 of 2 patients who received placebo. There were no deaths reported in the study. The number of patients with any AE was similar in all dose groups, with no evidence of a dose-response relationship, and at a similar level to placebo-treated patients.

More patients withdrew due to adverse events in the placebo group (Table 2), compared to those in the BT-061 treatment groups. Infections were reported in 2 patients (33%) who received BT-061, compared to 1 patient (7%) who received placebo. There were no reports of infections. All infections reported were mild or moderate in severity.

Conclusions

This is the first study of a CD4 antibody given via the s.c. route for the treatment of RA.

In this trial, in patients with a history of DMARD failure, clinical effects of BT-061 given as monotherapy were identified across the dose ranges tested. ACR responses could be demonstrated after a single s.c. dose at 25 mg. The ACR responses were observed after a single dose (Abufarag et al).

BT-061 is a novel immunomodulatory approach for management of RA. In addition, BT-061 has shown activity in patients showing long-standing clinical effects after a single dose (Rudnev et al).

References

1. Rudnev A, Rudnev E, Engler A et al. Selective activation of naturally occurring regulatory T cells (Tregs) by the monoclonal antibody (mAb) BT-061. Markers of Clinical Activity and Early Phase II Results in Patients with Rheumatoid Arthritis (RA).