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HEALTH TECHNOLOGY BRIEFING
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Belimumab in combination with rituximab for systemic lupus erythematosus (SLE)

NIHRIO ID	23788	**NICE ID**	10213
Developer/Company	GlaxoSmithKline UK Ltd	**UKPS ID**	650850

Licensing and market availability plans	Currently in phase III clinical development.

SUMMARY

Belimumab in combination with a cycle of rituximab is in clinical development for adults with Systemic Lupus Erythematosus (SLE). SLE is an autoimmune disease where the body's immune system attacks its own tissues and organs. Patients will often have periods where their symptoms flare-up and periods where their symptoms settle down. Mild SLE can cause joint problems and tiredness, whereas severe cases can be life threatening. Currently, conventional SLE treatments, such as corticosteroids and immunosuppressants, are known to have issues with efficacy and long-term toxicity.

Belimumab is a protein that works by reducing the activity of a type of white blood cell called B-cells that produce the antibodies. Belimumab is given by monthly intravenous (into vein) infusions or weekly subcutaneous (into skin) injection and is intended to be added on to current standard of care therapies. Rituximab binds specifically to a protein called CD20 located on pre-B and mature B lymphocytes inducing death of these cells, it is given intravenously. If licenced belimumab in combination with a cycle of rituximab could provide an additional treatment option for adults with SLE.

PROPOSED INDICATION

Adult patients aged 18+ years with systemic lupus erythematosus (SLE).[1]

TECHNOLOGY

DESCRIPTION

Belimumab is a human IgG1λ monoclonal antibody specific for soluble human B Lymphocyte Stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab blocks the binding of soluble BLyS, a B cell survival factor, to its receptors on B cells. Belimumab does not bind B cells directly, but by binding BLyS, belimumab inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells. BLyS levels are elevated in patients with SLE and other autoimmune diseases. There is an association between plasma BLyS levels and SLE disease activity. The relative contribution of BLyS levels to the pathophysiology of SLE is not fully understood.[2]

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1. Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes.[3] After binding to CD20, rituximab mediates B-cell lysis.[4]

In the phase III trial (NCT03312907), patients on the active arm receive belimumab SC 200mg/week for 52 weeks with a cycle of rituximab IV (1,000mg doses given at week 4 and week 6). Patients received a premedication regimen 30 minutes before each rituximab infusion, consisting of methylprednisolone IV 100mg or equivalent, an oral antihistamine and acetaminophen or equivalent.[5]

INNOVATION AND/OR ADVANTAGES

While the efficacy of belimumab has been demonstrated in patients with SLE, a proportion of patients maintain a degree of disease activity despite belimumab treatment. Therefore, additional effective and well-tolerated treatment options are required to further improve overall disease control.[5]

Combining belimumab with rituximab has a strong immunological rationale, as the drugs operate through complementary and perhaps synergistic mechanisms. Belimumab treatment results in the mobilization of memory B cells from tissues despite an overall decrease in peripheral B cell levels. This phenomenon will render tissue-resident B cells more susceptible to depletion by rituximab. In addition, blocking the effects of high serum BLyS levels might have favourable quantitative and qualitative effects on B cell reconstitution after depletion with rituximab. Synergistic or additive effects of such sequential therapy have been demonstrated in pre-clinical studies, and this hypothesis is further supported by case reports in patients with SLE.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Belimumab is licensed in the UK as add-on therapy in patients aged 5 years and older with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy, administered as an intravenous infusion.[2,6]

Belimumab is licensed in the EU as add-on therapy in adults with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy.[7-9]
Belimumab is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis, in the EU.[7-9]

Rituximab is licensed in the UK for the treatment of:[3,10]

- Severe active rheumatoid arthritis (in combination with methotrexate)
- Follicular non-Hodgkin's lymphoma
- Diffuse large B-cell non-Hodgkin's lymphoma (in combination with chemotherapy)
- Chronic lymphocytic leukaemia (in combination with chemotherapy)
- Induction of remission in patients with severe, active granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis (in combination with glucocorticoids)
- Moderate to severe pemphigus vulgaris (PV)

Although not licensed in the UK, rituximab is currently funded for use in specialised centers in England for patients with active SLE who have failed to respond, or had adverse events to, two or more standard immunosuppressive therapies (one of which must be either mycophenolate mofetil or cyclophosphamide, unless contraindicated) in combination with corticosteroids.[11]

