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Belimumab

Rec INN; USAN

Anti-BAFF Monoclonal Antibody
Treatment of Autoimmune Diseases

HGS-1006
LymphoStat-B®

Immunoglobulin G_1, anti-(human cytokine BAFF) (human monoclonal LymphoStat-B heavy chain), disulfide with human monoclonal LymphoStat-B λ-chain, dimer

CAS: 356547-88-1
EN: 290217

Abstract

Belimumab (LymphoStat-B®) is a fully human monoclonal antibody directed against soluble BAFF (B-cell-activating factor), which plays a role in B-cell maturation and survival, as well immunoglobulin (Ig) class switching. Its use is being investigated in autoantibody-mediated diseases and available data show that it is effective for reducing the signs and symptoms of systemic lupus erythematosus (SLE) in anti-dsDNA-seropositive patients. Both preclinical and phase I clinical studies showed that belimumab depleted B-cells and was safe and well tolerated. A phase II clinical study in rheumatoid arthritis demonstrated a relatively modest clinical benefit, and a phase II clinical study in SLE did not meet primary efficacy endpoints. Both phase II studies showed good safety and tolerability. Two phase III clinical trials in SLE are now open for recruitment.

Background

There has been tremendous growth in the understanding of the molecular mechanisms and immunology of autoimmune disease in the last decade. In parallel with this, there have been significant developments and expansion in the use of the so-called "biological agents" for a variety of diseases. Specific B-cell-directed therapies are now being intensively explored for the treatment of autoimmune diseases where B-cells or autoantibody production is thought to play a significant role. These diseases include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and autoimmune cytopenias.

Rituximab (Rituxan, MabThera; Roche, Biogen Idec, Genentech), a chimeric monoclonal antibody against CD20 originally used in the treatment of B-cell malignancies, is the most widely used B-cell-specific therapy at present. It was launched for use in RA in the U.S. and the U.K. in 2006 and is being tested in large double-blind, multicenter studies in SLE. Various other B-cell-directed therapies are in the pipeline.

Belimumab (LymphoStat-B®) is a human monoclonal antibody that binds to and neutralizes soluble BAFF (B-cell-activating factor), also known as BLyS (B-lymphocyte stimulator), THANK (TNF homologue that activates apoptosis, nuclear factor-κB and c-Jun *N*-terminal kinase), TALL-1 (TNF- and ApoL-related leukocyte-expressed ligand-1), TNFSF13B (TNF superfamily member 13b), zTNF4 and neutrokine-α. BAFF is secreted primarily by myeloid cells (monocytes, macrophages, dendritic cells) and plays a role in B-cell maturation and survival, immunoglobulin (Ig) class switch recombination, as well as T-cell co-stimulation (1). BAFF has also been found to be elevated in the serum of patients with autoimmune diseases such as SLE, RA and Sjögren's syndrome, as well as B-lymphocyte malignancies (1).

Persistent binding of BAFF to the BAFF receptor (BAFFR) results in constant activation of B-cells in SLE patients (2, 3). In RA, BAFF is thought to promote the formation of extrafollicular germinal centers in synovia (4). In addition, in a murine model of SLE, BAFF levels were found to be elevated and administration of soluble BAFFR ameliorated the disease (5). These observations highlighted the relevance of BAFF neutralization in SLE and RA.

Belimumab was developed by screening phage display libraries with subsequent affinity optimization mutagenesis (6). It has been shown to have *in vitro* and *in vivo* effects on B-cell development in murine models and cynomolgus monkeys. A single phase I study in SLE and two phase II clinical trials have been completed, one each in SLE and RA. Two phase III trials are currently under way in patients with SLE.

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Preclinical Pharmacology

Belimumab was developed by screening scFv phage display libraries for binding to human BAFF. The full IgG molecules were then assessed for neutralizing activity in a murine splenocyte *in vitro* proliferation assay. Further optimization of the lead candidates identified was performed by random replacement of the terminal 6 residues in the V_H CDR3 region. The most potent antibody identified was identified and designated belimumab and further characterized (6).

Belimumab was shown to bind to BAFF with an EC_{50} value of 0.024 nM in a BAFF-specific ELISA. Belimumab binding was inhibited by soluble BAFF with an IC_{50} value of 8.5 nM, implying that belimumab binds BAFF in both a solid-phase capture assay and in solution. Belimumab only bound to soluble BAFF and not membrane-bound BAFF in experiments using flow cytometry to evaluate binding to primary human cells and the K-562 myelogenous leukemia cell line. Using an electrochemiluminescence detection assay, belimumab was shown to inhibit BAFF binding to the extracellular domains of all three receptors —TACI (transmembrane activator and calcium-modulating cyclophilin ligand interactor), BCMA (B-cell maturation antigen) and BAFFR— with equivalent potency (IC_{50} = 0.10-0.11 nM). Belimumab inhibition of receptor-ligand expression was also demonstrated in a cell-based assay with full-length TACI, BCMA and BR3 using HEK-293T cells (6).

