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Belimumab: Present and future

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Abstract

Belimumab, a B lymphocyte stimulator (BLyS) inhibitor, recently approved for patients with active, autoantibody-positive systemic lupus erythematosus (SLE) has paved the way for newer drugs that could arrest the complex autoimmune process and reverse the disease pathology. However, there is a need to further delineate long term effects of belimumab on disease activity and progression in patients with lupus nephritis, pregnancy and paediatric populations. Here, we review the on-going clinical trials and registry studies of belimumab in different populations that could define its role in the SLE armamentarium.

Keywords: Belimumab; Lupus; Trial; BLyS; SLE; Treatment

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Introduction

Belimumab (Human Genome Sciences, Rockville, MD, USA/Glaxo Smith Kline, Uxbridge, UK), has been approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for patients with active, autoantibody-positive systemic lupus erythematosus (SLE) receiving standard therapy [1,2]. It is a fully human immunoglobulin (Ig) G1-λ monoclonal antibody (mAb) produced by recombinant DNA technology in a mammalian cell expression system that selectively targets B lymphocyte stimulator (BLyS). The activated BLyS attaches to three receptors: BR3 (BAFF receptor 3), TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor), and BCMA (B-cell maturation antigen) and allows the proliferation and differentiation of B lymphocytes into Ig-producing plasma cells. Belimumab selectively binds to BLyS; inhibiting the interaction of this receptor with BR3, TACI and BCMA and the resultant signal transduction pathways for B lymphocyte proliferation and differentiation [3,4]. This novel mechanism of action of belimumab translated into a clinically significant greater response in the SLE Responder Index (SRI), improved serologic activity, reduced corticosteroid use and flares, with acceptable safety profile in two multicentre, randomized, double-blind, placebo-controlled phase III trials (BLISS-52 and BLISS-76) and subsequent approval by the regulatory authorities [5,6].

The preclinical trials of belimumab in prototypical models of SLE nephritis in mice and cynomolgus monkeys suggested the expected pharmacologic activity; attenuated inflammation, and reduced B lymphocytes both in lymphoid tissues and peripheral blood [7,8]. The subsequent phase I dose-escalating trial of belimumab (dose of 1, 4, 10 or 20 mg/kg or placebo) in 70 patients of SLE with mild to moderate disease activity exhibited linear pharmacokinetics in this dose range and no significant differences in the incidence of adverse events (AEs) in the placebo and belimumab treatment groups [9]. The most common AEs were arthralgia, headache, rash, diarrhoea and nausea in patients treated with the study agent. The phase II double-blind, placebo-controlled safety efficacy trial of belimumab in patients with active disease on standard stable treatment demonstrated no significant differences between belimumab and placebo groups for the primary endpoint [10]. However, in the serologically active patient subgroup, belimumab resulted in significantly better responses at week 52 than placebo for SELENA-SLEDAI (Safety of Estrogens in Lupus Erythematosus National Assessment – Systemic lupus erythematosus Disease Activity Index), PGA (Physician's Global Assessment) and SF-36 PCS (Short Form 36 Physical Component Score scores). This formed the basis for the development of the SLE Responder Index (SRI), a robust responder index that was evaluated as the primary efficacy endpoint at 52 weeks for two large phase III trials [5,6]. Phase III (BLISS-52) trial results demonstrated that belimumab plus standard therapy (1 mg/kg; n=288, 10 mg/kg; n=290) and placebo (n=287) resulted in significantly higher SRI rates than with placebo at week 52. Belimumab reduced disease activity, severe flares and was well tolerated. A dose–response relation was observed, with belimumab 10 mg/kg resulting in greater response in all three SRI components (SELENA-SLEDAI, BILAG, (British Isles Lupus Assessment Group) domain scores and PGA) compared to 1 mg/kg which improved outcomes in two components (SELENA-SLEDAI and PGA) [5]. In another phase III (BLISS-76), multicenter, double-blind, placebo-controlled trial,

patients were randomized in a 1:1:1 ratio to receive either placebo or belimumab (1 or 10 mg/kg) by intravenous (iv) infusion over 1 h on days 0, 14, and 28 and every 28 days through to week 72. Belimumab 10 mg/kg plus standard therapy met the primary efficacy end point (significantly greater SRI response) at week 52, reduced SLE disease activity and severe flares, and was well tolerated. Patients with higher SELENA-SLEDAI score thresholds achieved a significantly better discrimination at weeks 52 and 76 compared to placebo [6]. Thus, a reduction in the incidence and severity of flares and an acceptable safety profile, belimumab in addition to standard therapy, offers a safe and effective option for patients with SLE. Belimumab has paved the way for newer drugs that could arrest the complex autoimmune process and reverse the disease pathology to ensure a better quality of life [11,12]. However, there is a need to further delineate long term effects of belimumab on disease activity and progression in patients with lupus nephritis, pregnancy and paediatric populations. Here, we review the on-going clinical trials and registry studies of belimumab in different populations that could define its role in the SLE armamentarium (Table 1).

