NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus (review of TA397) [ID1591]

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of belimumab within its licensed indication for the treatment of active autoantibody-positive systemic lupus erythematosus.

Background

Systemic lupus erythematosus (SLE) is a chronic autoimmune condition that causes inflammation in the body's tissues. The manifestations of SLE vary greatly between people and can affect the whole body including the skin, joints, internal organs and serous membranes. SLE can result in chronic debilitating ill health. The cause of SLE is unknown though a combination of genetic, environmental and hormonal factors is thought to play a role in disease development and progression. Disease activity varies over time and, at the onset, symptoms are very general and may include unexplained fever, extreme fatigue, muscle and joint pain and skin rash. Active SLE involves frequent flares and more severe symptoms compared with disease that is inactive or under control (in remission). SLE can lead to mucocutaneous disease, arthritis, kidney failure, heart and lung inflammation, central nervous abnormalities and blood disorders. Over 90% of people with SLE develop problems with their joints and muscles such as arthralgia (joint pain) and myalgia (muscle pain). Up to 40% develop renal disease, which significantly contributes to morbidity and mortality.[1] Persistent disease activity and side-effects from cumulative dose of corticosteroids contribute significantly to the accrual of irreversible long-term organ damage.

There are currently around 60,000 people with SLE in England and Wales and approximately 3000 people are being diagnosed with SLE each year.[2] The prevalence of SLE is significantly related to ethnicity, and is highest among people of African-Caribbean ethnicity. The prevalence of renal disease is also higher in Black, Asian and Hispanic populations, compared with the white population.[3] Although the severity of the disease is greater in the male population, SLE is approximately 6-9 times more common in women than men.[1,4] It mainly affects people between 15 and 60 years of age. However, when SLE presents in childhood it may have more severe disease presentation than in adults, with a higher incidence of major organ involvement and a more aggressive disease course.[5] It may also have a significant impact on a child’s education and social development, and introduce significant caring requirements for their parents.[5]

There is no cure for SLE. The aim of current treatments is to control and ease symptoms, and prevent organ damage and long-term complications. Standard therapy currently includes using:[6,7]

- non-steroidal anti-inflammatory drugs (NSAIDs),
- corticosteroids such as oral prednisolone,
- conventional disease-modifying anti-rheumatic drugs (DMARDs) such as antimalarials (for example, hydroxychloroquine) or immunosuppressive agents (for example, cyclophosphamide, azathioprine, methotrexate and mycophenolate mofetil), and
- biological DMARDs such as rituximab and belimumab.

Cyclophosphamide and biologics DMARDs are usually reserved for more severe and/or refractory disease, although the former is not frequently used in SLE due to the risk of side effects. Prednisolone, hydroxychloroquine and belimumab are the only drugs specifically licensed for the treatment of SLE. People with SLE may receive additional treatments to manage their comorbidities, such as drugs for thrombosis, arthritis, blood pressure, depression, osteoporosis, raised cholesterol and heart disease.[8] There is lack of evidence for therapeutic intervention specific to SLE in children. Treatment options are generally aligned with those for adult SLE.[5]
NICE technology appraisal 397 recommended belimumab as an option as add-on treatment for active autoantibody-positive SLE in adults only if all of the following apply:

- There is evidence for serological disease activity (defined as positive anti-double-stranded DNA and low complement) and a Safety of Estrogen in Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (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.
- The company provides belimumab with the discount agreed in the patient access scheme.
- Under the conditions for data collection, monitoring, patient eligibility and consent, ongoing treatment, cost to the NHS, and review by NICE as laid out in the managed access agreement.

The technology

Belimumab (Benlysta, GlaxoSmithKline) is a human monoclonal antibody that inhibits the biological activity of B-lymphocyte stimulator (BLyS). BLyS promotes survival and development of B-lymphocyte cells into antibody-producing mature plasma B cells. In SLE, elevated BLyS levels contribute to the production of autoantibodies and have been associated with increased SLE disease activity. Belimumab is administered intravenously or by subcutaneous injection, as an add-on to standard therapy. Subcutaneous injection is available for use in adults only.

Belimumab has a marketing authorisation as an add-on therapy in people aged 5 years and older with active, autoantibody-positive SLE with a high

degree of disease activity (for example, positive anti-dsDNA and low complement) despite standard therapy.

Intervention(s)	Belimumab as an add-on to standard therapy
Population(s)	People aged 5 years or more with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity despite standard therapy
Comparators	• Standard therapy alone For people in whom it is considered appropriate: • Rituximab plus standard therapy • Cyclophosphamide plus standard therapy
Outcomes	The outcome measures to be considered include: • disease activity • rate and duration of response • rate and duration of remission • incidence and severity of flares • impact on disease manifestations • incidence of long-term complications and/or organ damage • corticosteroid use • rate and duration of corticosteroid-free remission • mortality • health-related quality of life • adverse effects of treatment
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

	Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	Related Technology Appraisals: 'Belimumab for treating active autoantibody-positive systemic lupus erythematosus'. NICE Technology Appraisal 397. Review date April 2020. Related Evidence Summaries: 'Systemic lupus erythematosus: oral mycophenolate (ESUOM36)' (2014) Evidence summary Appraisals in development (including suspended appraisals): 'Prasterone for the treatment of systemic lupus erythematosus.' NICE Technology Appraisal (suspended appraisal).

References

[1] Fanouriakis A, Kostopoulou M, Cheema K et al. (2020) 2019 Update of the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) recommendations for the management of lupus nephritis Annals of the Rheumatic Diseases 79:713-723

[2] Rees F, Doherty M, Grainge M et al. (2016) The incidence and prevalence of systemic lupus erythematosus in the UK, 1999-2012. Ann Rheum Dis 75:13641

[3] Parikh SV, Almaani S, Brodsky S, Rovin BH (2020) Update on Lupus Nephritis: Core Curriculum 2020. American Journal of Kidney Diseases

[4] Weckerle CE, Niewold TB (2011) The unexplained female predominance of systemic lupus erythematosus: clues from genetic and cytokine studies. Clinical reviews in allergy & immunology 40(1): 42-49

[5] Lupus UK. Juvenile-onset lupus. Accessed July 2020

[6] Gordon C, Amissah-Arthur MB, Gayed M et al. (2018). The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. Rheumatology 57(1), pp.e1-e45

[7] Fanouriakis A, Kostopoulou M, Alunno A et al. (2019) 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis 78:736-745

[8] Lupus Trust. How lupus is treated. Accessed July 2020