Minimal change disease and focal segmental glomerulosclerosis in adults: rituximab

Evidence summary

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Key points from the evidence

The content of this evidence summary was up-to-date in November 2016. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are types of glomerulonephritis. MCD is an immune-mediated condition affecting the kidneys, FSGS is not a specific disease entity but a histological lesion, often of unknown aetiology, which is characterised by segmental areas of glomerular sclerosis. Most of the evidence for using rituximab in adults with MCD and FSGS comes from uncontrolled and

non-randomised observational studies performed outside the UK with small sample sizes. The populations in the included studies varied, as did the dose of rituximab used, adjuvant treatment, and follow-up time. The studies in people with MCD and FSGS in their native kidneys reported that treatment with rituximab reduced disease relapse rates, or achieved complete or partial remission. The study in renal transplant recipients with MCD and FSGS did not report any significant difference in treatment outcomes for those treated with rituximab compared to those receiving other immunosuppressants. However, the limitations outlined above make it difficult to draw firm conclusions on the efficacy and safety of rituximab for treating adults with MCD or FSGS.

Regulatory status: off-label. This topic was prioritised because there was a high volume of requests from the NHS.

Effectiveness	Safety
• A systematic review of 14 observational studies found that the rate of annual relapses and the number of immunosuppressants used in adults with steroid-dependent or frequently relapsing MCD or FSGS were statistically significantly reduced after treatment with rituximab when compared with before treatment (p<0.001). • The systematic review found that 72 out of 73 people with MCD had a response to rituximab treatment, and 6 out of 7 participants with FSGS achieved at least partial remission following treatment with rituximab. • A prospective observational study found a statistically significant decrease in urinary protein at 6 months after rituximab administration in adults with primary MCD (n=10) and FSGS (n=4; p<0.05). • The prospective observational study found that the mean dose of corticosteroid was statistically significantly reduced in adults with MCD at 6 months after rituximab treatment (p<0.05). The reduction in dose of corticosteroid in people with FSGS was not statistically significant. • A retrospective cohort study compared single-dose rituximab treatment for recurrent	• The summary of product characteristics (SPC) for rituximab describes that infusion-related reactions are very common (more than 1 in 10) in people treated with intravenous rituximab. Severe infusion-related reactions with a fatal outcome have been reported in post-marketing use. • Serious infections, including fatalities, can occur during rituximab therapy, and rituximab is contraindicated in people with an active, severe infection, and in people who are severely immunocompromised. • Very rare cases of fatal progressive multifocal leukoencephalopathy have been reported after using rituximab and people should be monitored at regular intervals for any new or worsening neurological symptoms or signs suggestive of this condition. • In the systematic review infusion-related reactions that consisted of transient hypotension, itchy red eyes, cough, hiccough and exanthema were reported. Bronchopneumonia was observed in 1 participant 2 months after treatment with rituximab. A long-term complication of mild leukopenia in 1 participant with MCD was also been observed. • The prospective observational study which investigated using rituximab for primary glomerular diseases reported

glomerulonephritis post-renal transplant with a control group that did not receive rituximab. No significant difference was found between the intervention and control groups in complete and partial response rates in adults with FSGS or MCD.	one person who received rituximab experienced a cutaneous eruption, which did not require the treatment to be stopped.
Patient factors • The studies included in this evidence summary used the intravenous formulation of rituximab (it is also available as a subcutaneous injection). • Rituximab is administered as an intravenous infusion over several hours.	**Resource implications** • The cost of rituximab 10 mg/ml concentrate for solution for intravenous infusion (MabThera, Roche Products Limited) is £349.25 for 2×10 ml vials and £873.15 for a 50 ml vial (excluding VAT; MIMS September 2016). • The dosing regimen of rituximab varied in the studies. • As an approximate guide, the cost for 1, 2, 3 or 4 doses of intravenous rituximab 375 mg/m^2 based on an adult with a body surface area of 1.86 m^2 is estimated to be £1222.40, £2444.80, £3667.20 and £4889.60, respectively (assuming wastage and excluding VAT; MIMS September 2016).

Introduction and current guidance

Minimal change disease (MCD) is an immune-mediated condition affecting the kidneys. It is usually of unknown cause, but can sometimes be associated with Hodgkin's disease or the use of nonsteroidal anti-inflammatory drugs (Oxford Textbook of Medicine, 5th Edition). Focal segmental glomerulosclerosis (FSGS) is not a specific disease entity but a histological lesion, often of unknown aetiology, which is characterised by segmental areas

of glomerular sclerosis ([Oxford Textbook of Medicine, 5th Edition](#)).