Ongoing Trials of Belimumab

As per regulatory requirements, additional studies of a newly approved drug are warranted in children, elderly, pregnancy and lactation. Accumulated evidence suggests that various autoimmune mechanisms influence a woman's reproductive life, manifesting as infertility or pregnancy loss [13,14]. Thus, a global Belimumab Pregnancy Registry (NCT01532310) has been established to collect prospective data on 500 pregnancies in women with lupus who have received belimumab within 4 months prior to and/or during pregnancy. Pregnancy outcomes (including spontaneous miscarriage, live births, stillbirths), and infant outcomes (birth defects up to one year after birth) assessment will complement reproductive data from animal toxicology studies [15]. Another phase II placebo-controlled study (NCT01649765) is being undertaken in paediatric patients (5 to 17 years of age) with active SLE. Enrolment in this study is staggered by age cohorts that would allow safety and pharmacokinetic interim analysis. The initial evaluations at 52 weeks include SLE Response Index (SRI), proportion of subjects with a sustained SRI and Parent Global Assessment response, adverse events and pharmacokinetic measures. Thereafter, long term safety follow up for up to 10 years from a subject's initial treatment with belimumab could provide additional data. This study is expected to be completed by January 2027 [16].

Patients during the course of their illness, require modifications in their existing treatment regimens leading to addition, withdrawal and reintroduction of one or more drugs. Thus, there is a need to understand the effects of belimumab's discontinuation on pathophysiology of disease and clinical response. A phase III trial (NCT02119156) is recruiting adults with stable low disease activity. This 52-week open-label study aims to assess the effect of a 24-week withdrawal of belimumab followed by a 28-week reintroduction of belimumab with standard therapy on immunogenicity, markers of biological activity (SELENA SLEDAI, SLE Flare Index efficacy) and safety. Additionally, rebound phenomenon in subjects who have permanently withdrawn from further belimumab treatment and maintained on standard of care would be assessed monthly for 52 weeks [17].

Observational studies are underway to collect long-term safety data on belimumab use. A prospective observational registry (NCT01729455) is recruiting 3000 autoantibody-positive adults with active SLE treated with or without belimumab in addition to standard therapy [18]. These participants would be followed at 6 monthly intervals for 5 years regardless of changes in their lupus medicines until study completion. Incidence of adverse events (malignancies, mortality, serious infections and serious psychiatric events) would be the primary outcome for assessment. Adverse events, changes in organ damage, disease activity, quality of life and rate of hospitalizations would also be evaluated. This study is expected to be completed by April 2025. Another phase 4 study (NCT01705977) is underway in 5000 autoantibody-positive adults with active SLE who have received belimumab for up to 52 weeks [19]. The evaluations include incidence of all-cause mortality and adverse events (serious infections, opportunistic infections, malignancies, psychiatric events) at the end of study period. Serious events that are uncommon or may only be seen with long-term treatment would be ascertained annually for 4 more years and assess participants' health status.

Lupus nephritis is one of the common manifestations of SLE [11]. There is a need for research into new treatments of lupus nephritis as existing drugs do not cure the disease and cause immunosuppression with serious adverse effects. Belimumab is being evaluated in 464 adult patients with active lupus nephritis in a phase 3, randomized, double-blind, placebo-controlled 104 weeks study (NCT01639339) [20]. At 104 weeks, participants would be evaluated for a renal response (efficacy) and adverse events (safety). This study is expected to be completed by March 2019.

There is abnormal B cell activation, increased sensitivity and proliferation in response to cytokines with resultant in increased Ig production in patients with SLE [21]. Rituximab, a chimeric monoclonal antibody directed against CD20+ B cells; approved for the treatment of various B cell neoplasms, is being investigated for lupus nephritis [11]. A phase II trial (NCT02284984) is underway to assess the efficacy of combining rituximab and belimumab in reducing the disease activity and its effects on the disease pathophysiology [22]. Adult patients with a severe SLE flare receiving both rituximab and belimumab would be evaluated for the reduction (and seroconversion) of pathogenic autoantibodies (anti-dsDNA autoantibodies). In addition, clinical improvement (renal response, reduction in SLEDAI scores, SLE responder index and flares), safety and feasibility (serious hypersensitivity or infusion reactions) of long-term B depletion would be assessed. This study is expected to be completed by March 2020. Another phase II study (NCT02260934) is recruiting adults with active proliferative lupus nephritis to receive rituximab and cyclophosphamide or rituximab, cyclophosphamide and belimumab [23]. These participants will be assessed for grade 3 or higher infectious adverse event as the primary outcome measure. Other measures include proportion of participants with B cell reconstitution, hypo-gammaglobulinemia, non-renal flares, complete or partial response and treatment failures.

