NHS England Evidence Review:

Obinutuzumab for systemic lupus erythematosus with secondary non-response to rituximab

NHS England URN: 2121

NHS England Evidence Review

Obinutuzumab for systemic lupus erythematosus (SLE) with secondary non-response to rituximab

Completed: July 2022

Prepared by NICE on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

In a substantial minority of people whose systemic lupus erythematosus (SLE) has previously responded to rituximab (an anti-CD20 monoclonal antibody), later treatment cycles become ineffective; this is called secondary non-response. Secondary non-response to rituximab is related to the development of anti-rituximab antibodies, which neutralise the drug and stop it from depleting B cells, a key mediator in the development of SLE.

When secondary non-response to rituximab occurs, there is some evidence that switching to an alternative anti-CD20 therapy restores clinical response. Unlike rituximab, which is a chimeric mouse/human anti-CD20 monoclonal antibody, obinutuzumab is a humanised anti-CD20 monoclonal antibody. This means it may be less likely to be affected by anti-drug antibodies. Also, *in vitro* studies have shown that obinutuzumab depletes B cells more than rituximab.

This evidence review aims to examine the clinical effectiveness, safety and cost effectiveness of obinutuzumab compared with immunosuppressant therapies in people with SLE who have demonstrated secondary non-response to rituximab therapy. Obinutuzumab is licensed for chronic lymphocytic leukaemia and follicular lymphoma and use for SLE is off label (Summary of product characteristics).

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with obinutuzumab more than others, as well as the criteria used by the included studies to define secondary non-response to rituximab in SLE, and the dose and/or frequency of obinutuzumab that was used.

2. Executive summary of the review

This evidence review aims to examine the clinical effectiveness, safety and cost effectiveness of obinutuzumab compared with immunosuppressant therapies in people with SLE who have demonstrated secondary non-response to rituximab therapy. The searches for evidence were conducted on 25 April 2022 and identified 98 references. The titles and abstracts were screened and 6 full text papers were obtained and assessed for relevance.

One paper was included in the evidence review (Arnold et al. 2022). The study is a retrospective case series that summarised data from 6 centres in England for 9 people with SLE who had secondary non-response to rituximab therapy and received obinutuzumab. No evidence was found comparing obinutuzumab with immunosuppressant therapies. The included study has no comparator.

In terms of clinical effectiveness:

Critical outcomes

- Improvement in disease activity scores. The case series found very low certainty evidence that obinutuzumab statistically significantly improves disease activity scores from baseline over 6 months in people with SLE who had secondary non-response to rituximab. Median SLEDAI-2K scores improved from 12 to 6 points (p=0.014) and median numeric BILAG-2004 scores improved from 21 to 2 points (p=0.009). These changes in disease activity scores are likely to be clinically meaningful, suggesting obinutuzumab improves disease activity in this population. However, the study lacks statistical power to show definitively that this treatment improved outcomes.
- Quality of life. No evidence was identified for this outcome.
- Improvement in lupus nephritis renal disease. No renal function evidence was identified for this outcome. However, some information on lupus nephritis renal disease is available using disease activity scores, which improved after obinutuzumab treatment in 2 out of 4 people with BILAG A/B renal disease (very low certainty evidence).

Important outcomes

- Change in glucocorticoid dose requirements. The case series found very low certainty evidence that there was no statistically significant difference between prednisolone dosages at baseline and at 6 months (mean dosage 17.8 mg daily compared with 14.4 mg daily, p=0.34). Four out of 9 participants had clinically meaningful outcomes (prednisolone dosage reduced to 5 mg daily and achieved Lupus Low Disease Activity State [LLDAS]), however no statistical analyses were reported for this result and no conclusions can be drawn about whether obinutuzumab reduces glucocorticoid dose requirements in people with SLE who have secondary non-response to rituximab.
- Treatment failure. In the case series, treatment failure occurred in 1 person out of 9 people with SLE who had secondary non-response to rituximab. No conclusions can be drawn about whether obinutuzumab reduces treatment failure in this population. The evidence is of very low certainty.
- Mortality. No evidence was identified for this outcome.
- Retreatment interval with obinutuzumab. No evidence was identified for this outcome.

In terms of safety:

- Little information on adverse effects was reported in the case series and it provides only very low certainty evidence on the safety of obinutuzumab.
- In the study, 2/9 patients (22%) had serious adverse events (no statistical analysis). One patient had an episode of SLE enteritis and 1 unvaccinated patient died from severe COVID-19 infection.
- The authors reported that obinutuzumab was generally well tolerated, and infusion reactions did not occur or were mild.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- No evidence was identified regarding subgroups of patients that may benefit from obinutuzumab more than the wider population of interest.

In terms of criteria used to define secondary non-response to rituximab in SLE:

- Although not clearly defined in the paper, 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.

In terms of the dose and/or frequency of obinutuzumab used:

- In the study, 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.

Please see the results table (section 5) in the review for further details of outcomes and definitions.