The general management of MCD and FSGS in adults includes controlling the condition, and preventing end-stage renal disease and associated complications. Evidence-based recommendations on the management of the various types of glomerulonephritis, including MCD and FSGS, were published by the International Society of Nephrology in 2012 in the [KDIGO clinical practice guideline for glomerulonephritis](#). Treatment with a corticosteroid such as prednisolone is recommended for the initial episode of MCD or FSGS. For adults with MCD, a calcineurin inhibitor (such as ciclosporin or tacrolimius) or oral cyclophosphamide are alternatives for those with relative contraindications or intolerance to corticosteroids. A calcineurin inhibitor, cyclophosphamide or mycophenolate mofetil are recommended for frequently relapsing MCD. For adults with FSGS, calcineurin inhibitors can be considered as alternatives for those with relative contraindications or intolerance to corticosteroids. Relapses of FSGS are managed using the same treatment as in MCD. Ciclosporin is recommended for steroid-resistant FSGS. Combination treatment with mycophenolate mofetil and high-dose dexamethasone is recommended for people with steroid-resistant FSGS who are intolerant to ciclosporin ([KDIGO clinical practice guideline for glomerulonephritis](#)). However, specialists involved in the production of this evidence summary commented that prednisolone is usually used in the UK, rather than dexamethasone.

Not all of these drugs are licensed specifically for use in people with MCD or FSGS and use of some of these drugs would be off-label (see the [summaries of product characteristics](#) for the individual drugs for specific prescribing information).

[Full text of introduction and current guidance](#).

Product overview

Rituximab concentrate for solution for intravenous infusion ([MabThera](#), Roche Products Limited) is licensed in adults for treating non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, and granulomatosis with polyangiitis and microscopic polyangiitis. It is administered as an intravenous infusion, which can take several hours, depending on the dose and rate of infusion.

Rituximab is not licensed for treating MCD or FSGS and so use for this indication is off-label.

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using rituximab outside its authorised indications.

Rituximab 10 mg/ml concentrate for solution for intravenous infusion (MabThera, Roche Products Limited) costs (excluding VAT; MIMS September 2016):

- 2×10 ml=£349.25

- 1×50 ml=£873.15

Full text of product overview.

Evidence review

- A systematic review of 14 observational studies (Kronbichler et al. 2014) assessed the efficacy of rituximab treatment in adults with frequently relapsing or steroid-dependent nephrotic syndrome caused by MCD (n=77) or FSGS (n=9). Commonly used rituximab dosing regimens were single dose ranging from 375 mg/m^2 to a fixed administration of 500–1000 mg or 4 consecutive infusions of 375 mg/m^2. Follow-up time varied amongst the included studies from 5.1 to 82 months. The authors report that the median follow-up was 12 months.

  — Relapse was defined as proteinuria greater than 3.0–3.5 g of protein per day as measured by a 24-hour urine collection or 300–350 mg/mmol if spot urine was used for analysis. The median relapse rate before treatment with rituximab was 1.3 (range 0 to 9) per year; this was reduced to 0 (range 0 to 2) relapses per year after treatment with rituximab (p<0.001). The results were combined for MCD and FSGS.

  — Response to treatment was categorised by the authors of the systematic review as complete or partial remission. Complete remission was considered as a proteinuria value of 300 mg/day or less. Partial remission was considered as a decrease of the initial urinary protein loss by at least 50% and a proteinuria value of 3.5 g/day or less. Of the participants with MCD treated with rituximab, 72 out of 73 had a response to treatment. Out of the 7 participants with FSGS, 6 achieved complete or partial remission. The authors were unable to obtain information on the response rate for 6 of the participants with MCD (n=4) and FSGS (n=2).

- — The intensity of concomitant immunosuppressive therapy (measured using a semi-quantitative scoring system) was statistically significantly reduced (p<0.001) following treatment with rituximab. The number of participants receiving concomitant immunosuppressants other than steroids was reduced from 60 at the time of first treatment with rituximab to 12 at the time of last follow-up (p<0.001). The number of participants receiving steroids was also reduced from 84 at the time of first treatment with rituximab to 27 at the time of last follow-up. The results were combined for MCD and FSGS.

- A prospective observational study (Sugiura et al. 2011) examined the efficacy and safety of single-dose rituximab for adults (n=24) with primary glomerular disease including MCD (10 people), FSGS (4 people), membranous nephropathy (4 people), membranoproliferative glomerulonephritis (1 person) and immunuoglobulin A nephropathy (5 people). Four participants (all with MCD) had steroid-dependent nephrotic syndrome. Ten participants had steroid-resistant nephrotic syndrome and included people with MCD, FSGS, membranous nephropathy and membranoproliferative glomerulonephritis. Rituximab was administered by intravenous infusion as a single dose of 375 mg/m^2 body surface area (maximum 500 mg). Follow-up times were at 1, 3 and 6 months after rituximab infusion.

  - — There was a statistically significant decrease in mean (± standard deviation) observed urinary protein at 6 months after rituximab administration compared with baseline. For participants with MCD the levels decreased from 3.8±4.1 g/day at baseline to 0.42±1.2 g/day at 6 months (p<0.05). For participants with FSGS the levels decreased from 5.2±2.4 g/day at baseline to 2.3±2.8 g/day at 6 months to (p<0.05).

