CLINICAL PRIORITIES ADVISORY GROUP
10 07 2023

Agenda Item No	
National Programme	Internal Medicine
Clinical Reference Group	Specialised Rheumatology
URN	2121

Title
Obinutuzumab for systemic lupus erythematosus with secondary non-response to rituximab (adults and post-pubescent children)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its relative prioritisation

Proposition
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 and premature mortality. Inadequately treated active disease causes damage of the affected organs and systems thus increasing complications, morbidity and can lead to both a higher and earlier death rate. The aim of treatment is to suppress disease activity, prevent organ damage such as kidney failure and improve quality of life. Obinutuzumab is proposed for use in a particular subset of patients with severe lupus that is no longer responding to treatment with rituximab, the current last line therapy. This is called secondary non-response to rituximab. Obinutuzumab has the potential to be organ sparing or lifesaving in these patients who currently have no other treatment options.

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy proposition.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In individuals with systemic lupus erythematosus (SLE) who have demonstrated secondary non-response to rituximab therapy, what is the clinical effectiveness and safety of obinutuzumab when compared with immunosuppressant therapies?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Improvement in disease activity scores **Certainty of evidence:** very low	Disease activity scores are important to patients because they reflect treatment effect (either suppression or failure) of obinutuzumab. One retrospective case series (n=9) provided evidence relating to improvement in disease activity scores after 6 months. The study had no comparator treatment. For both scales used to assess disease activity in the study (BILAG-2004 and SLEDAI-2K), higher numerical scores indicate worse disease activity. For BILAG-2004, A on the alphabetical scale indicates the most severe disease, whereas E indicates that the disease has never been active. A meaningful clinical response for alphabetical BILAG grades can be defined by reduction of all baseline BILAG As to B or less, and no more than one persistent BILAG B. A clinically meaningful improvement in SLEDAI-2K is defined as a reduction by 4 or more points. In the case series, statistically significant improvements from baseline were seen in disease activity scores at 6 months. Median SLEDAI-2K scores improved from 12 to 6 points (p=0.014). This 6-point reduction is clinically meaningful **(VERY LOW)**

	Median numeric BILAG-2004 scores improved from 21 to 2 points (p=0.009). This 19-point reduction is likely to be clinically meaningful. **(VERY LOW)** The study was not powered for statistical hypothesis testing and the data should be regarded as descriptive only. Before obinutuzumab, 6/9 patients had BILAG A/B grade mucocutaneous, 6/9 had BILAG A/B musculoskeletal and 4/9 had BILAG A/B renal disease. After obinutuzumab, 1/9 patients had BILAG B mucocutaneous, no patients had BILAG A/B musculoskeletal and 2/9 patients had BILAG A/B renal disease (no statistical analyses). Overall, some patients in the study experienced clinically meaningful reductions in disease activity. **(VERY LOW)** **Very low certainty evidence from 1 small case series suggests that obinutuzumab statistically significantly improves disease activity scores over 6 months in people with SLE who have demonstrated secondary non-response to rituximab therapy. The evidence also suggests that changes in disease activity are clinically meaningful. However, the study lacks statistical power to show that treatment improved outcomes.**
Quality of Life Certainty of evidence: Not applicable	Quality of life is important to patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. **No evidence was identified for this outcome.**
Improvement in lupus nephritis renal disease Certainty of evidence: Not applicable	Renal disease activity is important to patients because it reflects treatment effect (either suppression or failure) of obinutuzumab. However, treatment effect on disease activity may also affect other systems involved, due to the multi-system nature of SLE. No evidence was identified for this outcome in terms of measures of renal function (specified on the PICO). However, 2/9 patients had BILAG A/B renal disease after obinutuzumab, compared with 4/9 patients before obinutuzumab (see disease activity outcome above; no statistical analysis). **(VERY LOW)** **No renal function evidence was identified for this outcome.**
Important outcomes	
Change in glucocorticoid dose requirements **Certainty of evidence:** very low	When SLE is poorly controlled, glucocorticoids are frequently used at increasing doses. Any response to obinutuzumab should also occur in the context of either a stable or reduced glucocorticoid dose requirement compared to baseline. This is important to patients because of the significant side effects associated with glucocorticoid treatment such as weight gain, osteoporosis, depression, infection and early cardiovascular disease. One retrospective case series (n=9) provided evidence relating to change in glucocorticoid dose requirements after 6 months. The study had no comparator treatment. A sustained dose of prednisolone 7.5mg or less per day (or equivalent) is a commonly agreed meaningful goal of treatment. Before receiving obinutuzumab, all 9 patients in the case series took prednisolone (mean dosage 17.8 mg daily, range 10 mg to 50 mg daily). The mean dosage of prednisolone was lower after obinutuzumab (14.4 mg daily, range 5 mg to 60 mg daily); however, there was no statistically significant difference before and after treatment (p=0.34). After receiving obinutuzumab, 5/9 patients (56%) taking between 10 mg and 30 mg prednisolone daily at baseline had their dosage reduced. In 2 patients, the dosage was increased and in another 2 there was no change. **(VERY LOW)**