Limitations

It is difficult to conduct high quality studies in rare diseases such as SLE with secondary non-response to rituximab because of the small size of the eligible population with severe disease and treatment resistance. Although the study by Arnold et al. (2022) was well designed and reported, and considered objective outcomes, it has many limitations. For example, treatment with obinutuzumab was open label, there was no comparator, the sample size was small (n=9) and follow up was short (6 months). As with many small case series, the study was not powered for statistical hypothesis testing and the data should be regarded as descriptive only. Case series are subject to bias and confounding and cannot prove that an intervention (such as obinutuzumab) caused a particular outcome, only that it is associated with that outcome. Results of the study should be considered hypothesis generating only.

The study summarised data from BILAG centres in England and is, therefore, relevant to clinical practice in this country. Five people were of South Asian ancestry, 2 people were of Afro-Caribbean ancestry and 2 people were of European ancestry; therefore, it is unclear how the

results of the study apply to people with different ethnic origins. The study authors report that people with non-European ancestry are known to experience worse SLE and have poorer responses to conventional therapies. All participants in the study were female and their mean age was 33 years (standard deviation 7 years), so it is unclear if the results are applicable to men, children and older people. Participants had high levels of disease activity (mean SLEDAI score 14 and mean numeric BILAG score 21) and their SLE had failed to respond to conventional immunosuppressants as well as rituximab (due to secondary non-response).

Some of the outcomes assessed in the study have minimum clinically important differences (MCIDs); for example, SLEDAI, BILAG and prednisolone dosage. These can help to determine whether any observed changes seen in the study are clinically meaningful to patients and clinicians. No information is available on long-term treatment; therefore, it is unclear whether any improvements in disease activity seen at 6 months are maintained long term.

Conclusion

This evidence review found very low certainty evidence from 1 small case series of 9 people for the efficacy and safety of obinutuzumab for people with SLE who have demonstrated secondary non-response to rituximab therapy. 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.

The findings of this evidence review are important for people with SLE who have secondary non-response to rituximab because they have exhausted standard treatment options. An alternative treatment is needed to prevent organ damage (such as renal failure), frequent hospitalisations to manage severe disease flares, and complications from the disease and long-term corticosteroid treatment (such as stroke, severe infection or avascular necrosis).

Evidence from the case series suggests that obinutuzumab (two 1000 mg infusions given 2 weeks apart) statistically significantly improves disease activity scores over 6 months in people with SLE who have secondary non-response to rituximab. The evidence also suggests that changes in disease activity are clinically meaningful, with the difference noticeable to patients or clinicians.

The study also suggests that the dosage of prednisolone needed to control SLE can be reduced in some people with SLE who have secondary non-response to rituximab, and that some people may have clinically meaningful outcomes such as LLDAS. However, overall, there was no statistically significant difference between prednisolone dosages at baseline and 6 months.

Over 6 months, treatment failure occurred in 1 person out of 9 people with SLE who had secondary non-response to rituximab.

Case series have many limitations because unknown or unmeasured factors may have influenced the findings, and the evidence for all outcomes is of very low certainty. Although statistical analyses were performed for some outcomes, it is important to note that the study included only 9 patients and was not powered for statistical hypothesis testing. The data should be regarded as descriptive only and interpreted cautiously because they cannot definitively show that obinutuzumab improves outcomes, only that it is associated with improved outcomes in some patients.

Any potential benefits of treatment must be balanced against the adverse effect profile of obinutuzumab in people with SLE who have secondary non-response to rituximab. Little information on adverse effects was reported in the case series. The authors reported that obinutuzumab was generally well tolerated, and infusion reactions did not occur or were mild.

See the Summary of product characteristics or British National Formulary for more information on adverse effects of obinutuzumab.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In individuals with SLE who have demonstrated secondary non-response to rituximab therapy, what is the clinical effectiveness of obinutuzumab when compared with immunosuppressant therapies?
2. In individuals with SLE who have demonstrated secondary non-response to rituximab therapy, what is the safety of obinutuzumab when compared with immunosuppressant therapies?
3. 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?
4. From the evidence selected, are there any subgroups of patients that may benefit from obinutuzumab more than the wider population of interest?
5. From the evidence selected, what are the criteria used by the research studies to define secondary non-response to rituximab in SLE?
6. From the evidence selected, what dose and/or frequency of obinutuzumab was used?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 25 April 2022.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full texts of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

One paper was identified for inclusion (Arnold et al. 2022). Table 1 provides a summary of this study and full details are given in Appendix E. The study is a retrospective case series that summarised data from 6 centres in England for 9 people with systemic lupus erythematosus (SLE) who had secondary non-response to rituximab therapy and received obinutuzumab.

No evidence was found comparing obinutuzumab with immunosuppressant therapies. The included study has no comparator.