  - — In the participants with MCD and FSGS, the mean (± standard deviation) corticosteroid dose (prednisolone or methylprednisolone) was reduced from 21.0±12.7 to 11.5±11.8 mg/day (p<0.05) and from 23.8±12.5 to 10.0±9.1 mg/day (not statistically significant), respectively at 6 months after administration with rituximab.

  - — Two out of 10 participants with MCD and 1 out of 4 participants with FSGS were able to discontinue their corticosteroids 6 months after administration with rituximab.

- A retrospective cohort study (Spinner et al. 2015) compared single-dose rituximab treatment (median 200 [range 100 to 1000] mg) for recurrent glomerulonephritis post-renal transplant with a control group who did not receive rituximab. The forms of

glomerulonephritis included FSGS, MCD, membranoproliferative glomerulonephritis, membranous nephropathy, lupus nephritis, Wegener's granulomatosis and immunoglobulin A nephropathy. Of the 48 included adults, 25 (n=0 with MCD and n=7 with FSGS) received treatment with rituximab and 23 (n=1 with MCD and n=6 with FSGS) did not receive rituximab. Both groups received other treatments for recurrent glomerulonephritis and anti-rejection therapy. The median follow-up time in the intervention group was 769 (range 363 to 1301) days compared with 1358 (range 236 to 2710) days for the control group (p=0.18). Only 20 participants in the control group (6 with FSGS and 0 with MCD) and 13 people (4 with FSGS and 1 with MCD) in the intervention were assessed for treatment response outcomes because of various exclusions.

- The authors included an analysis which assessed the response to treatment based on the type of glomerulonephritis. Out of 6 participants with FSGS treated with rituximab, 2 achieved complete response, 1 achieved partial response and 3 did not respond to treatment. In 4 participants with FSGS who were not treated with rituximab, 2 achieved complete response, 1 achieved partial response and 1 participant did not respond to treatment. The participant with MCD in the control group achieved partial response; however, there were no participant(s) in the intervention group with MCD. The authors reported no significant difference between the intervention and control groups in complete and partial response rates in adults with FSGS or MCD (p=1.00 for both comparisons).

- Adverse events reported in the systematic review (Kronbichler et al. 2014) included infusion-related reactions that consisted of transient hypotension (3 people), itchy red eyes (1 person), cough (2 people), hiccough (1 person) and exanthema (1 person). Bronchopneumonia was observed in 1 person 2 months after treatment with rituximab. A long-term complication of mild leukopenia in 1 person with MCD had also been observed. In the study by Sugiura et al. (2011), 1 participant experienced an adverse event; a cutaneous eruption which did not require discontinuation of rituximab infusion (type of primary glomerular disease not reported).

- The SPC for rituximab describes that infusion-related reactions are very common in people treated with intravenous rituximab for any licensed indication. Severe infusion-related reactions with a fatal outcome have been reported in post-marketing use. Serious infections, including fatalities, can occur during rituximab therapy, and rituximab is contraindicated in people with an active, severe infection (for example, tuberculosis, sepsis and opportunistic infections), and in people who are severely immunocompromised. Cases of hepatitis B reactivation, including those with a fatal

outcome, have been reported in people receiving rituximab. Hepatitis B virus screening should be performed in all people before starting treatment with rituximab and people with active hepatitis B infection should not be treated with the drug. Very rare cases of fatal progressive multifocal leukoencephalopathy have been reported after use of rituximab and people should be monitored at regular intervals for any new or worsening neurological symptoms or signs suggestive of this condition. See the SPC for rituximab for full details of warnings, contraindications and adverse events.

- Most of the evidence for using rituximab in adults with MCD and FSGS comes from uncontrolled observational studies outside of the UK, with no randomisation and no comparator arm (the exception being Spinner et al. 2015, who used a non-randomised control group as a comparator in their retrospective study). The studies, Kronbichler et al. (2014), Spinner et al. (2015) and Sugiura et al. (2011) all had small sample sizes. Kronbichler et al. (2014) included a total of 86 people, 77 with MCD and 9 with FSGS from 14 studies. However the individual included studies only contained between 1 and 25 people with MCD, and 1 and 3 people with FSGS. Spinner et al. (2015) and Sugiura et al. (2011) included a total of 14 (MCD=1, FSGS=13; and MCD=10, FSGS=4 respectively) people with MCD or FSGS. The populations in the included studies varied in terms of cause of glomerulonephritis and disease characteristics (such as albumin levels, duration and treatment of disease). The dose of rituximab used, treatment with concomitant steroids and immunosuppressants (some of which are not available in the UK) and follow-up time also varied. Clinical outcome measures also varied across studies. For some outcomes, the studies reported pooled data for MCD, FSGS and other forms of glomerulonephritis; it may not be appropriate to pool data from people with different disease processes. There were limited data on the effect of rituximab on kidney function. All of these factors make it difficult to draw firm conclusions about the effect of rituximab in people with MCD or FSGS from the evidence reviewed.