Very common adverse events (frequency ≥ 1/10) of belimumab as monotherapy include: bacterial infections, e.g. bronchitis, urinary tract infection, diarrhoea and nausea.[2] Very common adverse events (frequency ≥ 1/10) of rituximab as monotherapy include: bacterial infections, viral infections, bronchitis, neutropenia, leucopenia, febrile neutropenia, thrombocytopenia, infusion-related reactions, angioedema, nausea, pruritus, rash, alopecia, fever, chills, asthenia and headache.[3]

Belimumab after a single course of rituximab is in phase II clinical trials for membranous nephropathy, systemic sclerosis, ANCA associated vasculitis and Sjogren's syndrome.[12]

PATIENT GROUP

DISEASE BACKGROUND

SLE is a chronic multisystem inflammatory autoimmune disease associated with impaired health-related quality of life.[5] The condition can affect any organ system, sequentially or at the same time.[11] In people with SLE, cells that have undergone apoptosis are not cleared away properly. The relationship between this and the cause or features of SLE are unclear but researchers suggest that these dead cells may release substances that cause the immune system to react inappropriately and attack the body's tissues, resulting in the signs and symptoms of SLE.[13]

The signs and symptoms of SLE vary among affected individuals and can involve many organs and systems including mostly the skin, joints, kidneys, lungs, central nervous system and haematopoietic system.[14] Some patients experience periods where their disease flares up (relapses) and periods where their symptoms settle down (remission) whereas some patients do not notice any difference and symptoms are constant.[15] Mild SLE causes joint and skin problems and tiredness. Moderate SLE causes inflammation of other parts of the skin and body, including the lungs, heart and kidneys. Severe SLE causes life-threatening involvement to the heart, lungs, brain, bone marrow or kidneys and are more likely to cause irreversible damage accrual in the first years of disease.[15]

The causes of SLE are unknown but are believed to be linked to environmental, genetic and hormonal factors.[16] Some of the environmental triggers linked to SLE include; excessive sun exposure, viruses and other infections, household chemicals and toxic exposures.[17] Normal variations (polymorphisms) in many genes can affect the risk of developing SLE and in most cases multiple genetic factors are thought to be involved. In rare cases, SLE is caused by mutations in single genes. Most of the genes associated with SLE are involved in immune system function and variations in these genes likely affect proper targeting and control of the immune response.[14]

CLINICAL NEED AND BURDEN OF DISEASE

There are approximately 15,000 people in England and Wales with SLE, predominantly women, with a peak incidence at the age of 25-30 years old. The incidence, prevalence and severity of SLE is higher in African-Caribbean, South Asian and Chinese populations compared to European whites. In these racial/ethnic groups there is a higher incidence of renal involvement, which is associated with a higher mortality rate and end-stage kidney disease may occur in up to 40% of cases.[11]

Approximately 20-30% of patients continue to have high disease activity despite standard therapies, or have major organ involvement particularly associated with a worse prognosis (e.g. renal, neuropsychiatric, haematological involvement). These groups require therapy with more potent immunosuppression such as IV cyclophosphamide or mycophenolate mofetil.[11]

A proportion of these patients will, however, continue to have active uncontrolled disease despite therapy, or will have unacceptable toxicities from such drugs. In others, disease control will require an unacceptably high dose of corticosteroids which, in this population, is associated with the development of significant co-morbidities (irreversible organ damage) such as bone, cardiovascular, neuropsychiatric and metabolic consequences. These refractory patients (<10% of all cases of SLE) require access to treatment with a biologic drug such as rituximab.[11]

In England, in 2019-2020, there were 6,644 finished consultant episodes (FCE) for SLE (ICD-10 code M32) which resulted in 5,982 admissions and 7,584 FCE bed days.[18] In 2019, there were 84 deaths from SLE (ICD-10 code M32) in England and Wales.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Currently there is no cure for SLE but there are a series of general measures, that include sun protection, avoid smoking and controlling obesity, hypertension and other co-morbidities. The medications available can help relieve the symptoms and try to reduce the chances of organ damage.[20,21] The drugs used to treat lupus will depend on the severity of disease and which parts of the body are affected, but their use may be limited due to adverse events and co-morbidities.[22]

CURRENT TREATMENT OPTIONS

Belimumab is recommended by NICE as an option as add-on treatment for active autoantibody-positive systemic lupus erythematosus in adults only if all of the following apply:[23]

- There is evidence for serological disease activity (defined as positive anti-double-stranded DNA and low complement) and a SELENA-SLEDAI score of greater than or equal to 10 despite standard treatment.
- Treatment with belimumab is continued beyond 24 weeks only if the SELENA-SLEDAI score has improved by 4 points or more.