Table 1: Summary of included study

Study	Population	Intervention and comparison	Outcomes reported
Arnold J, et al. (2022) Retrospective observational longitudinal cohort study (case series) 6 BILAG centres in England	All people with SLE who had been treated with rituximab but switched to obinutuzumab because of secondary non-response (n=9) All 9 participants (100%) were female. Their mean age was 33 years 5 people were of South Asian ancestry, 2 people were of Afro-Caribbean ancestry and 2 people were of European ancestry The mean number of previous cycles of rituximab was 2.78 All 9 people (100%) took prednisolone (mean dose 17.8 mg) at baseline	**Intervention** 2 obinutuzumab 1000 mg infusions 2 weeks apart (preceded by methylprednisolone 100 mg) **Comparators** No comparator	**Critical outcome** • Improvement in disease activity scores (SLEDAI-2K scores and numeric BILAG-2004 scores) **Important Outcomes** • Change in glucocorticoid dose requirements • Treatment failure **Safety** • Adverse events

Abbreviations

BILAG, British Isles Lupus Assessment Group, (the BILAG index is a measure of lupus disease activity, higher numerical scores indicate worse disease activity); SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index (used to assess changes in disease activity, higher scores indicate worse disease activity)

5. Results

In individuals with 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

6. Discussion

The study included in the evidence review (Arnold et al. 2022) has serious limitations for determining the efficacy and safety of obinutuzumab for treating people with SLE who have demonstrated secondary non-response to rituximab therapy. All outcomes were considered to have very low certainty using modified GRADE.

No evidence was found comparing obinutuzumab with immunosuppressant therapies. The study by Arnold et al. (2022) is a retrospective case series with no comparator.

The study provided no evidence to determine whether obinutuzumab improves quality of life or measures of renal function in lupus nephritis renal disease (critical outcomes). However, some information on lupus nephritis renal disease is available using disease activity scores, with 2 out of 4 people with BILAG A/B renal disease activity improving after obinutuzumab treatment (very low certainty evidence). No evidence was found for the retreatment interval with obinutuzumab or mortality (important outcomes). Little information was available for the safety of obinutuzumab in people with SLE who have secondary non-response to rituximab.

It is difficult to conduct high quality studies in rare diseases such as SLE with secondary non-response to rituximab. Although the study by Arnold et al. (2022) was well designed and reported, and considered objective outcomes, it has many limitations. For example, treatment with obinutuzumab was open label, there was no comparator, the sample size was small (n=9) and follow up was short (6 months). As with many small case series, the study was not powered for statistical hypothesis testing and the data should be regarded as descriptive only. Case series are subject to bias and confounding and cannot prove that an intervention (such as obinutuzumab) caused a particular outcome, only that it is associated with that outcome.

The study summarised data for people with SLE who had secondary non-response to rituximab and were treated with obinutuzumab in BILAG centres in England and is, therefore, relevant to clinical practice in this country. Five people were of South Asian ancestry, 2 people were of Afro-Caribbean ancestry and 2 people were of European ancestry; therefore, it is unclear how the results of the study apply to people with different ethnic origins. The study authors report that people with non-European ancestry are known to experience worse SLE and have poorer responses to conventional therapies. All participants in the study were female and their mean age was 33 years (standard deviation 7 years), so it is unclear if the results are applicable to men, children and older people. Participants had high levels of disease activity (mean SLEDAI score 14 and mean numeric BILAG score 21) and all were taking prednisolone daily at a mean dosage of 17.8 mg, putting them at significant risk of adverse effects. Participants' SLE had failed to respond to conventional immunosuppressants as well as rituximab (due to secondary non-response).

Some of the outcomes assessed in the study have minimum clinically important differences (MCIDs); for example, SLEDAI, BILAG and prednisolone dosage. These can help to determine whether any observed changes seen in the study are clinically meaningful to patients and clinicians.

No evidence was identified regarding subgroups of patients that may benefit from obinutuzumab more than the wider population of interest. No information is available on long-term treatment; therefore, it is unclear whether any improvements in disease activity seen at 6 months are maintained long term. The paper does not report how frequently cycles of obinutuzumab were repeated.

No evidence was identified regarding the cost effectiveness of obinutuzumab for people with SLE who had secondary non-response to rituximab.

7. Conclusion

This evidence review found very low certainty evidence for the efficacy and safety of obinutuzumab for people with SLE who have demonstrated secondary non-response to rituximab therapy.

One case series (Arnold et al. 2022) was included in the evidence review. 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.

The findings of this evidence review are important for people with SLE who have secondary non-response to rituximab because they have exhausted standard treatment options. An alternative treatment is needed to prevent organ damage (such as renal failure), frequent hospitalisations to manage severe disease flares, and complications from the disease and long-term corticosteroid treatment (such as stroke, severe infection or avascular necrosis),

The study had no comparator, treatment with obinutuzumab was open label, the sample size was small (n=9) and follow up was short (6 months). As with all case series, unknown or unmeasured factors may have influenced the findings reported. Case series cannot prove cause and effect and should only be considered hypothesis generating.

The study found very low certainty evidence that obinutuzumab statistically significantly improves the critical outcome, disease activity scores, from baseline over 6 months in people with SLE who have secondary non-response to rituximab. Median SLEDAI-2K scores improved from 12 to 6 points (p=0.014) and median numeric BILAG-2004 scores improved from 21 to 2 points (p=0.009). These changes in disease activity scores are likely to be clinically meaningful, suggesting obinutuzumab improves disease activity in this population. However, the study lacks statistical power to show definitively that treatment improved outcomes.

