Belimumab

Belimumab (trade name **Benlysta**, previously known as **LymphoStat-B**) is a human monoclonal antibody that inhibits B-cell activating factor (BAFF),[1] also known as B-lymphocyte stimulator (BLyS).[2] B cells are responsible for part of the normal immune response, and also for the over-aggressive immune response in autoimmune diseases like systemic lupus erythematosus (SLE).

Belimumab is approved in the United States, Canada and Europe for treatment of SLE. However, the major phase III trials excluded the more severe cases of SLE with kidney and brain damage, so its effectiveness has not been demonstrated in those cases. A Phase III study for SLE patients with kidney disease is now recruiting.[3]

U.S. F.D.A. reviewers were concerned that belimumab is only "marginally" effective, and that there were more deaths in the treatment group.

Belimumab's defenders said that in addition to its modest efficiency, belimumab allowed patients to significantly reduce their use of corticosteroids.[4]

Belimumab is expensive, typically $28,000 for the first year. The UK National Institute for Health and Care Excellence (NICE) calculated the cost of belimumab at £61,200 per quality-adjusted life year (QALY), which is more than the normally accepted £20,000 to £30,000.

Phase II trials of belimumab for rheumatoid arthritis were unsuccessful. Phase II trials for Sjögren's Syndrome were more successful.

Belimumab was developed by Human Genome Sciences (HGS) and Cambridge Antibody Technology.[5] GlaxoSmithKline acquired HGS, took belimumab through Phase III clinical trials, and markets belimumab.[6]

1 Uses

1.1 Systemic lupus erythematosus

While belimumab appears safe in systemic lupus erythematosus, the magnitude of benefit is small.[7] Black/African American patients did not show a benefit. The most severe cases, with kidney and central nervous system involvement, were excluded from the trials.

The efficacy and safety of belimumab was demonstrated in 2 Phase III randomized, controlled studies, BLISS-52[8] and BLISS-76.[9] The 2 studies had a total of 1,684 patients, with scores of ≥6 on the SELENA-SLEDAI assessment. They were divided into a placebo and 2 dosage groups of belimumab, in addition to standard therapy. The primary end point was a reduction of ≥4 on the SELENA-SLEDAI assessment, and several other factors, at 52 weeks. Belimumab significantly improved the response rate, reduced disease activity and severe flares, and was well tolerated. 58% had SELENA-SLEDAI scores reduced by ≥4 points during 52 weeks with belimumab 10 mg/kg compared to 46% with placebo.

Benlysta was the first new drug to treat lupus after 56 years. Sales rose to $31.2 million in the first quarter of 2012.[10] It is marketed by GlaxoSmithKline and sold for about US$35,000 per year per patient.

1.2 Rheumatoid arthritis

In phase II clinical trials for rheumatoid arthritis.[11] belimumab was not effective.[7]

1.3 Sjögren's Syndrome

Belimumab has completed phase II trials for Sjögren's Syndrome.[12]

2 Side effects

Common adverse effects reported with belimumab include nausea, diarrhea, fever, as well as hypersensitivity and infusion-site reactions (severe in 0.9% of patients). It is suggested that patients be treated with an antihistamine prior to a belimumab infusion.[13]

A greater number of serious infections and deaths were reported in patients treated with belimumab than in those treated with placebo. Infections are due to the immunosuppressant properties of the drug.[14]

3 Interactions

No interaction studies have been carried out. Combination of belimumab with other immunosuppressants, especially those targeting B lymphocytes such as anti-CD20 therapies, could increase the risk of severe infections. Likewise, the combination with intravenous cyclophosphamide is not recommended, as well

as administering live vaccines during treatment with belimumab.[13][15]

4 Mechanism of action

B lymphocytes (B cells) are one of the immune cells responsible for the damage in autoimmune disease. B cells develop in the bone marrow and continue to mature peripherally in secondary lymphoid organs and (as recently discovered) in the gut. When autoimmune B cells attack the body's own tissues, they are normally destroyed by cell suicide (apoptosis). In order to survive, B cells need survival factors. Researchers theorize that SLE is caused when autoimmune B cells proliferate, and survival factors protect them from cell suicide.

B-cell activating factor (BAFF), also called B-lymphocyte stimulator (BLyS), is required for the development and survival of B cells. In SLE, BAFF is overexpressed. Researchers theorize that BAFF overexpression causes autoimmune B cell proliferation and survival, which causes SLE.

Belimumab is a human antibody that binds to BAFF, preventing BAFF from binding to B cells. Without the survival factor BAFF, B cells commit suicide, and no longer contribute to the autoimmune damage of SLE.

BAFF is secreted by a variety of cells: monocytes and macrophages, bone marrow stromal cells, astrocytes, synoviocytes during rheumatoid arthritis, salivary epithelial cells during Sjögren's syndrome, astrocytes in certain glioblastomas.