Patients who experience joint or muscle pain as a result of SLE are often prescribed anti-inflammatory, immunomodulatory and immunosuppressive drugs by physicians to ease symptoms including:[20,24]

- Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibruprofen, naproxen and diclofenac
- Corticosteroids such as prednisolone[25]
- Hydroxychloroquine[26]
- Immunosuppressants such as azathioprine[27], methotrexate, mycophenolate mofetil (MMF), tacrolimus and cyclophosphamide.

Rituximab is not licenced for SLE but can be considered for moderate or severe refractory SLE with active disease, who have failed to respond or have had adverse events to 2 or more immunosuppressive therapies.[28]

PLACE OF TECHNOLOGY

If licenced, belimumab with a cycle of rituximab could provide an additional treatment option for adults with SLE.

CLINICAL TRIAL INFORMATION

Trial	**BLISS-BELIEVE;** NCT03312907, 2016-003050-32; A Phase 3, Multi-Centre, Randomized, Double-Blind, Placebo-Controlled, 104-Week Study to Evaluate the Efficacy and Safety of Belimumab Administered in Combination With Rituximab to Adult Subjects With Systemic Lupus Erythematosus (SLE) **Phase III** - Active, not recruiting **Location(s):** EU countries (not including UK), Canada, United States and other countries. **Primary completion date:** May 2020 **Estimated Study Completion Date**: July 2021
Trial design	Randomised, parallel assignment, double-blind
Population	N = 292 (actual), clinical diagnosis of SLE based on 4 or more of the 11 American College of Rheumatology (ACR) criteria and who have a screening SLEDAI-2K score >=6, and are aged 18 years and older.
Intervention(s)	Belimumab administered as subcutaneous injection once weekly and rituximab administered as IV infusion of 1000mg at Week 4 and Week 6 and Standard therapy (excluding Immunosuppressants).
Comparator(s)	• Standard of care therapy (excluding immunosuppressants) • Belimumab plus standard therapy (including immunosuppressants)
Outcome(s)	Primary outcome(s);

	• Proportion of subjects with a state of disease control at week 52 [Time Frame: Week 52] Key secondary endpoint: • State of clinical remission defined as Clinical SLEDAI-2K score =0 achieved without immunosuppressant and with corticosteroids at a prednisone equivalent dose of 0 mg/day [Time Frame: Week 64] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**SynBioSe-2;** NCT03747159; A Randomized Trial to Investigate the Reset of Humoral Autoimmunity by Combining Belimumab With Rituximab in Severe Systemic Lupus Erythematosus **Phase II** - Recruiting **Location(s):** Netherlands **Primary completion date:** September 2023
Trial design	Randomised, parallel assignment, open label.
Population	N = 70 (estimate), severe, active SLE disease, aged 18 years and older .
Intervention(s)	Subcutaneous weekly injections with 200mg of belimumab prior to two intravenous infusions of 1000mg rituximab with continuation of the belimumab as maintenance therapy and standard of care.
Comparator(s)	Standard of care treatment arm
Outcome(s)	Primary outcome(s); • Treatment failure rate [Time Frame: 104 weeks] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Belimumab is already marketed in the UK. One vial of belimumab 120mg powder for concentrate for solution for infusion costs £121.50 and one vial of belimumab 400mg powder for concentrate for solution for infusion costs £405.00.[6]

Rituximab is already marketed in the UK. One vial of Rituximab 500mg/50ml powder for concentrate for solution for infusion costs £873.15.[10]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance – proposed. Anifrolumab for treating active autoantibody-positive systemic lupus erythematosus (GID-TA10676). Expected publication date: April 2022.
- NICE technology appraisal guidance in development. Belimumab for treating active autoantibody-positive systemic lupus erythematosus (GID-TA10626). Expected publication date: July 2021.
- NICE technology appraisal. Belimumab for treating active autoantibody-positive systemic lupus erythematosus (TA397). June 2016.
- NICE evidence summary. Systemic lupus erythematosus: oral mycophenolate (ESUOM36). November 2014.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Rheumatology Services (Adult). A13/S/a.
- NHS England. 2020. Clinical Commissioning Policy Rituximab for refractory Systemic Lupus Erythematosus (SLE) in adults and post-pubescent children [200402P]

OTHER GUIDANCE

- European League of Associations for Rheumatology (EULAR). Update of the EULAR recommendations for the management of systemic lupus erythematosus. 2019.[29]
- British Society for Rheumatology. Guideline for the management of systemic lupus erythematosus in adults. January 2018.[30]

ADDITIONAL INFORMATION

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