No evidence was identified for the critical outcomes, quality of life and improvement in renal function in lupus nephritis renal disease. Disease activity improved after obinutuzumab treatment in 2 out of 4 people with BILAG A/B renal disease (very low certainty evidence).

For the important outcome, change in glucocorticoid dose requirements, the study found that there was no statistically significant difference between prednisolone dosages at baseline and 6 months (mean dosage 17.8 mg daily compared with 14.4 mg daily, p=0.34, very low certainty evidence). Four out of 9 participants had clinically meaningful outcomes (prednisolone dosage reduced to 5 mg daily and achieved LLDAS), however no statistical analyses were reported for this result and no conclusions can be drawn about whether obinutuzumab reduces glucocorticoid dose requirements in people with SLE who have secondary non-response to rituximab.

In the study, the important outcome of treatment failure occurred in 1 person out of 9 people with SLE who had secondary non-response to rituximab. No conclusions can be drawn about whether obinutuzumab reduces treatment failure in this population.

No evidence was identified for the important outcomes of mortality and retreatment interval with obinutuzumab. 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.

Any potential benefits of treatment must be balanced against the adverse effect profile of obinutuzumab in people with SLE who have secondary non-response to rituximab. Little

information on adverse effects was reported in the case series and it provides only very low certainty evidence on the safety of obinutuzumab. In the study, 2/9 patients (22%) had serious adverse events (no statistical analysis). One patient had an episode of SLE enteritis and 1 unvaccinated patient died from severe COVID-19 infection. The authors reported that obinutuzumab was generally well tolerated, and infusion reactions did not occur or were mild. See the Summary of product characteristics or British National Formulary for more information on adverse effects of obinutuzumab.

No evidence was identified regarding subgroups of patients that may benefit from obinutuzumab more than the wider population of interest, or regarding the cost effectiveness of obinutuzumab for people with SLE who have secondary non-response to rituximab.

Appendix A PICO document

The review questions for this evidence review are:

1. In individuals with SLE who have demonstrated secondary non-response to rituximab therapy, what is the clinical effectiveness of obinutuzumab when compared with immunosuppressant therapies?
2. In individuals with SLE who have demonstrated secondary non-response to rituximab therapy, what is the safety of obinutuzumab when compared with immunosuppressant therapies?
3. 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?
4. From the evidence selected, are there any subgroups of patients that may benefit from obinutuzumab more than the wider population of interest?
5. From the evidence selected, what are the criteria used by the research studies to define secondary non-response to rituximab in SLE?
6. From the evidence selected, what dose and/or frequency of obinutuzumab was used?

P-Population and Indication	People with SLE who previously responded to rituximab and then demonstrated secondary non-response to rituximab; these patients may or may not have had belimumab. Subgroups of interest: - Adults - Children [Secondary non-response defined as: those individuals who have received rituximab with initial good response, however, on subsequent infusions have no response; this is often accompanied by a severe infusion reaction which might be referred to as an allergic reaction.]
I-Intervention	Obinutuzumab with or without conventional background immunosuppressants [Obinutuzumab is a humanised type 2 monoclonal antibody. It is delivered as an intravenous infusion.] [Conventional immunosuppressant standard therapy including but not limited to steroids, hydroxychloroquine, azathioprine, methotrexate, mycophenolate and cyclophosphamide.]
C-Comparator	Immunosuppressant therapies [There are currently no routinely available anti-CD20 alternatives to obinutuzumab if secondary non-response to rituximab in SLE occurs but other humanised anti- CD 20 drugs could be used.] [Immunosuppressants include but are not limited to conventional immunosuppressants as described above or other monoclonal antibodies.]