Full text of evidence review.

Context and estimated impact for the NHS

People with MCD or FSGS undergoing treatment with corticosteroids may exhibit steroid resistance, steroid dependence or complications of steroid therapy such as cataracts, diabetes and osteoporosis. Immunosuppressants such as ciclosporin also have significant adverse effects, which limit their long-term use in people presenting with nephrotic syndrome. Low quality evidence suggests that rituximab could be considered for use in people who experience these complications.

Comparing the cost of rituximab with other therapies for MCD or FSGS is difficult because there is a lack of evidence to establish an optimal dose and drug regimen (including using either a fixed or multiple dosage, and combination with other treatments).

Most of the studies in this evidence summary used rituximab as a single dose or multiple doses ranging from 375 mg/m^2 to a fixed administration of 100–1000 mg or consecutive infusions (no more than 4) of 375 mg/m^2. Costs would vary depending on the height and weight of a person.

As an approximate guide, the cost for 1, 2, 3 or 4 doses of intravenous rituximab 375 mg/m^2 based on an adult with a body surface area of 1.86 m^2 is estimated to be £1222.40, £2444.80, £3667.20 and £4889.60, respectively (assuming wastage and excluding VAT; MIMS September 2016).

Full text of context and estimated impact for the NHS.

Information for the public

A plain English summary is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with minimal change disease or focal segmental glomerulosclerosis who are thinking about trying rituximab.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance**.

Full evidence summary

Introduction and current guidance

Minimal change disease (MCD) is an immune-mediated condition affecting the kidneys. It is usually of unknown cause, but can sometimes be associated with Hodgkin's disease or the use of nonsteroidal anti-inflammatory drugs (Oxford Textbook of Medicine, 5th Edition). Focal segmental glomerulosclerosis (FSGS) is not a specific disease entity but a histological lesion, often of unknown aetiology, which is characterised by segmental areas of glomerular sclerosis (Oxford Textbook of Medicine, 5th Edition). Both MCD and FSGS can lead to nephrotic syndrome, which is characterised by proteinuria, oedema and hypoalbuminemia. Other complications include end-stage renal disease, hyperlipidaemia, hypertension, hypercoagulability and risk of infection.

The general management of MCD and FSGS in adults includes controlling the condition, and preventing end-stage renal disease and associated complications. Evidence-based recommendations on the management of the various forms of glomerulonephritis, including MCD and FSGS were published by the International Society of Nephrology in 2012, KDIGO clinical practice guideline for glomerulonephritis. Specialists who commented on this evidence summary have advised that the KDIGO guideline for glomerulonephritis is the guideline they refer to for treating people with uncomplicated MCD or FSGS. However, for people with more complex disease, expert consensus opinion is sought.

MCD accounts for 10 to 15% of cases of primary nephrotic syndrome in adults (Waldman et al. 2007). MCD may occur at any age, but it is most common in childhood. The disease causes damage to the glomeruli in the kidney which affects filtration and can cause proteinuria, oedema and hypoalbuminemia. Management of MCD is aimed at reducing the frequency of relapse and achieving remission. Treatment with a corticosteroid such as prednisolone is recommended for the initial episode of nephrotic syndrome (KDIGO clinical practice guideline for glomerulonephritis). Specialists who commented on this evidence summary advised that corticosteroids could be used for second and subsequent episodes of MCD or FSGS provided the frequency of relapse is not too high (for example, fewer than 4 relapses in 12 months [Kronbichler et al. 2014]). A calcineurin inhibitor (such as ciclosporin or tacrolimius) or oral cyclophosphamide are alternatives for adults with relative contraindications or intolerance to corticosteroids (KDIGO clinical practice guideline for glomerulonephritis). Specialists who reviewed this evidence summary suggest that alternative treatments to prednisolone such as calcineurin inhibitors can be

used as steroid-sparing agents in people whose disease becomes steroid-dependent. A calcineurin inhibitor, cyclophosphamide or mycophenolate mofetil are recommended for frequently relapsing disease, based mainly on observational studies or case reports (KDIGO clinical practice guideline for glomerulonephritis).

FSGS may be: primary - which is by definition of unknown cause, but in about 30% of cases is associated with a circulating protein factor that causes an increase in glomerular permeability; or secondary - the end product of a variety of pathological processes including glomerular hyperfiltration, healed glomerulonephritis, viral infection (HIV), and genetic mutation. Most patients with FSGS present with nephrotic syndrome (FSGS is the underlying diagnosis in 20% of adults with nephrotic syndrome), some with persistent proteinuria, and a few have haematuria as well as proteinuria. (Oxford textbook of Medicines, 5th Edition).

