TheraMAB

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New mechanism of action for treatment of autoimmune diseases

TheraMAB is progressing clinical development of its new regulatory T cell activator for use in rheumatoid arthritis and other autoimmune disorders on the strength of encouraging results in recent phase 1 trials.

TheraMAB is an emerging biopharmaceutical company that is developing a new approach to treating autoimmune diseases that aims to control autoimmunity without causing general immunosuppression. Existing treatments act in various ways to suppress or block the immune system, which carries the risk of side effects such as infections and lymphoma, whereas a conceptually different approach could offer more efficient and safer drugs.

Regulatory T cells (T_{reg} cells) are known to play a key role in the pathogenesis of autoimmune inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus (SLE), psoriasis and multiple sclerosis, which are associated with defects in the number or function of T_{reg} cells.

A new type of monoclonal antibody specific for the cell-surface transmembrane glycoprotein CD28, which is expressed on T lymphocytes, has been shown to preferentially activate T_{reg} cells in rodents and *in vitro* in humans.

This CD28 superagonist is also highly efficacious in numerous preclinical models of autoimmunity, inflammation, transplantation and tissue repair[1].

"The key advantage over existing blocking therapies, like infliximab, is that you do not need to continuously load the body with high levels of a blocking antibody," said Thomas Hünig, a professor at the Institute for Virology and Immunobiology at the University of Würzburg, an inventor and a scientific adviser for TheraMAB. "Instead, by applying much lower doses of CD28 superagonist, you transiently kick off a wave of T_{reg} cell activation, and these cells then swarm through the body and seek out the site of inflammation, where they remain to do their job while the rest of the system goes back to normal." (**Fig. 1.**)

TheraMAB was incorporated in 2009 by the Moscow-based investment fund Bioprocess Capital Ventures and the German biotechnology company TheraMAB GmbH. The company has resumed clinical development of the CD28 superagonist TGN1412 under the new name TAB08 (theralizumab). TheraMAB has demonstrated that TAB08 can be administered safely to both healthy volunteers and patients with rheumatoid arthritis, and preliminary phase 1b findings show promising efficacy results.

TheraMAB is now seeking further investment to help it complete the next stages of clinical development of this first-in-class, humanized monoclonal antibody of the IgG4 subclass.

Progressing the science

The well-known first-in-human trial that began in London in March 2006 ended abruptly when six healthy volunteers experienced a life-threatening cytokine release syndrome that had not been predicted by preclinical testing[2]. Subsequent research has revealed several limitations of the *in vitro* assays and animal models that were used to calculate a starting dose of antibody, which resulted in a dramatic overdose of the drug[3].

TheraMAB has heeded the lessons and has brought TAB08 back into clinical development based on new evidence from different preclinical studies. A pivotal factor was the invention of a new *in vitro* cell-based assay called RESTORE (RESetting T cells to Original REactivity), which improves the reactivity of circulating T cells to soluble stimulants. The RESTORE protocol involves two days of preculture at a tenfold-higher cell density than is usually used for standard *in vitro* assays and thus mimics tissue-like conditions and restores T cell responsiveness to TAB08[4].

The patented RESTORE assay has been used to re-examine the *in vitro* activity of TAB08 in a series of experiments using blood cells from both healthy volunteers and patients with rheumatoid arthritis[1]. The results confirmed that TAB08 administration at low doses does not trigger cytokine release and leads to preferential expansion and activation of T_{reg} cells.

Individualized approach

The RESTORE assay has the potential to fill the gap between *in vitro* testing and animal models prior to first-in-human trials as it enables personalized testing of immunogenicity, toxicity and response to new immunomodulatory drug candidates; this can be especially important if an animal model is not available or is ethically unacceptable. TheraMAB has already trialed this approach successfully as part of the safety precautions for its open-label phase 1a study, which assessed the pharmacokinetics and tolerability of a single intravenous infusion of TAB08 in healthy adult volunteers. Each volunteer was prescreened with the RESTORE assay to determine individual sensitivity of blood cells to stimulation with TAB08.