O-Outcomes	**Clinical Effectiveness** • Minimally Clinical Important Differences (MCIDs) are not known unless stated. • The expected timeframe for outcomes is stated individually if known. *Critical to decision-making:* • **Improvement in disease activity scores** Disease activity scores are important to patients because it reflects treatment effect (either suppression or failure) of obinutuzumab [Examples include but are not limited to: o **BILAG score** is the British Isles Lupus Assessment Group scoring system. Each organ system (domain) is rated from A (most severe) to D (inactive disease). As for rituximab, a meaningful clinical response can be defined by reduction of all baseline BILAG As to B or less, and no more than one persistent BILAG B. o **SLEDAI-2K** is the Systemic Lupus Erythematosus Disease Activity Index 2000 that can be used as an alternative to the BILAG, although the former is preferred. This is a numerical scale with different points values assigned to various clinical features. A clinically meaningful improvement is defined as a reduction by 4 or more points. Responses may be described as complete or partial.] • **Quality of Life** 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. [Examples of methods to assess quality of life include but are not limited to: o SF36 o SF20 o SF20+ o QOLS o LupusQoL o Systemic Lupus Activity Questionnaire (SLAQ) o Interview methods.] • **Improvement in lupus nephritis** 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. [Examples of assessment of renal response based on laboratory parameters include but are not limited to: o **Proteinuria** is the most common manifestation of lupus nephritis and in measured as the urine protein: creatinine ratio (UPCR) o **eGFR** is a derived value of kidney function based on the individual's creatinine, age, sex and race. It is measured in ml/min/1.73m2.] o Haematuria measured using urine dipsticks or laboratory assessment o Serum albumin levels, which reflect the degree of urinary protein loss These assessments are supplemented by clinical assessment including blood pressure and oedema. The level of change in these parameters required to constitute satisfactory response depends on the biopsy appearances and baseline status, but typically physicians would expect to see reduction in proteinurea, improvement or stabilisation of eGFR, and improvement in serum albumin within 12 months of therapy. Another key difference in assessment of response in lupus nephritis is that once a satisfactory response is achieved, the induction therapy (e.g. obinutuzumab) may not need to be continued long-term, but conventional agents such as mycophenolate mofetil can be used to maintain response.] *Important to decision-making:* • **Increase, reduction or stability in glucocorticoid dose requirements** 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. [A sustained dose of prednisolone 7.5mg or less per day (or equivalent) is a commonly agreed meaningful goal of treatment (Fanouriakis et al, 2019)] • **Retreatment interval with obinutuzumab** Time to retreatment is important to patients as it represents the length of time the patient has had improvement in their SLE before flaring. This is measured in months and should not be more frequent than every 6 months. Longer retreatment interval has implications for cost effectiveness.

	• **Treatment failure** 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. [Examples include but not limited to: o New or recurrent clinical event(s) indicating severe SLE after 6 months of effective treatment. o Requirement for another therapy in place of obinutuzumab such as cyclophosphamide] • **Mortality** 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. **Safety** 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. [Examples include, but not limited to: o Frequency of adverse events e.g. infection, infusion reactions, neutropenias, low immunoglobulin levels (IgG). o Frequency of serious adverse events o Adverse events leading to discontinuation o Grades 3 to 4 laboratory abnormalities.] **Cost effectiveness** Data in the literature in this population may be limited to simple data such as quantity of drug prescribed and hospitalisations.
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages

Date limits	2012-2022
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search dates: 25 April 2022

Database: Medline

Platform: Ovid
Version: 1946 to April 22 2022
Search date: 25/04/2022
Number of results retrieved: 12
Search strategy:

Database: Ovid MEDLINE(R) <1946 to April 22, 2022>
Search Strategy:
---
1 (obinutuzumab or gazyvaro or gazyva or GA101 or GA 101 or RO 5072759 or RO5072759 or afutuzumab or "r 7159" or r7159 or "rg 7159" or rg7159).tw. (548)
2 exp Lupus Erythematosus, Systemic/ (64255)
3 (lupus or libman or dermatovisceritism or erythematodes visceralis or lupovisceritis or sle).tw. (79937)
4 2 or 3 (89342)
5 1 and 4 (15)
6 animal/ not human/ (4964108)
7 5 not 6 (14)
8 limit 7 to english language/ (13)
9 limit 8 to yr="2012 -Current" (12)

Database: Medline in-process

Platform: Ovid
Version: 1946 to April 22 2022
Search date: 25/04/2022
Number of results retrieved: 0

Strategy as above

Database: Medline epubs ahead of print

Platform: Ovid
Version: April 22 2022
Search date: 25/04/2022
Number of results retrieved: 2
Search strategy:

Database: Ovid MEDLINE(R) Epub Ahead of Print <April 22, 2022>
Search Strategy:
---
1 (obinutuzumab or gazyvaro or gazyva or GA101 or GA 101 or RO 5072759 or RO5072759 or afutuzumab or "r 7159" or r7159 or "rg 7159" or rg7159).tw. (21)
2 exp Lupus Erythematosus, Systemic/ (0)

3 (lupus or libman or dermatovisceritism or erythematodes visceralis or lupovisceritis or sle).tw. (943)
4 2 or 3 (943)
5 1 and 4 (3)
6 animal/ not human/ (0)
7 5 not 6 (3)
8 limit 7 to english language/ (2)

Database: Embase

Platform: Ovid
Version: 1974 to 2022 April 22
Search date: 25/04/2022
Number of results retrieved: 75 (main search); conferences not required; 25 removed
Search strategy:

Database: Embase <1974 to 2022 April 22>
Search Strategy:
---
1 obinutuzumab/ (3353)
2 (obinutuzumab or gazyvaro or gazyva or GA101 or GA 101 or RO 5072759 or RO5072759 or afutuzumab or "r 7159" or r7159 or "rg 7159" or rg7159).tw. (2256)
3 1 or 2 (3563)
4 systemic lupus erythematosus/ (100874)
5 (lupus or libman or dermatovisceritism or erythematodes visceralis or lupovisceritis or sle).tw. (125946)
6 4 or 5 (147034)
7 3 and 6 (118)
8 nonhuman/ not human/ (4966833)
9 7 not 8 (117)
10 (letter or editorial).pt. (1944273)
11 9 not 10 (112)
12 (conference abstract or conference paper or conference proceeding or "conference review").pt. (5151003)
13 11 not 12 (87)
14 limit 13 to english language/ (84)
15 limit 14 to yr="2012 -Current" (75)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley
Version:
CDSR –Issue 4 of 12, April 2022
CENTRAL – Issue 3 of 12, March 2022
Search date: 25/04/2022
Number of results retrieved: CDSR 0 ; CENTRAL 26
Search Name: Obinutuzumab lupus