Murine and human BAFF share only 63% homology and, unfortunately, belimumab is unable to antagonize BAFF activity in murine models of autoimmune disease. Consequently, belimumab activity *in vivo* was assessed using a mouse model with exogenously administered human BAFF, and measuring spleen weight, serum IgA levels and mature splenic B-cells. Co-administration of belimumab resulted in a dose-dependent reduction in the effects of BAFF, with complete inhibition observed between 1.5 and 5.0 mg/kg belimumab (6).

The *in vivo* effects of belimumab were also assessed in cynomolgus monkeys as cynomolgus BAFF is 96% identical to human BAFF (7). Belimumab was well tolerated up to doses of 50 mg/kg for up to 26 weeks, with no treatment-related infections. Pathology endpoints were evaluated at 13 and 26 weeks and after a 34-week treatment-free (recovery) period. Monkeys treated with belimumab had decreases in peripheral blood B-lymphocytes by 13 weeks of exposure and this continued into the recovery period. Spleen and lymph node B-lymphocyte representation was also decreased at 13 and 26 weeks, and there was a reduction in the number and size of lymphoid follicles in the white pulp of the spleen. Belimumab did not affect globulins or Ig subclasses in this study. All the findings were reversible within the recovery period.

Pharmacokinetics and Metabolism

In murine and monkey models, the half-life of belimumab after single doses was 2.5 and 11-14 days, respectively (6). Multiple-dose pharmacokinetics have only been evaluated in cynomolgus monkeys (7). Two studies of 4 and 26 weeks' duration were conducted with belimumab doses of 0, 5, 15 and 50 mg/kg. In the 4-week study, belimumab was given weekly and serum concentrations measured up to 8 weeks (n=10 and 4 monkeys in each group through day 29 and day 56, respectively). In the 26-week study, belimumab was given every 2 weeks and serum concentrations measured prior to each dose of belimumab and throughout the recovery period (n=16, 10 and 4 monkeys in each group through weeks 13, 26 and 60, respectively). The pharmacokinetics of belimumab following 4 weekly doses were found to concur with the single-dose study, showing that the pharmacokinetics do not change with multiple dosing. It was also noted that complete pharmacokinetic parameters were not determined in the 26-week study, but exposure was similar to that predicted from single-dose kinetics. Elimination half-lives determined after multiple dosing were similar to the single-dose terminal half-life, with a range between 9 and 16 days. However, 2 monkeys who developed anti-belimumab antibodies were excluded from analysis in the 26-week study.

The pharmacokinetics of belimumab were investigated in a randomized, double-blind, placebo-controlled phase I study in patients with stable mild to moderate SLE on a stable standard-care regimen 2 months prior to enrollment. Belimumab subjects (n=57, 91% female, average age of 41 years) were given four different doses (1, 4, 10 and 20 mg/kg) either as a single i.v. infusion or two infusions 21 days apart and compared to placebo subjects (n=13). The study showed that the pharmacokinetics of single doses were dose-proportional. There was a long half-life (13-17 days), slow clearance (4.00 ± 1.56 ml/day/kg) and a small volume of distribution (68.19 ± 20.83 ml/kg), all consistent with a fully humanized monoclonal antibody (8).

Safety

The safety of belimumab was assessed in a single phase I study in 70 SLE patients and two phase II studies involving 449 patients with SLE and 283 patients with RA. Patients in the phase I study were followed for 84-105 days and the overall incidence of adverse events was similar in the treatment and placebo groups. There was no increased incidence of infections. Six patients experienced serious adverse events, although frequencies were similar in the belimumab and placebo groups. One patient experienced an infusion reaction at the highest dose and another developed neutralizing antibodies against belimumab (8).

In the phase II RA study, there was no significant difference in the incidence of severe or serious adverse events analyzed by system organ classification or any laboratory abnormalities among all active doses (1, 4 or 10 mg/kg on days 0, 14 and 28, then every 28 days for 24 weeks) compared to placebo. Sinusitis (9%) and pruritus (11%) were the only adverse effects occurring more fre-

quently in the active treatment group. There was no significant difference in the incidence of infections between the active and placebo groups. One case of pneumonia was the only treatment-related serious adverse effect and 1 death due to cardiac arrest occurred in the placebo group (9).

In the phase II SLE study, there were also no clinically significant differences in adverse events, adverse event severity, infections or laboratory toxicity. Fewer treatment subjects had pleurisy and more had urticaria (4% *vs.* 0%). Infusion reactions were rare and immunogenicity was only seen in 1 subject (10).

Clinical Studies

The phase I trial demonstrated reductions of 12-47% in $CD20^+$ B-cells in all patients treated with belimumab, although no change in SLE disease activity was noted over the short exposure period.