	The study was not powered for statistical hypothesis testing and the data should be regarded as descriptive only. In 4/9 patients (44%) prednisolone dosage was reduced to 5 mg daily (from 10 mg to 15 mg daily at baseline) and they had LLDAS. No statistical analysis was reported for this outcome but the study authors report that LLDAS is a clinically meaningful outcome. **(VERY LOW)** **Very low certainty evidence from 1 small case series suggests that the dosage of prednisolone needed to control SLE can be reduced in some individuals with SLE who have demonstrated secondary non-response to rituximab therapy. However, there was no statistically significant difference between prednisolone dosages at baseline and 6 months. This may have been because the study lacked statistical power.** **In the case series, prednisolone dosage was reduced to 5 mg daily in 4 out of 9 people who also had LLDAS (clinically meaningful outcomes). However, this result is of very low certainty, and no conclusions can be drawn.**
Retreatment interval with obinutuzumab Certainty of evidence: Not applicable	Time to retreatment is important to patients as it represents the length of time the patient has had improvement in their SLE before flaring. **No evidence was identified for this outcome.**
Treatment failure Certainty of evidence: very low	Treatment failure is important to patients as it reflects the effectiveness of the intervention. Clinical conditions (severe organ threatening) occur in advanced SLE disease as a consequence of failure to achieve B cell suppression and with advanced immunosuppression. These conditions are associated with significant patient morbidity and mortality. One retrospective case series (n=9) provided evidence relating to treatment failure after 6 months. The study had no comparator treatment. Treatment failed in 1/9 patients (11%). 1 person who was not initially improving was given oral prednisolone then rescue therapy with cyclophosphamide before month 6. At the time of the study, 6/9 patients (67%) remained well-controlled with repeat obinutuzumab cycles and no additional immunosuppression. No statistical analyses were reported. **(VERY LOW)** **Very low certainty evidence from 1 small case series suggests that, by 6 months, treatment failure occurs in about 1 person out of 9 people with SLE who have demonstrated secondary non-response to rituximab therapy. However, no conclusions can be drawn.**
Mortality Certainty of evidence: Not applicable	Mortality is important to patients as individuals with advanced SLE have a high mortality rate due to progressive disease activity causing organ damage, infection and cardiovascular disease. Interventions which improve the survival outcome are important markers of effective SLE treatment. Some of the effect of therapies on mortality may not be manifest for years. **No evidence was identified for this outcome.**
Safety	
Serious adverse events Certainty of evidence: very low	Safety of obinutuzumab is important to patients as it reflects the risks involved in taking this medication and allows a risk to benefit assessment to be undertaken. It also allows comparison of interventional approaches. One retrospective case series (n=9) provided evidence relating to serious adverse events after 6 months. The study had no comparator treatment.

	2/9 patients (22%) had serious adverse events (no statistical analysis). One patient had an episode of SLE enteritis and 1 unvaccinated patient became acutely unwell with COVID-19 infection and died. No cases of progressive multifocal leukoencephalopathy were seen. **(VERY LOW) Little information on adverse effects is reported in the case series and it provides only very low certainty evidence on the safety of obinutuzumab. The authors report that obinutuzumab was generally well tolerated, and infusion reactions did not occur or were mild.**
Abbreviations BILAG, British Isles Lupus Assessment Group, (the BILAG index is a measure of lupus disease activity across 8 organ systems, higher numerical scores indicate worse disease activity [A=12, B=8, C=1, D=0 and E=0], on the alphabetical scale A indicates the most severe disease whereas E indicates that the disease has never been active); LLDAS, Lupus Low Disease Activity State (a measure of low disease activity using several criteria); SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index (used to assess changes in disease activity, higher scores indicate worse disease activity)	

In individuals with SLE who have demonstrated secondary non-response to rituximab therapy, what is the cost effectiveness of obinutuzumab when compared with immunosuppressant therapies?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified regarding the cost effectiveness of obinutuzumab for individuals with SLE who have demonstrated secondary non-response to rituximab therapy.**
Abbreviations SLE, systemic lupus erythematosus	

From the evidence selected, are there any subgroups of patients that may benefit from obinutuzumab more than the wider population of interest?

Outcome	Evidence statement
Subgroups	**No evidence was identified regarding subgroups of patients that may benefit from obinutuzumab more than the wider population of interest.**
Abbreviations SLE, systemic lupus erythematosus	

From the evidence selected, what are the criteria used by the research studies to define secondary non-response to rituximab in SLE?