ID Search Hits
#1 (obinutuzumab or gazyvaro or gazyva or GA101 or GA 101 or RO 5072759 or RO5072759 or afutuzumab or "r 7159" or r7159 or "rg 7159" or rg7159):ti,ab,kw 531
#2 MeSH descriptor: [Lupus Erythematosus, Systemic] explode all trees 1155

#3 (lupus or libman or dermatovisceritism or erythematodes visceralis or lupovisceritis or sle):ti,ab,kw 3879
#4 #2 or #3 3879
#5 #1 and #4 with Cochrane Library publication date Between Jan 2012 and Apr 2022 26

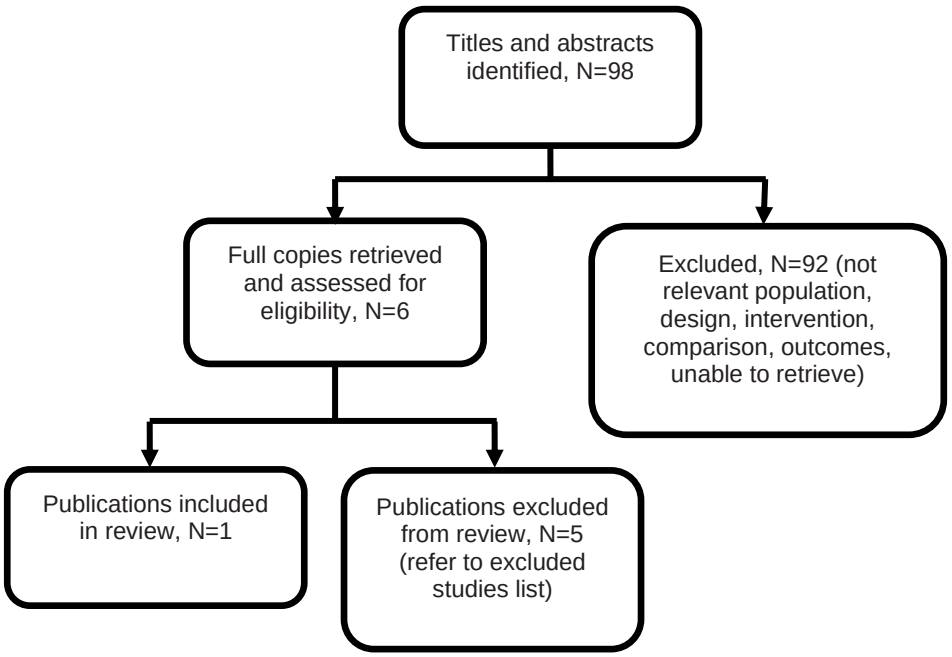
Reference list checking

Reference lists of included studies were manually checked. 0 additional references were deemed relevant and added to EPPI reviewer.

Appendix C Evidence selection

The literature searches identified 98 references. These were screened using their titles and abstracts and 6 references were obtained in full text and assessed for relevance. Of these, 1 reference is included in the evidence summary. The remaining 5 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Furie, RA et al. (2021) B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis*. 81, p100–107.	Incorrect population: not people with secondary non-response to rituximab
Yusof, Md et al. (2017) Predicting and managing primary and secondary non-response to rituximab using B-cell biomarkers in systemic lupus erythematosus. *Ann Rheum Dis*. 76, p1829–1836.	Incorrect intervention: does not study obinutuzumab
Hassan, SU et al. (2020) Biologic Sequencing in Systemic Lupus Erythematosus: After Secondary Non-response to Rituximab, Switching to Humanised Anti-CD20 Agent Is More Effective Than Belimumab. *Front. Med*. 7, p498.	Reports outcomes for ocrelizumab, ofatumumab and obinutuzumab combined: results for obinutuzumab (n=1) are not reported separately

Appendix D Excluded studies table

Study reference	Reason for exclusion
Furie, RA et al. (2021) B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis*. 81, p100–107.	Incorrect population: not people with secondary non-response to rituximab
Hassan, SU et al. (2020) Biologic Sequencing in Systemic Lupus Erythematosus: After Secondary Non-response to Rituximab, Switching to Humanised Anti-CD20 Agent Is More Effective Than Belimumab. *Front. Med*. 7, p498.	Reports outcomes for ocrelizumab, ofatumumab and obinutuzumab combined: results for obinutuzumab (n-1) are not reported separately
Montigny, P et al. (2022) New Treatment Options in Lupus Nephritis. *Archivum Immunologiae et Therapiae Experimentalis.* 70, p11	Literature review
Narain, S et al. (2020) Biologics in the treatment of Sjogren's syndrome, systemic lupus erythematosus, and lupus nephritis. *Current opinion in rheumatology*. 32, p609-616	Literature review
NasrAllah, M et al. (2022) Obinutuzumab in Kidney Transplantation: Effect on B-cell Counts and Crossmatch Tests. *Transplantation*. 106, p369-372	Incorrect population: not people with secondary non-response to rituximab