Table 1 Belimumab in ongoing clinical trials for lupus.

Trial number	Study title	Age and gender of participants	Number of participants	Phase	Study start date	Study completion date
NCT01705977	A Randomized, Double-Blind, Placebo-Controlled 52-Week Study to Assess Adverse Events of Special Interest in Adults With Active, Autoantibody-Positive Systemic Lupus Erythematosus Receiving Belimumab	18 year and older; both gender	5000		November 2012	January 2023
NCT01649765	A Multi-centre, Randomized, Placebo-Controlled Trial to Evaluate the Safety, Efficacy, and Pharmacokinetics of Belimumab, a Human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Paediatric Patients With Systemic Lupus Erythematosus	5-17 years; both gender	100	II	September 2012	January 2027
NCT02119156	An Open-label, Non-randomized, 52-Week Study to Evaluate Treatment Holidays and Rebound Phenomenon After Treatment With Belimumab 10 mg/kg in Systemic Lupus Erythematosus Subjects	18 year and older; both gender	135	III	May 2014	January 2019
NCT02284984	Synergetic B-cell Immodulation in SLE	18 Year to 64 Year; both gender	15	II	March 2014	March 2020
NCT01729455	A 5-Year Prospective Observational Registry to Assess Adverse Events of Interest and Effectiveness in Adults With Active, Autoantibody-Positive Systemic Lupus Erythematosus Treated With or Without BENLYSTA™ (Belimumab)	18 Year and older; both gender	3000		February 2013	April 2025
NCT01532310	Belimumab (BENLYSTA®) Pregnancy Registry (BPR) - Prospective Cohort Study of Pregnancy Outcomes Following Benlysta Exposure Within 4 Months Prior to and/or During Pregnancy	Pregnant women	500		July 2012	November 2021
NCT01597622	BEL114333, a Multicentre, Continuation Study of Belimumab in Subjects With Systemic Lupus Erythematosus (SLE) Who Completed the Phase III Study BEL113750 in Northeast Asia or Completed the Open-label Extension of HGS1006-C1115 in Japan	18 Year and older; both gender	420	III	June 2012	January 2016
NCT01639339	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Belimumab Plus Standard of Care Versus Placebo Plus Standard of Care in Adult Subjects With Active Lupus Nephritis	18 Year and older; both gender	464	III	July 2012	March 2019
NCT02260934	Rituximab Plus Cyclophosphamide Followed by Belimumab for the Treatment of Lupus Nephritis (ITN055AI)	18 Year and older; both gender	40	II	October 2014	January 2019
NCT01632241	A Phase 3/4, Multi-Centre, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Adult Subjects of Black Race With Systemic Lupus Erythematosus (SLE)	18 Year and older; both gender	816	III/IV	February 2013	January 2018

Drug response is known to be variable in different populations. Hence, belimumab is being evaluated in patients of different races in varied geographic areas. Adult patients of black race with lupus are being recruited for a phase 3/4, multi-centre, randomized, double-blind, placebo-controlled, 52-week study (NCT01632241) to receive belimumab with standard therapy [24]. At 52 weeks, response rate will be measured by the SLE Responder Index (SRI). The study would also evaluate SLE Flare Index and adverse events

and is expected to be completed by January 2018. Another multicentre, phase III, continuation study (NCT01597622) is underway in Northeast Asia and Japan [25]. Participants who had previously completed 48 weeks treatment with either placebo or belimumab would now receive belimumab (10 mg/kg intravenously every 4 weeks) with standard therapy. The primary outcome measures the long-term safety/adverse events (for up to 5 years) of belimumab use. In addition, SLE responder index would be monitored for efficacy in these participants.

Conclusion

Existing studies indicate that belimumab is effective in adult autoantibody positive SLE patients with moderately active disease (SLEDAI score $\geq$ 6) with predominant muco-cutaneous and/or musculoskeletal manifestations. It still remains to be proved that belimumab could serve as a steroid-sparing agent enabling reduction in the dose or discontinuation of existing therapy. Ongoing trials could provide valuable long term safety data in varied populations enabling long term use with an acceptable safety profile.

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