The phase 1a study tested 9 ascending doses of TAB08, from 0.1 µg per kg of body weight up to 7 µg/kg, with escalation of each dose of TAB08 approved by an independent drug safety expert council after careful analysis of interim safety reports. The healthy volunteers were given adequate premedication, including antihistamines and paracetamol, and TAB08 was administered by slow infusion over 4–12 hours. Volunteers received close clinical surveillance for 48 hours followed by repeated clinical tests for 8 weeks.

None of the 30 volunteers enrolled presented a cytokine release syndrome during the study, which was completed in 2013[1]. Assessment of the cytokine response showed that the key cytokine release syndrome –promoting cytokines: tumor necrosis factor, interferon-γ and interleukin-2, remained at baseline levels over the full range of doses and observation time. The drug was well tolerated with no dose-limiting adverse events observed. Notably, the key anti-inflammatory T_{reg} cell signature cytokine interleukin-10 was detected in the plasma of the cohorts that received the highest doses of study drug (5 µg/kg and 7 µg/kg, which were 15–20 times lower than the dose used in the 2006 trial), indicating that TAB08 had stimulated an anti-inflammatory response.

"Our positive results to date are due to a combination of serious scientific analysis, a novel, thoroughly designed preclinical program and a careful, stepwise clinical strategy of the evaluation of safety parameters," said Dmitry Tyrsin, CEO of TheraMAB.

Clinical trial program

Following this successful clinical study, a phase 1b trial was started in 2013 to assess the safety, tolerability, pharmacodynamics and efficacy of multiple TAB08 doses in patients with moderate-to-severe active rheumatoid arthritis who had an inadequate response to methotrexate at a dose ≥10 mg/week. The open-label trial has enrolled 9 patients who were divided into 3 cohorts to test 3 different doses of TAB08: 5, 7 and 10 µg/kg of body weight. The study regimen of four intravenous infusions of TAB08 at the assigned dose was given once weekly for four weeks. Infusion time was decreased gradually over the study period from a maximum of eight hours for the first dose to a minimum of one hour for the final dose.

Results to date support the good tolerability of TAB08 that was observed in the phase 1a trial. No serious adverse events occurred and no dose-limiting toxicities were detected during the study.

Although efficacy assessment was not the primary objective of the study, all participants experienced some beneficial treatment effects, with some patients experiencing marked improvements in rheumatoid arthritis symptoms at eight weeks after the final infusion of TAB08. Assessments using the American College of Rheumatology (ACR) response criteria at the 8-week follow-up showed that ACR 20 responses