Management of FSGS aims to induce remission or control the condition and slow down the progression to end-stage renal disease. Corticosteroids and immunosuppressants are recommended only for people with primary FSGS and features of the nephrotic syndrome. Recommended initial treatment is with corticosteroids. Calcineurin inhibitors can be considered as alternatives for adults with relative contraindications or intolerance to steroids. Ciclosporin is recommended for steroid-resistant FSGS. Combination treatment with mycophenolate mofetil and high-dose dexamethasone is recommended for people with steroid-resistant FSGS who are intolerant of ciclosporin (KDIGO clinical practice guideline for glomerulonephritis). However, specialists involved in the production of this evidence summary commented that prednisolone is usually used in the UK, rather than dexamethasone.

Prednisolone is licensed for renal disorders that include minimal change glomerulonephritis and nephrotic syndrome. Ciclosporin is licensed for the treatment of nephrotic syndrome including that caused by primary glomerular diseases such as minimal change nephropathy and focal and segmental glomerulosclerosis. The use of cyclophosphamide, tacrolimus and mycophenolate mofetil would be off-label (see the summaries of product characteristics for the individual drugs for specific prescribing information).

At the time of writing this evidence summary (September 2016), rituximab was not included in the recommendations on treating MCD or FSGS in the KDIGO clinical practice guideline for glomerulonephritis. NHS England has published commissioning policies on the use of rituximab for treating relapsing-steroid sensitive nephrotic syndrome and steroid-resistant nephrotic syndrome in children.

This evidence summary considers the use of rituximab for treating adults with MCD or FSGS in their own native kidneys and in those who have had a kidney transplant.

Rituximab is available as a solution for intravenous infusion, and as a subcutaneous injection. Studies included in this evidence review used the intravenous formulation of rituximab, and so the evidence summary focuses on the intravenous formulation only. Specialists who commented on this evidence summary advised that in UK practice, the intravenous formulation is used to treat people with MCD or FSGS.

Product overview

Drug action

Rituximab (MabThera, Roche Products Limited) is a monoclonal antibody that targets the CD20 surface antigen, which is expressed on normal and malignant B cells. Rituximab binds to the CD20 surface antigen on B cells mediating cell lysis, and inducing cell death by apoptosis (summary of product characteristics [SPC] for rituximab [MabThera]).

Regulatory status

Rituximab concentrate for solution for intravenous infusion (MabThera, Roche Products Limited) is licensed in adults for treating non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, and granulomatosis with polyangiitis and microscopic polyangiitis. It is administered as an intravenous infusion which can take several hours, depending on the dose and rate of infusion.

Rituximab is not licensed for treating MCD or FSGS and so use for these indications would be off-label.

NICE has published evidence summaries on other off-label use of rituximab:

- Immune (idiopathic) thrombocytopenic purpura: rituximab (ESUOM 35)

- Autoimmune haemolytic anaemia: rituximab (ESUOM 39)

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using rituximab outside its authorised indications. Supporting information and advice is also

available from the GMC.

Cost

Rituximab 10 mg/ml concentrate for solution for intravenous infusion (MabThera, Roche Products Limited) costs (excluding VAT; MIMS September 2016):

- 2×10 ml=£349.25

- 1×50 ml=£873.15

Evidence review

This summary discusses the best available evidence for using rituximab for treating MCD or FSGS in adults.

The evidence that is reviewed in this summary includes a systematic review of observational studies (Kronbichler et al. 2014), 1 prospective observational study (Sugiura et al. 2011) and 1 retrospective cohort study (Spinner et al. 2015). Each of the studies looked at the use of rituximab in different populations.

Clinical effectiveness

Rituximab for steroid-dependent or frequently relapsing MCD or FSGS

A systematic review of observational studies (Kronbichler et al. 2014) assessed the efficacy of rituximab treatment in adults with frequently relapsing or steroid-dependent nephrotic syndrome caused by MCD or FSGS. The review included a total of 14 studies; 12 retrospective studies and 2 prospective studies.

The systematic review included a total of 86 participants (53 men, 33 women) of which 77 had MCD and 9 had FSGS. The median age of people in the included studies when they first received rituximab was 27.5 years (range 18 to 73 years). Diagnosis was confirmed by a renal biopsy and all participants included in the review were classified as steroid-dependent or frequently relapsing. The authors defined steroid-dependent nephrotic syndrome as 'a relapse upon tapering steroid therapy or within 2 to 4 weeks of stopping the steroid and the need for long-term maintenance steroids'. Frequently relapsing

nephrotic syndrome was defined by the authors as '2 or more relapses within 6 months after completing initial treatment or 4 relapses within any period of 12 months including relapses during initial treatment'.