In the phase II RA trial, a heterogeneous population of 283 patients with active RA despite stable standard-of-care treatment were randomized to belimumab (1, 4 or 10 mg/kg) or placebo on days 0, 14 and 28 and every 28 days through to 24 weeks. The primary outcome measure was the ACR20 at 24 weeks. Overall, 29% of patients treated with belimumab achieved ACR20 compared with 16% of patients on placebo (9). When subgroup analysis was performed, the response to belimumab was statistically significant in patients who were rheumatoid factor (RF)-positive (29% *vs.* 12%), TNF inhibitor-naïve (40% in the lowest dose group *vs.* 13% on placebo) or methotrexate partial responders (37% *vs.* 7%) (11). There were no significant differences in RF-negative or TNF inhibitor-experienced patients. There was also a statistically significant response in patients who were anti-cyclic citrullinated peptide (CCP)-positive compared to placebo (30% *vs.* 14%) (12). B-cell reductions (in $CD20^+$, $CD19^+$, naïve and activated B-cells) of at least 20% were also noted by day 56 in all treatment groups compared to placebo, although this did not correlate with improvement in Disease Activity Score (DAS28) (13). No reductions were seen in plasma cells and increases were seen in memory B-cells at day 28, which persisted for the duration of the study and were correlated with modest improvement in the DAS28 (13).

The phase II SLE trial involved 449 patients by ACR criteria and screening SLE Disease Activity Index (SELENA SLEDAI, SS) score of at least 4, who were randomized to receive 1, 4 or 10 mg/kg belimumab or placebo on days 0, 14, 28 and monthly. Dosing was for 76 weeks and placebo patients were switched to belimumab at week 52. Efficacy measures included 1-2 monthly assessments by SS score, SLE flare index and physician's global assessment (PGA). Primary efficacy endpoints were percent decrease in SS score at week 24 and time to SLE flare over 52 weeks. Unfortunately, primary efficacy endpoints did not reach statistical significance, although the SS score was reduced by 29% at week 52 in antinuclear antibody (ANA)-positive patients and flares decreased during weeks 24-52. It should be noted, however, that only 71.5% of patients were ANA-positive at the start of the study. PGA improved by week 16 through week 52 (10). There was a statistically significant improvement in health-related quality-of-life scores in seropositive patients with active disease (14, 15). Subjects treated with belimumab also had reduced or stable B-cell subsets (activated, memory, plasmacytoid and total B-cells) at 52 and 76 weeks. Plasma cells were increased over baseline compared to placebo. Ig isotypes were reduced (10-35%) and anti-dsDNA antibodies were reduced by 30%. A 50% or greater reduction in anti-dsDNA was associated with a greater reduction in the modified SS score (16).

Two phase III studies in patient with SLE are now open for recruitment (17, 18).

Conclusions

Initial clinical studies suggest that belimumab is effective in reducing autoantibody formation and B-cell counts, and a modest clinical benefit was also seen. However, belimumab does not appear to be as effective as rituximab (19, 20). For example, in one study, 73% of patients receiving rituximab and methotrexate achieved an ACR20 response and 43% achieved an ACR50 response compared to 38% and 13% of patients receiving placebo and methotrexate, respectively (21). Although, these are not head-to-head comparisons, the most obvious reason for the differences might be due to the fact that rituximab can completely abolish B-cells whereas belimumab only reduces their number. Consequently, belimumab might be less effective, but also less likely to cause adverse effects and infection. Further trials will be required to compare the efficacy of the two agents in the treatment of autoimmune disease. In addition, combination of the two agents for enhancement of B-cell depletion is also a possibility. Other B-cell-specific therapies, including epratuzumab (anti-CD22), are still in very early development and it will be interesting to see how these compare with rituximab and belimumab.

Several other issues have been noted as worthy of further consideration. These include the lack of dose-response relationship, the increase in plasma cells in belimumab-treated patients and the improved responses in certain patient subgroups. The lack of a dose-response relationship might be simply due to the fact that the doses used in the trials were not optimal for the treatment of RA and SLE, or that a saturating dose of monoclonal antibody had been achieved. It has been noted that a similar phenomenon occurs with rituximab and the reasons for this are unclear (22).

Belimumab was associated with an increase in plasma cells in the SLE trial and memory B-cells in the RA trial. The reasons for this are not clear, although it has been suggested that an increase in memory B-cells might be detrimental in RA (despite the improvement seen in the DAS28), as memory B-cells are needed to regenerate short-lived autoantibody-secreting plasma cells, which are associated with more aggressive articular disease

(22). Similarly, the increase in plasma cells in SLE could potentially be detrimental if they secrete autoantibody, although there are no data regarding this at present.

Finally, current data seem to indicate that belimumab had greater efficacy in subgroups associated with autoantibody formation (including RF, CCP and ANA). The presence of autoantibodies could reflect the fact that there are distinct disease subgroups in SLE and RA, with different levels of B-cell contribution to pathology. The use of belimumab, which primarily interferes with B-cell development, would be expected to have the greatest effect when B-cells are playing a significant role (possibly as demonstrated by autoantibody formation). However, further work is required to determine exactly which subgroups will benefit most from therapy.

In summary, belimumab represents a further development in specific B-cell-targeted therapies and is currently in phase III studies in SLE. It is well tolerated and significantly reduces B-cells and autoantibodies. There is a modest clinical benefit, although its value remains to be proven in further trials.

Sources

Human Genome Sciences, Inc. (US) (originally developed in collaboration with Cambridge Antibody Technology); developed worldwide in collaboration with GlaxoSmithKline.

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