Clinical Commissioning Policy
Obinutuzumab for systemic lupus erythematosus with secondary non-response to rituximab (adults and post-pubescent children) 2121

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Commissioning position

Summary

Obinutuzumab is not recommended to be available as a routine commissioning treatment option in refractory systemic lupus erythematosus (SLE) within the criteria set out in this document.

The policy is restricted to adults and post-pubescent children, via the Medicines for Children policy, as there is insufficient evidence to confirm safety and it is not recommended to be used in those age groups not included in the policy.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Executive summary

This policy is for the use of obinutuzumab by adult and post-pubescent patients with refractory SLE who have demonstrated secondary non-response to rituximab.

The independent evidence review returned evidence for obinutuzumab which is presented for a not for routine commissioning position.

Plain language summary

Systemic lupus erythematosus (SLE, also known as lupus) is a long-term autoimmune condition (a condition where your immune system attacks the body) that causes swelling, soreness and inflammation in the body. It affects the whole body including the skin, joints and internal organs and results in long-term ill health.

In 2012, SLE affected approximately 1 in 1000 people in the UK. It is more common in people of African-Caribbean and South Asian backgrounds and more common in women than men. SLE can cause different symptoms in different people. Patients are prone to flares of their disease. SLE can cause arthritis, kidney inflammation, rashes, heart and lung inflammation, central nervous system abnormalities and blood disorders. Renal (kidney) disease occurs in up to 40% of people with SLE and significantly contributes to long-term ill health, including kidney failure requiring dialysis and death in some lupus patients.

Inadequately treated active disease causes damage of the affected systems/organs thus increasing complications, morbidity and can lead to an early death. The aim of treatment is to suppress disease activity, prevent organ damage and improve quality of life.

Four drugs are currently licensed and available for use in adults with SLE: hydroxychloroquine (an anti-malarial), azathioprine (a conventional DMARD (Disease Modifying Anti Rheumatic Drugs)), prednisolone (a corticosteroid), and belimumab (a biological DMARD). Treatment regimens for SLE vary depending on disease severity, which can be mild, moderate, or severe. For mild disease, standard therapy is usually a combination of non-steroidal anti-inflammatory drugs (NSAIDs), hydroxychloroquine and low dose steroids e.g., an occasional intramuscular corticosteroid injection. The current NHS England treatment pathway for moderate or severe SLE is for conventional immunosuppressants. First line options include oral medications such as azathioprine, methotrexate, mycophenolate, or hydroxychloroquine. Cyclophosphamide is also a first line option, and this is usually given intravenously. These immunosuppressants are associated with potential side effects and toxicity.

For patients with refractory SLE (high disease activity scores, high doses of steroids and have failed 2 other immunosuppressant therapies), they may be eligible for treatment with rituximab (an anti-CD20 drug), as per the NHS Clinical Commissioning Policy for this. In a small minority of patients who have previously responded to rituximab, later cycles become ineffective – this is called secondary non-response. There is some evidence in SLE that in this clinical scenario switching to an alternative similar therapy (namely a fully humanised anti-CD20 drug) restores clinical response. Obinutuzumab is being proposed as this alternative similar therapy.

Obinutuzumab is a biological medicine that selectively targets B cells, cells that are part of the body's immune system that act to reduce the inflammatory response. It is usually given as an intravenous infusion. Obinutuzumab is currently not licensed for the treatment of SLE (BNF 2022).

What we have decided

NHS England has carefully reviewed the evidence to treat patients with systemic lupus erythematosus with obinutuzumab. NHS England recognises that the published evidence identifies that, at present, there is sufficient evidence to commission this treatment. However, following the relative prioritisation process undertaken in July 2023 for funding interventions in 2023/24, NHS England has concluded that, balanced against other relative priorities that were also considered during this process, obinutuzumab for systemic lupus erythematosus with secondary non-response to rituximab will not be funded at this time within the resources available.