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Full citation Arnold J, et al. (2022) Efficacy and safety of obinutuzumab in systemic lupus erythematosus patients with secondary non-response to rituximab. Rheumatology 00: 1–5 **Study location** 6 centres in England **Study type** Retrospective observational longitudinal cohort study (case series) **Study aim** The study aimed to 'summarise data from all patients receiving obinutuzumab for 2NDNR in BILAG centres' **Study dates** Not reported	**Inclusion criteria** People with SLE who had been treated with rituximab but switched to obinutuzumab because of 2NDNR **Exclusion Criteria** None reported **Total sample size** 9 people **No. of participants in each treatment group** All 9 participants received obinutuzumab **Baseline characteristics** All 9 participants (100%) were female. Their mean age was 33 years 5 people were of South Asian ancestry, 2 people were of Afro-Caribbean ancestry and 2 people were of European ancestry All 9 people (100%) took prednisolone (mean dosage 17.8 mg) The mean number of previous cycles of rituximab was 2.78 The mean SLEDAI score was 14.22 and the mean total numeric BILAG score was 21.3	**Interventions** 2 obinutuzumab 1000 mg infusions 2 weeks apart (preceded by methylprednisolone 100 mg) **Comparators** No comparator	**Critical outcomes** **Improvement in disease activity scores** After 6 months, statistically significant improvements from baseline were seen in: • median SLEDAI-2K scores (from 12 to 6 points, p=0.014) • median numeric BILAG-2004 scores (from 21 to 2 points, p=0.009) 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) **Important outcomes** **Change in glucocorticoid dose requirements** Before receiving obinutuzumab, all 9 patients took prednisolone (range 10 mg to 50 mg daily) After receiving obinutuzumab, 5/9 patients (56%) had their prednisolone dosage reduced (from 10 mg to 30 mg daily at baseline). In 2 patients, the dosage was increased and in another 2 there was no change. Although the mean dosage of prednisolone was lower after obinutuzumab (14.4 mg daily, range 5 mg to 60 mg daily), there was no statistically significant difference before and after treatment (p=0.34) In 4/9 patients (44%) prednisolone dosage was reduced to 5 mg daily (from 10 mg to 15 mg	This study was appraised using the JBI Critical Appraisal Checklist for Case Series. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes Other comments: The study is a case series and, as such, is rated as poor in the hierarchy of study designs. However, there are few eligible participants for studies using unlicensed medicines in rare diseases (such as SLE with 2NDNR), meaning it is difficult to conduct high quality studies. Taking this into account, the study is well designed and reported, and outcomes are objective. Key limitations are that treatment with obinutuzumab was open label, there was no comparator, the sample size was small (n=9) and follow up was short (6 months). As with many case series, the study was not powered for statistical hypothesis testing and the data should be regarded as descriptive only. Case series have no comparators and unknown or unmeasured factors may have influenced the findings reported. Case series cannot prove

			daily at baseline) and they had LLDAS (no statistical analysis) **Treatment failure** 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 (675) remained well-controlled with repeat obinutuzumab cycles and no additional immunosuppression (no statistical analysis) **Safety** Obinutuzumab was generally well tolerated. Infusion reactions did not occur or were mild 2 serious adverse events were reported, an episode of SLE enteritis and a death from severe COVID-19 infection in an unvaccinated patient No cases of progressive multifocal leukoencephalopathy were seen	cause and effect and should only be considered hypothesis generating. Source of funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors

Abbreviations

2NDNR, secondary non-depletion non-response; BILAG, British Isles Lupus Assessment Group, (the BILAG index is a measure of lupus disease activity, higher numerical scores indicate worse disease activity, 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)

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

Table 2: Question: In individuals with SLE who have demonstrated secondary non-response to rituximab therapy, what is the clinical effectiveness and safety of obinutuzumab? (no comparator treatment)