BAFF interacts with three membrane receptors on B lymphocytes:

- BAFF-R (BAFF receptor)
- BCMA (B cell maturation antigen)
- TACI (transmembrane activator and calcium modulator and cyclophylin ligand interactor)

When BAFF binds to BAFF-R and BCMA on B cells, levels of Bcl-2, a survival factor, are increased.

When all three BAFF receptors are stimulated, levels of NF kappa B, which contributes to cell proliferation and differentiation, are increased in the nucleus.

Another B-cell activator like BAFF is APRIL (a proliferation-inducing ligand),[16] but APRIL only activates BCMA and TACI, not BAFF-R.

Belimumab reduces the number of circulating B cells, but anti-CD20 monoclonal antibodies reduce the number even more. It is possible that belimumab binds primarily to circulating soluble BAFF, therefore not inducing antibody-dependent cellular cytotoxicity that could be expected from this IgG1-type antibody.[17][Better, more current citation needed]

5 Discovery and history

B-cell activating factor is a naturally occurring protein that was discovered by researchers from National Jewish Health (previously the National Jewish Medical and Research Center) and the University of Colorado, who collaboratively published a paper detailing their findings in May 1999, naming the protein *TALL-1*.[18] The same protein was named *BAFF* in another paper published in June 1999; and in a paper published in July of that year, Human Genome Sciences (HGS) referred to it as *BLyS* (or B lymphocyte stimulator).[19] Six years later, the key role of BLyS in B cell differentiation, survival and activation was published.[20]

Five years prior, in October 2000, HGS and Cambridge Antibody Technology (CAT) agreed to co-develop monoclonal antibodies targeted at BLyS. Under this agreement, CAT would identify antibodies and HGS would select appropriate ones to take into clinical trials.[21] In 2003, CAT researchers reported that, by using phage display technology, they had elicited an array of over 1000 distinct antibodies, half of which inhibited binding of BLyS to its receptor.[5] Later that year, one of these antibodies was isolated and characterized. It was named LymphoStat-B and subsequently called belimumab.[22]

In August 2006, HGS and GlaxoSmithKline (GSK) entered into a co-development and commercialization agreement under which HGS would conduct Phase 3 trials for belimumab with assistance from GSK. The companies would share equally in Phase 3/4 development costs, sales and marketing expenses, and profits of any product commercialized under the agreement.[21] On February 13, 2007, HGS and GSK announced the initiation of the first of two pivotal Phase 3 clinical trial of belimumab in patients with active lupus erythematosus.[6]

6 FDA approval

Under its trade name *Benlysta*, belimumab was approved by the U.S. Food and Drug Administration (FDA) for treatment of SLE on March 9, 2011.[23] The FDA Advisory committee approved it with a 13-to-2 vote, despite reservations that the improvement of only 4 points on the SELENA-SLEDA scale was only marginally effective, and despite reservations about additional deaths in the treatment group.[24][25] Based on the number needed to treat, approximately eleven patients must be treated for one to benefit. It was not tested in severe forms of SLE, which involve active damage to the kidneys or central nervous system in the phase III trials. Subjects with active kidney disease were included in the Phase II trials of the drug.[26] "Patients with active lupus that involved the kidneys ... were excluded from participating in the trials. Study participants of African American or African descent did not significantly respond to

belimumab."[24][27][28] It has subsequently been approved for use in Europe and Canada.[29]

7 Costs

Belimumab is expensive. At a typical U.S. academic center, the total cost for the first year of treatment is $28,000. Annual prices of generic prescription drugs are prednisone, $140; hydroxychloroquine, $132; oral methotrexate, $432; azathioprine, $468; and mycophenolate mofetil, $1,224.[30] In the UK, the National Institute for Health and Care Excellence (NICE) calculated the cost of belimumab at £61,200 per quality adjusted life year (QALY). This is more than the normally accepted cost of £20,000 to £30,000 per QALY. The manufacturer offered the UK National Health Service a discount, the amount of which were confidential, which still did not bring it into the acceptable range.[31]

8 Other drugs addressing B lymphocyte hyperactivity

Atacicept is a recombinant fusion protein built with the extracellular ligand binding portion of TACI. It blocks activation of TACI by APRIL and BLyS. It failed a phase II trial for multiple sclerosis.[32]

Blisibimod, an inhibitor of both soluble and membrane bound BAFF, has demonstrated similar reductions of B cells in clinical trials and is being investigated in a phase 2 clinical study for patients with lupus erythematosus.

BR3-Fc is a recombinant fusion protein built with the extracellular ligand-binding portion of BAFF-R. It blocks activation of this receptor by BLyS, and is in early stage pharmaceutical development.[33]

Of anti-CD20 monoclonal antibodies, rituximab has been approved for some indications. Ocrelizumab, ofatumumab and "third generation" anti-CD20 monoclonals are in development.

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