The studies included in the systematic review each used different rituximab dosing regimens, including single-dose regimens ranging from 375 mg/m^2 to a fixed administration of 500–1000 mg, or 4 consecutive infusions of 375 mg/m^2. Clinicians administered a second dose of rituximab in 10 out of 45 participants due to an increase in peripheral circulating B cells. One study included a second fixed infusion of 375 mg/m^2 (maximum 500 mg) 6 months after the first infusion. The follow-up time varied amongst the included studies from 5.1 to 82 months. The authors reported that the median follow-up was 12 months.

The systematic review reported a statistically significantly reduced rate of annual relapses (relapse was defined as proteinuria greater than 3.0–3.5 g of protein per day as measured by a 24 hour urine collection or 300–350 mg/mmol if spot urine was used for analysis) following treatment with rituximab. The median relapse rate before treatment with rituximab was 1.3 (range 0 to 9) per year; this was reduced to 0 (range 0 to 2) relapses per year after treatment with rituximab (p<0.001). The results for this outcome were pooled and were not reported separately for MCD and FSGS.

In 81 participants with a follow-up time of at least 12 months following treatment with rituximab, 54 were free from clinical relapses. Baseline characteristics of participants with subsequent relapse and those without relapse were analysed. The authors found that participants with 1 or more relapses had used a higher number of immunosuppressants before treatment with rituximab (p=0.018) and their serum albumin (Alb) was lower compared with those without relapse (p=0.018). A numerically higher baseline proteinuria was also observed in participants with relapse, but this was not statistically significant (p=0.051).

The authors categorised response to treatment as complete or partial remission. Complete remission was defined as a proteinuria value of 300 mg/day or less. Partial remission was defined as a decrease of the initial urinary protein loss by at least 50% and a proteinuria value of 3.5 g/day or less.

A total of 80 participants (73 with MCD and 7 with FSGS) were evaluated for this outcome as response rate data was not available for 6 participants (4 with MCD and 2 with FSGS). Of the participants with MCD treated with rituximab, the authors reported that 72 out of

73 were responsive to treatment. Out of the 7 participants with FSGS, 6 achieved complete or partial remission.

The intensity of concomitant immunosuppressant therapy was analysed using a semi-quantitative score system which allocated medicines a particular points value and summed the score up to a maximum of 5. The review found that the intensity of concomitant immunosuppressive therapy prior to treatment scored 2 (range 0 to 5); this was statistically significantly reduced to 0 (range 0 to 2; p<0.001) following treatment with rituximab. The authors reported that the number of participants receiving concomitant immunosuppressants other than steroids was reduced from 60 at the time of first treatment with rituximab to 12 at the time of last follow-up (p<0.001). The number of participants receiving steroids was also reduced from 84 at the time of first treatment with rituximab to 27 at the time of last follow-up. Results were not reported separately for participants with MCD or FSGS.

The systematic review also reported an increase in serum albumin from a median of 2.9 (range 1.2 to 4.6) g/l at the time of treatment with rituximab to a median of 4 (range 1.8 to 5.09) g/l at the time of last assessment (p=0.001).

Rituximab for primary MCD and FSGS

A Japanese prospective observational study (Sugiura et al. 2011) examined the efficacy and safety of single-dose rituximab for adults with primary glomerular disease. This study included 24 adults (mean age 37.8 years) with MCD (10 participants), FSGS (4 participants), membranous nephropathy (4 participants), membranoproliferative glomerulonephritis (1 participant) and immunuoglobulin A nephropathy (5 participants). All but one participant had a history of treatment with steroids or immunosuppressants such as ciclosporin and mycophenolate mofetil and the study did not require these to be discontinued. Four participants (all with MCD) had steroid-dependent nephrotic syndrome. Ten participants had steroid-resistant nephrotic syndrome and included participants with MCD, FSGS, membranous nephropathy and membranoproliferative glomerulonephritis.

Rituximab was administered by intravenous infusion as a single dose of 375 mg/m^2 body surface area (maximum 500 mg). Cyproheptadine hydrochloride (antihistamine) and paracetamol were administered 30 minutes prior to rituximab infusion to minimise the risk of infusion reactions. Participants were followed up at 1, 3 and 6 months after rituximab infusion. The study aimed to taper the dose of, or discontinue corticosteroids by 6 months.

In the participants with MCD and FSGS, the mean (± standard deviation) corticosteroid dose (prednisolone or methylprednisolone) was reduced from 21.0±12.7 to 11.5±11.8 mg/day (p<0.05) and from 23.8±12.5 to 10.0±9.1 mg/day (not statistically significant), respectively at 6 months after administration with rituximab. Two of the 10 participants with MCD were able to discontinue their corticosteroids 6 months after administration with rituximab. One of the 4 participants with FSGS was able to discontinue their steroid treatment 6 months after administration with rituximab.

There was a statistically significant decrease in mean (± standard deviation) urinary protein at 6 months after rituximab administration compared with baseline. For participants with MCD the levels decreased from 3.8±4.1 g/day at baseline to 0.42±1.2 g/day at 6 months (p<0.05). For participants with FSGS the levels decreased from 5.2±2.4 g/day at baseline to 2.3±2.8 g/day at 6 months to (p<0.05).