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
							Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Baseline**	**Obinutuzumab**	**Result**		
Improvement in disease activity scores (1 retrospective case series)									
Improvement in median SLEDAI-2K scores from baseline to 6 months (higher scores indicate worse disease activity)									
Retrospective case series (Arnold et al. 2022)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	12	6	Statistically significant improvement, p=0.014 A reduction of 4 points is considered clinically meaningful. Therefore, this 6-point reduction is clinically meaningful The study was not powered for statistical hypothesis testing and the data should be regarded as descriptive only.	Critical	Very low
Improvement in median numeric BILAG-2004 scores from baseline to 6 months (higher numerical scores indicate worse disease activity)									
Retrospective case series (Arnold et al. 2022)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	21	2	Statistically significant improvement, p=0.009 This reduction in disease activity of 19 points is likely to be clinically meaningful The study was not powered for statistical hypothesis testing and the data should be regarded as descriptive only.	Critical	Very low
Change in BILAG-2004 grades from baseline to 6 months (A on the alphabetical scale indicates the most severe disease, whereas E indicates that the disease has never been active)									
Retrospective case series (Arnold et al. 2022)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	6/9 patients had BILAG A/B grade mucocutaneous, 6/9 had BILAG A/B musculoskeletal and 4/9 had	1/9 patients had BILAG B mucocutaneous, no patients had BILAG A/B musculoskeletal and 2/9 patients	No statistical analyses reported A meaningful clinical response can be defined by reduction of all baseline BILAG As to B or less, and no more than one persistent BILAG B.	Critical	Very low

					BILAG A/B renal disease	had BILAG A/B renal disease	Overall, some patients in the study experienced clinically meaningful reductions in disease activity		
Change in glucocorticoid dose requirements (1 retrospective case series)									
Reduction in prednisolone dosage after taking obinutuzumab from baseline to 6 months (a lower dosage is preferable)									
Retrospective case series (Arnold et al. 2022)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	9/9 patients (100%) took prednisolone at a dosage of at least 10 mg daily. Mean dosage 17.8 mg daily (range 10 mg to 50 mg daily)	5/9 patients (56%) had their prednisolone dosage reduced (from 10 mg to 30 mg daily at baseline). In 2 patients, the dosage was increased and in another 2 there was no change. Mean dosage 14.4 mg daily (range 5 mg to 60 mg) In 4/9 patients (44%) the dosage was reduced to 5 mg daily (from 10 mg to 15 mg daily at baseline) and they had LLDAS (no statistical analysis)	There was no statistically significant difference in prednisolone dosages before and after obinutuzumab treatment (p=0.34) The study was not powered for statistical hypothesis testing and the data should be regarded as descriptive only. A sustained dose of prednisolone 7.5mg or less per day (or equivalent) is a commonly agreed meaningful goal of treatment LLDAS is also a clinically meaningful outcome	Important	Very low
Treatment failure (1 retrospective case series)									
Treatment failure over 6 months									
Retrospective case series (Arnold et al. 2022)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	Not applicable	1/9 patients (11%) had treatment failure	No statistical analysis reported At the time of the study, 6/9 patients (67%) remained well-controlled with repeat obinutuzumab cycles and no additional immunosuppression	Important	Very low
Safety (1 retrospective case series)									
Serious adverse events over 6 months									

Retrospective case series (Arnold et al. 2022)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	Not applicable	2/9 patients (22%)	No statistical analysis reported Obinutuzumab was generally well tolerated. Infusion reactions did not occur or were mild. 2 serious adverse events were reported, an episode of SLE enteritis and a death from severe COVID-19 infection in an unvaccinated patient No cases of progressive multifocal leukoencephalopathy were seen	Safety	Very low

Abbreviations

BILAG, British Isles Lupus Assessment Group; LLDAS, Lupus Low Disease Activity State; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index

1 Only 9 patients were included in the study

Glossary

British Isles Lupus Assessment Group (BILAG) index	A score providing measures of disease activity across 8 organ systems on a scale of A (most severe) to E (indicating that the disease has never been active). A numerical scoring scheme is also used. Higher scores are associated with worse disease (A=12, B=8, C=1, D=0 and E=0). A meaningful clinical response can be defined by reduction of all baseline BILAG As to B or less, and no more than one persistent BILAG B.
Lupus Low Disease Activity State (LLDAS)	A measure of low disease activity based on the following criteria: 1. SLEDAI-2K of 4 points or less, with no activity in major organ systems and no hemolytic anemia or gastrointestinal activity 2. no new lupus disease activity since the previous assessment 3. SELENA-SLEDAI physician's global assessment of disease activity score of 1 point or lower on a scale of 0–3 points 4. current prednisolone or equivalent dose of 7.5 mg per day or lower, and 5. well-tolerated maintenance doses of immunosuppressive agents and approved biologics.
Statistical power	The ability of a study to demonstrate an association or causal relationship between 2 variables (if an association exists) means that the study is statistically significant. The statistical power of a study is primarily related to the number of people included. If too few people are included, any differences in the outcomes will not be statistically significant.
Systemic Lupus Erythematosus Disease Activity (SLEDAI) score	A global index of SLE disease activity over the previous 10 days, including measures of manifestations in 9 organ systems. Higher scores are associated with worse disease (a score of 0 indicates no disease activity and a score of 20 or more indicates very high disease activity). There are several versions of the scale, including the SLEDAI-2K. A clinically meaningful improvement is defined as a reduction by 4 or more points.

References

Included study

- Arnold J, Dass S, Twigg S, et al. (2022) Efficacy and safety of obinutuzumab in systemic lupus erythematosus patients with secondary non-response to rituximab. Rheumatology 00: 1–5

NHS England and NHS Improvement
Skipton House
80 London Road
London
SE1 6LH