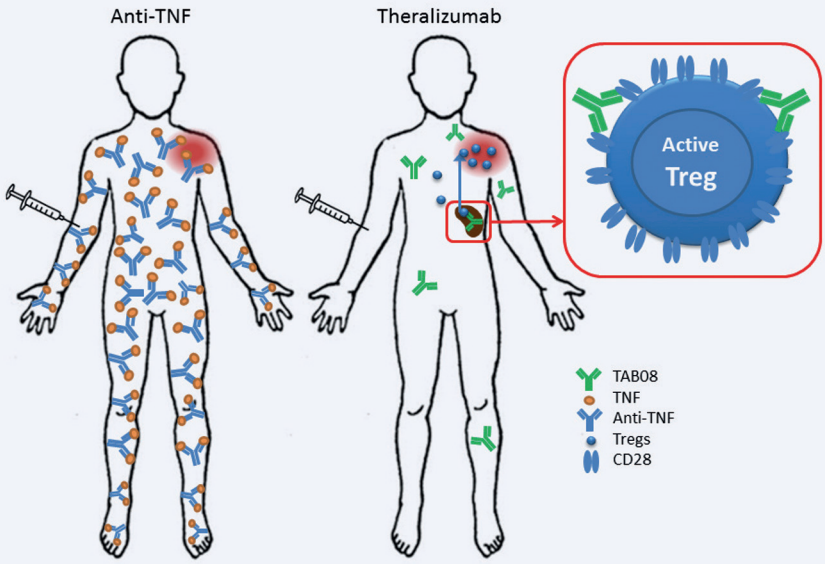

Figure 1. The new mechanism of action of CD28 superagonists means that they require much lower doses than anti–tumor necrosis factor antibodies to treat rheumatoid arthritis. Infliximab neutralizes tumor necrosis factor (TNF) both locally and systemically (left) and needs to be supplied at high doses in order to block TNF at the site of inflammation. In contrast, the CD28 superagonist TAB08 (theralizumab) is effective at low doses (at least 100-fold less than doses of cytokine-neutralizing antibodies) because it activates regulatory T cells (T_{reg} cells) in tissues, which migrate to the inflamed joint (right).

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(decrease of disease activity by at least 20%) were observed in 5 of the 9 patients treated with TAB08. In addition, 2 patients had improvements in response criteria of 50% (ACR 50), whereas 1 patient achieved complete remission (markedly over ACR 70), which has been sustained for longer than 4 months. Importantly, improvements in some ACR parameters were already observed after the first infusion of TAB08, and those changes became more pronounced after four weeks of the therapy.

Individual components of the ACR score, tender joint count and swollen joint count, were also analyzed. An improvement of at least 20% for both tender and swollen joint count was reported in 8 of the 9 patients at the end of 4 weeks of treatment. In addition, an improvement of at least 50% was reported in 5 patients, while 2 patients reported at least 70% improvement.

An additional analysis of pharmacodynamic data from the phase 1b trial indicated that longer administration of TAB08 could provide higher efficacy and that the drug could be administered less frequently (every other week or monthly infusions) for longer periods. Overall, the results support a favorable risk-to-benefit ratio for TAB08 use in patients with rheumatoid arthritis and justify further clinical studies.

"The presentation of our phase 1a/1b results at recent meetings has drawn significant interest from both scientists and clinicians," said Tyrsin. "The results obtained are very encouraging. TAB08 has the potential to meet the substantial medical need of patients suffering from rheumatoid arthritis and other autoimmune diseases."

TheraMAB is now seeking a partner to help support the ongoing clinical development of TAB08. The next step will be a randomized, double-blind phase 2a study, which is expected to begin in the first quarter of 2015. Up to 150 patients with rheumatoid arthritis will be randomized to 1 of 3 arms to compare the effects of 2 different doses of TAB08 with placebo. The treatment regimen will be given in combination with methotrexate and will involve a four-week cell-loading therapy of weekly intravenous infusions followed by support therapy of monthly intravenous infusions for four months. Assessments will include dose-limiting toxicity and adverse events as well as pharmacokinetics, immunogenicity, ACR 20/50/70 response rates, European League Against Rheumatism (EULAR) response criteria and patient-reported outcomes. In addition, new preclinical studies of subcutaneous use of TAB08 have been initiated, and there are plans to develop a new formulation of TAB08 for subcutaneous administration.

The mechanism of action and good preclinical data suggest that TAB08 may also be effective for treating other autoimmune diseases such as SLE and psoriasis, which are characterized by acute and chronic inflammation of various tissues of the body. The available therapies for SLE have limited efficacy and are often associated with severe side effects. TheraMAB plans to submit a clinical study protocol to the regulatory bodies in the first quarter of 2015 for a phase 2 study in patients with SLE.

Hünig believes the potential for TAB08 is even broader. "There are more than 20 published preclinical models showing the benefits of using CD28 superagonists for a wide range of autoimmune diseases," he said. "Basically, everywhere the T_{reg} cells do their job, one can apply this approach of transient T_{reg} cell activation. Thus, TAB08 has the potential to meet the significant medical needs of patients suffering from various autoimmune disorders."

References

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