Links and updates to other policies

This document is linked to the following NHS England policy:

- NHS England. 2020. Rituximab for refractory Systemic Lupus Erythematosus (SLE) in adults and post-pubescent children [200402P]. Available at: https://www.england.nhs.uk/publication/rituximab-for-refractory-systemic-lupus-erythematosus-sle-in-adults-and-post-pubescent-children/

This document is linked to the following NICE technology appraisal:

- Belimumab for treating active autoantibody-positive systemic lupus erythematosus [ta752]. Available at: https://www.nice.org.uk/guidance/ta752/chapter/1-Recommendations

Committee discussion

See the committee papers (link) for full details of the evidence.

The condition

Systemic lupus erythematosus (SLE, also known as lupus) is a chronic multisystem autoimmune disease that causes inflammation in multiple organs ranging from rash and arthritis to life-threatening involvement of kidneys and other internal organs and can result in long-term ill health, impaired quality of life, organ failure and death. It typically affects patients in a

relapsing pattern, although some patients will experience constant symptoms. Onset is typically in young women, with non-European ancestries being more frequently and severely affected. Although uncommon with prevalence approximately 0.1% (Barber et al, 2021), it has a devastating impact on health with (i) mortality increased over 3-fold compared to the general population (Lee et al, 2016); (ii) costs to the UK economy ~£8,000 per patient per year in direct and indirect healthcare costs (Khamashta et al, 2014); and (iii) severely impaired quality of life similar to chronic diseases such as heart failure (Jolly, 2005; Katz et al, 2020); (iv) only 47% of SLE patients are employed and 34% have work disability (Baker et al, 2009).

SLE is biologically characterised by loss of self-tolerance, primarily through B cell hyperactivity which leads to immune responses toward endogenous nuclear and cytoplasmic material. In response to these autoantigens, clones of plasma cells produce autoantibodies which may induce inflammation through formation of immune complexes and activation of Fc-gamma receptors. B cells play additional roles in the pathogenesis of SLE including unique roles in antigen presentation, toll like receptor-mediated signalling, and cytokine production. Through targeting CD20 (a B cell surface marker) monoclonal antibodies can lead to the depletion of B cells, and an improvement in the clinical syndrome of SLE.

Rituximab, a chimeric anti-CD20 monoclonal antibody currently commissioned for refractory SLE, is given in cycles. With each cycle of treatment (2 infusions 2 weeks apart) there is profound depletion of B cells for at least 6 months, leading to a period of sustained clinical response. Following return of circulating B cells, patients relapse and require a repeat cycle. The duration of response, and therefore time to retreatment varies with median approximately 15 – 18 months (Yusof et al. 2017).

In a substantial minority of patients who have previously responded to rituximab, later cycles become ineffective – this is called secondary non-response. This has been shown to be related to a large extent to the development of anti-rituximab antibodies, which neutralise the drug and stop it from depleting B cells. There is some evidence in SLE that in this scenario switching to an alternative fully human or humanised anti-CD20 therapy restores B cell depletion and clinical response. Obinutuzumab is being proposed as one alternative anti-CD20 therapy. This is on the basis of greater efficacy, durability of response than Rituximab and cost effectiveness.

Current treatments

There are currently only four drugs licenced in the UK for use in SLE – prednisolone, hydroxychloroquine, azathioprine, and most recently belimumab in 2011. Various immunosuppressants are frequently used off-label in SLE by experienced physicians, namely methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide, and rituximab.

Treatment regimens for SLE vary on disease severity which can be mild, moderate, or severe. The current NHS England treatment pathway for SLE is for conventional immunosuppressants (e.g., azathioprine, methotrexate, mycophenolate, cyclophosphamide (usually intravenous)) and hydroxychloroquine first-line.

Prior to consideration of belimumab and rituximab patients are considered for eligibility for any trials. If patients meet NICE criteria (SLEDAI score ≥ 10, dsDNA antibody positive and/or low complement) they may receive belimumab. If patients have non-response to mycophenolate and/or cyclophosphamide, have active disease (e.g., BILAG 1xA or 2xB or SLEDAI ≥6) or need unacceptable doses of glucocorticoids to prevent active disease, then they may receive rituximab. There is no recommended line of therapy after rituximab.