Outcome	Evidence statement
Criteria	Criteria for secondary non-response to rituximab in SLE and inclusion are not clearly defined in the paper reporting the case series. In the introduction, the authors state: 'some rituximab-treated patients who initially respond well develop neutralising antibodies with repeat cycles on treatment. Infusion reactions followed by failure of B cell depletion and treatment inefficacy, termed as secondary non-depletion non-response, occur in around 14% of patients. This is associated with high levels of anti-rituximab antibodies, high levels of pre-treatment plasmablasts and a lack of concomitant immunosuppression.'

	Although not clearly defined, the criteria that appear to have been used in the case series to define secondary non-response to rituximab in SLE are infusion reactions, failure of B cell depletion and inefficacy of rituximab treatment.
Abbreviations SLE, systemic lupus erythematosus	

From the evidence selected, what dose and/or frequency of obinutuzumab was used?

Outcome	Evidence statement
Dosage	**Obinutuzumab was administered as two 1000 mg infusions given 2 weeks apart (preceded by methylprednisolone 100 mg). The paper does not report how frequently treatment cycles were repeated.**
Abbreviations SLE, systemic lupus erythematosus	

Patient Impact Summary

The condition has the following impacts on the patient's everyday life:

- **mobility:** Patients have moderate to severe problems in walking about
- **ability to provide self-care:** Patients have moderate to severe problems in washing or dressing
- **undertaking usual activities:** Patients have moderate to severe problems in doing their usual activities
- **experience of pain/discomfort:** Patients have severe to extreme pain or discomfort
- **experience of anxiety/depression:** Patients are severely to extremely anxious or depressed

Further details of impact upon patients:

SLE is an immune mediated multi-system disorder potentially affecting any organ system.

Fatigue is one of the most commonly reported symptoms and is also often attributed as the most debilitating symptom to live with by patients. Most current therapies are unable to satisfactorily address this symptom.

People with severe disease are facing high morbidity and mortality and living with the unpredictability of flares which can come at any time with any degree of severity; this takes an understandable toll on people's mental health, and SLE is linked to anxiety and depression, as well as other psychiatric disorders caused by inflammation.

SLE can be organ threatening and is associated with a reduced life expectancy. According to the BILAG Biologics Registry, the most common manifestations in patients with SLE include the following: rashes covering the face, torso and arms; alopecia (hair loss); severe mouth ulcers; arthritis; inflammation and damage to the kidneys; neurological dysfunction including confusion and

seizures; pericardial effusions; and severe anaemia. Young women are affected by pregnancy-related complications, and may experience recurrent miscarriage, pre-eclampsia, and preterm deliveries.

These manifestations are generally reversible initially but, if not treated promptly, or if there is no response to initial therapy, can lead to organ damage that is irreversible. Patients with the most severe SLE are usually treated with rituximab, which is often effective. However, a proportion of these patients experience secondary loss of response on later cycles of rituximab therapy. Given that these patients have already failed to respond to other standard therapies and have severe SLE, this is a particular concern since they will return to life- or organ-threatening disease activity. To treat this, they will often be given high dose steroids to suppress disease progression. Long term steroid use leads to long term side effects such as weight gain, osteoporosis, depression, infection, and early cardiovascular disease.

Further details of impact upon carers:

Those living with and caring for people with SLE may find themselves in this role suddenly and it can require a complete upheaval in the way they are living their life.

Often, they might be providing help with medication, hospital appointments or emergency attendances and hospitalisations and this requires a lot of organisation and time whilst trying to balance other responsibilities such as employment or childcare. Carers of people with SLE often reduce their working hours or give up work to provide care.

The unpredictability of disease flares and the relapsing course of the disease mean that planning life is challenging. There are often mixed emotions associated with this including guilt, bitterness and sadness. This affects carers' mental health and the relationship between carers and people living with SLE. These challenges are only more substantial for carers of people with severe disease and limited treatment options, who live with more uncertainty and morbidity.

Considerations from review by Rare Disease Advisory Group

There were supportive comments from RDAG. One RDAG member highlighted that the safety evidence is based on a very small group of patients and that the adverse events reported should be better reflected in the evidence summary.

Pharmaceutical considerations

The Clinical Commissioning Policy proposition recommends obinutuzumab as a treatment option in adults with refractory SLE, who have demonstrated secondary non-response to rituximab. This recommendation is outside obinutuzumab's marketing authorisation, so use is off label. Obinutuzumab is excluded from tariff. Post-pubescent children will be able to access obinutuzumab under the Medicines for Children policy.

Considerations from review by National Programme of Care

1) The proposal received the full support of the Internal Medicine PoC on the 28th February 2023.