Rituximab for recurrent MCD or FSGS post-renal transplant

An American retrospective cohort study (Spinner et al. 2015) investigated single-dose rituximab treatment for recurrent glomerulonephritis in 48 adult renal transplant recipients. The forms of glomerulonephritis included FSGS (13 participants), MCD (1 participant), membranoproliferative glomerulonephritis (11 participants), membranous nephropathy (8 participants), lupus nephritis (5 participants), Wegener's granulomatosis (1 participant) and immunoglobulin A nephropathy (9 participants). Data was collected from a transplant research database, electronic medical records and paper charts from January 1998 to April 2012.

Of the 48 adults with recurrent glomerulonephritis post-renal transplant, 25 (median age 36 years) received treatment with rituximab (intervention) as part of their therapy and 23 (median age 45 years) received no treatment with rituximab (control). The intervention group had 7 participants with FSGS and no participants with MCD. The control group had 6 participants with FSGS and 1 participant with MCD. Single doses of rituximab used in the study varied. Two participants received a 100 mg dose, 12 participants received a 200 mg dose, 5 participants received a 500 mg dose and 1 participant received a 1000 mg dose. Six participants received a second dose of rituximab. Both groups received other treatments for recurrent glomerulonephritis and anti-rejection therapy.

The median follow-up time in the intervention group was 769 (range 363 to 1301) days compared with 1358 (range 236 to 2710) days for the control group (p=0.18). Response to treatment was assessed using urinary protein/creatinine ratio values.

People were excluded from the treatment response analyses if they did not have proteinuria at the time of recurrence of glomerulonephritis, were missing urinary protein/ creatinine data, had an adverse reaction to rituximab leading to discontinuation or were on rituximab treatment for concomitant acute rejection. This left a total of 20 participants in the control group (6 with FSGS and 0 with MCD) and 13 people (4 with FSGS and 1 with MCD) in the intervention group that were assessed for treatment response outcomes.

Most of the results of the study were combined for all types of glomerulonephritis; however the authors included an analysis which assessed the response to treatment based on the type of glomerulonephritis. A total of 10 participants with FSGS were included, 6 in the intervention group and 4 in the control group and 1 participant in the control group with MCD was included. Out of the 6 participants with FSGS treated with rituximab, 2 achieved complete response, 1 achieved partial response and 3 did not respond to treatment. In the 4 participants with FSGS who were not treated with rituximab, 2 achieved complete response, 1 achieved partial response and 1 participant did not respond to treatment. The participant with MCD in the control group achieved partial response; there were no participants in the intervention group with MCD. The authors reported no significant difference between the intervention and control groups in complete and partial response rates in adults with FSGS or MCD (p=1.00 for all comparisons).

Safety and tolerability

In the systematic review of observational studies performed by Kronbichler et al. (2014), frequent reported adverse events included infusion-related reactions that consisted of transient hypotension (3 people), itchy red eyes (1 person), cough (2 people), hiccough (1 person) and exanthema (1 person). Bronchopneumonia was observed in 1 person 2 months after treatment with rituximab. The authors reported that a long-term complication of mild leukopenia in 1 person had been observed. Adverse events were not reported separately for MCD or FSGS.

In the study by Sugiura et al. (2011), 1 participant experienced an adverse event; a cutaneous eruption which did not require discontinuation of rituximab infusion (type of primary glomerular disease not reported).

The study reported by Spinner et al. (2015) compared the incidence in the rituximab and control groups of endpoints such as death (0/20 people compared with 2/13 people, p=0.2); overall incidence of infection through to follow-up (7/20 people compared with 11/ 13 people, p=0.16); and overall incidence of infection in the first 6 months after treatment

(6/20 people compared with 7/13 people, p=0.59). The 2 groups had a similar incidence of viral and fungal infections (p=0.14, p=0.50 respectively). Bacterial infections were reported to be statistically significantly more common in the group treated with rituximab compared with the control group (5 infections compared with 1 infection, p=0.013). The authors stated that this is similar to previously reported rates of infection in renal transplant recipients (Spinner et al. 2015). Adverse events were not reported separately for each form of glomerulonephritis in the study.

The summary of product characteristics (SPC) for rituximab (MabThera, Roche Products Limited) lists contraindications and adverse events separately for each licensed indication (see the SPC for more information).

In people treated with intravenous rituximab, signs and symptoms suggestive of an infusion-related reaction have been reported in more than 50% of participants in clinical trials across rituximab's licensed indications, with 12% of participants experiencing severe reactions (SPC for rituximab). Severe infusion-related reactions with a fatal outcome have been reported in post-marketing use. Premedication with an anti-pyretic and an antihistamine (for example, paracetamol and diphenhydramine) should always be given before administration of intravenous rituximab. In addition, premedication with a glucocorticoid should be given (except in people with non-Hodgkin's lymphoma or chronic lymphocytic leukaemia who are receiving rituximab in combination with glucocorticoid-containing chemotherapy).