Proposed treatments

Obinutuzumab is an alternative humanised anti-CD20 monoclonal antibody. As a type 2 monoclonal antibody, obinutuzumab can lead to B cell depletion through binding to the CD20 molecule on the B cell surface and generating programmed cell death and antibody dependent cell mediated cytotoxicity. For the purposes of this policy there are two key differences: (i) it is humanised, so the patient is less likely to develop anti-drug antibodies; (ii) it is glycoengineered

to induce more effective B cell depletion. There is therefore a good rationale for it to restore B cell depletion to patients with secondary non-response to rituximab.

It is currently licenced in the UK for use in chronic lymphocytic leukaemia and follicular lymphoma. The benefit of obinutuzumab in lupus nephritis has been described in a published phase 2 randomised controlled trial (Furie et al, 2022) as well as a UK case series in the specific rituximab secondary non-response population proposed. (Arnold et al., 2022)

It is given as two 1000mg intravenous infusions at 2 weeks apart, and its use in SLE is off label. In commissioned treatment with anti-CD20 therapy per se subsequent doses are permitted if there is improvement in clinical assessment scores and/or organ-threatening disease but this re-treatment interval varies from person to person. This should not be more frequent than every 6 months.

Epidemiology and needs assessment

The population for this policy is patients with SLE who previously responded to rituximab but, on a second or subsequent cycle exhibit secondary non-response. This is frequently accompanied by an unusually severe infusion reaction and incomplete depletion of B cells. Using British Isles Lupus Assessment Group Biologics Registry (BILAG-BR) data from 2018 - 2020 demonstrates that approximately 204 patients per year are initiated on rituximab in the UK for SLE. Of these, approximately 60% have a clinical response and are eligible for repeat cycles. Patients with SLE who previously responded to rituximab but, on a second cycle exhibit secondary non-response have been estimated to be approximately 14% of patients (Md Yusof et al, 2017). Therefore, it is anticipated that approximately 17 patients per year to be eligible for obinutuzumab.

Evidence summary

An independent evidence review was conducted for the use of obinutuzumab. The evidence review which informs this commissioning position can be accessed here.

Audit requirements

All patients receiving obinutuzumab for SLE should be registered with the BILAG-BR (www.bilagbr.org). The information is collected to inform future revisions of this policy.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base, then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

British Isles Lupus Assessment Group (BILAG)	This is a network of UK Rheumatologists with a specific clinical and research interest in lupus.
The British Isles Lupus Assessment Group 2004 (BILAG-2004) disease activity index	Evaluates SLE disease activity over the preceding 28 days and can be used to assess flare and response to treatment using 97 items in 9 organ systems. A graded (letter)

	score can be calculated. The letter score (A to E) indicates the severity of disease activity ranging from A being severe disease activity to E being no disease activity ever in an organ system.
BILAG Biologics Register (BILAG-BR)	This is a registry that was established by BILAG to investigate and record the response to and safety of biologic treatments in SLE compared with standard therapy (McCarthy et al, 2018).
Disease modifying anti-rheumatic drugs (DMARDs)	These are drugs that dampen down the immune system. There are conventional DMARDs e.g. mycophenolate mofetil, cyclophosphamide and biological DMARDs e.g. rituximab and belimumab.
End stage renal disease (ESRD)	The last stage of chronic kidney disease. This means that the kidneys cannot remove waste and fluids from the body effectively and patients require high-cost renal replacement therapy e.g., long term haemodialysis, peritoneal dialysis, or a kidney transplant.
Post-pubescent children	This policy refers to post-pubescent children in line with the considerations outlined in the Commissioning Medicines for Children in Specialised Services policy. (NHS England 170001/P, 2017).
Lupus Glomerulonephritis/Nephritis	SLE that affects the kidneys, leading to kidney inflammation and potentially long - term renal disease and renal failure that may require renal replacement therapy.
Immunosuppressive therapies	This refers to a group of drugs that suppress the immune system. In this document this term includes anti-malarial agents, glucocorticoids and DMARDs.
Refractory systemic lupus erythematosus (SLE)	Patients with refractory SLE are defined as those who have used 2 or more DMARDs (one of which must be EITHER mycophenolate or cyclophosphamide, unless contraindicated), and patients still either have: 1) ongoing moderate to severe active disease OR 2) require excessive use of glucocorticoids (over 7.5mg prednisolone per day) to maintain lower levels of disease activity.
SLE Disease Activity Index 2000 (SLEDAI-2K)	A global numerical scoring system that evaluates SLE disease activity over the preceding 10 or 28 days using 24 items. A score of 6 or more is consistent with significant disease activity (and requiring initiation or escalation of immunosuppressive therapy).
Primary definition of response	This is defined as the loss of all A and B BILAG scores to ≤ 1B score with no new A or B scores in other organ domains at 6 months.

	This is a clinically meaningful response. This is the most commonly used definition of response in clinical practice.
Major clinical response	This is defined in BILAG - BR as BILAG-2004 C, D and Es in all systems with SLEDAI-2K ≤ 4 and daily oral prednisolone dose ≤ 7.5mg at 6 months. This can equate to clinical remission (McCarthy et al 2018).

References

Arnold, J., Dass, S., Twigg, S., Jones, C., Rhodes, B., Hewins, P., Chakravorty, M., Courtney, P., Ehrenstein, M., Md Yusof, M. and Vital, E., 2022. Efficacy and safety of obinutuzumab in systemic lupus erythematosus patients with secondary non-response to rituximab. Rheumatology.

Baker K, Pope J, Fortin P, Silverman E, Peschken C, Faces of Lupus I, et al. Work disability in systemic lupus erythematosus is prevalent and associated with socio-demographic and disease related factors. Lupus. 2009;18(14):1281-8.

Barber MRW, Drenkard C, Falasinnu T, Hoi A, Mak A, Kow NY, et al. Global epidemiology of systemic lupus erythematosus. Nat Rev Rheumatol. 2021;17(9):515-32.

Furie RA, Aroca G, Cascino MD, Garg JP, Rovin BH, Alvarez A, Fragoso-Loyo H, Zuta-Santillan E, Schindler T, Brunetta P, Looney CM, Hassan I, Malvar A. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. Ann Rheum Dis. 2022 Jan;81(1):100-107. doi: 10.1136/annrheumdis-2021-220920. Epub 2021 Oct 6. PMID: 34615636; PMCID: PMC8762029.

Jolly M. How does quality of life of patients with systemic lupus erythematosus compare with that of other common chronic illnesses? J Rheumatol. 2005;32(9):1706-8.

Katz P, Wan GJ, Daly P, Topf L, Connolly-Strong E, Bostic R, et al. Patient-reported flare frequency is associated with diminished quality of life and family role functioning in systemic lupus erythematosus. Quality of Life Research. 2020;29(12):3251-61.

Khamashta MA, Bruce IN, Gordon C, Isenberg DA, Ateka-Barrutia O, Gayed M, et al. The cost of care of systemic lupus erythematosus (SLE) in the UK: annual direct costs for adult SLE patients with active autoantibody-positive disease. Lupus. 2014;23(3):273-83.

Lee YH, Choi SJ, Ji JD, Song GG. Overall and cause-specific mortality in systemic lupus erythematosus: an updated meta-analysis. Lupus. 2016.

McCarthy E, Sutton E, Nesbit S, White J, Parker B, Jayne D, Griffiths B, Isenberg D, Rahman A, Gordon C, D'Cruz D, Rhodes B, Lanyon P, Vital E, Yee C, Edwards C, Teh L, Akil M, McHugh N, Zoma A, Bruce I. 2018. Short-term efficacy and safety of rituximab therapy in refractory systemic lupus erythematosus: results from the British Isles Lupus Assessment Group Biologics Register. Rheumatology, 57(3):470-479

Md Yusof M Y, Sha, D, El-Sherbiny YM, Dunn E, Rawstron AC, Emery P, Vital EM. 2017. Predicting and managing primary and secondary non-response to rituximab using B-cell biomarkers in systemic lupus erythematosus. Annals of the rheumatic diseases, 76(11), 1829–1836. https://doi.org/10.1136/annrheumdis-2017-211191