Very rare cases of fatal progressive multifocal leukoencephalopathy have been reported after use of rituximab and people should be monitored at regular intervals for any new or worsening neurological symptoms or signs suggestive of this condition (SPC for rituximab).

Serious infections, including fatalities can occur during rituximab therapy, and rituximab is contraindicated in people with an active, severe infection (for example, tuberculosis, sepsis and opportunistic infections), and in people who are severely immunocompromised. In addition, cases of hepatitis B reactivation, including those with a fatal outcome, have been reported in people receiving rituximab. Hepatitis B virus screening should be performed in all people before starting treatment with rituximab and people with active hepatitis B infection should not be treated with the drug (SPC for rituximab).

Severe skin infections, such as toxic epidermal necrolysis and Stevens–Johnson syndrome (some with fatal outcome), have been reported in people receiving rituximab. Treatment

with rituximab should be stopped if such an event occurs (SPC for rituximab).

See the SPC for rituximab for full details of warnings, contraindications and adverse events.

Evidence strengths and limitations

The evidence for using rituximab in adults with MCD and FSGS comes from observational studies performed outside the UK. Those studies looking at disease in native kidneys had with no randomisation and no comparator arm. Kronbichler et al. (2014) included published studies that reported efficacy and safety outcomes of rituximab treatment in people with MCD and FSGS and was the largest study in this evidence review with 86 participants. Spinner et al. (2015), in their cohort study of renal transplant recipients with MCD and FSGS, did use a control group of renal transplant recipients not treated with rituximab over the same retrospective time period as a comparator.

The included studies, Kronbichler et al. (2014), Spinner et al. (2015) and Sugiura et al. (2011) all had small sample sizes. Kronbichler et al. included a total of 86 people, 77 with MCD and 9 with FSGS from 14 studies. However the individual included studies only contained between 1 and 25 people with MCD, and 1 and 3 people with FSGS. Spinner et al. (2015) and Sugiura et al. (2011) included a total of 14 (MCD=1, FSGS=13; and MCD=10, FSGS=4 respectively) people with MCD or FSGS. The populations in the included studies varied in terms of cause of glomerulonephritis and disease characteristics (such as albumin levels, duration and treatment of disease). The dose of rituximab used, treatment with concomitant steroids and immunosuppressants (some of which are not available in the UK) and follow-up time also varied. Clinical outcome measures varied across studies. For some outcomes, the studies reported pooled data for MCD, FSGS and other forms of glomerulonephritis; it may not be appropriate to pool data from people with different disease processes. There were limited data on the effect of rituximab on kidney function. All of these factors make it difficult to draw firm conclusions about the effect of rituximab in people with MCD or FSGS from the evidence reviewed.

The systematic review reported by Kronbichler et al. (2014) included adults with native kidneys who have steroid-dependent or frequently relapsing MCD or FSGS, so their results may not have a wider applicability. The review included a large proportion of adults with MCD (77/86) and the majority of reported data was combined making it difficult to assess outcomes separately for MCD and FSGS. The authors discussed that publication and observer bias towards reporting a favourable disease course may have been present

because the majority of the included studies were retrospective in nature. The reduction in mean daily steroids was not analysed due to heterogeneity of the data and so the steroid reducing effect of rituximab could not be determined. The included studies did not report data on clinically important endpoints such as end-stage renal disease or death.

There were several limitations in the study by Sugiura et al. (2011). The study had a relatively short evaluation period of 6 months and was small, 10 people with MCD and 4 with FSGS out of the included 24 with primary glomerular disease. Although the study reported separate results (clinical and laboratory parameters) for each form of glomerular disease, relapse rates and partial and complete remission rates were not reported. The authors reported that there was no protocol used for discontinuation or tapering of prednisolone or other immunosuppressants during the study which could have affected the response to treatment and clinical and laboratory parameters.

The study by Spinner et al. (2015) was limited by its retrospective nature as it may have been subject to selection bias. Whilst it was a cohort study, the authors reported that it was not possible to match the cases and controls. The study was small and generated non-significant results that the authors stated should be interpreted with caution. Efficacy outcomes for people with MCD or FSGS were based on a small sample size of 14 people (1 had MCD and 13 had FSGS) out of the 48 participants with post-renal transplant recurrent glomerulonephritis, Specialists who commented on this evidence summary highlighted that it is rare for people with MCD to undergo a renal transplant, which may explain the low numbers of participants with MCD included in this study. Although the use of concomitant therapy was similar between the 2 groups, the authors reported that it was difficult to account for specific treatments used with rituximab which may have affected outcomes. The very low numbers of adults with MCD and FSGS included in the study, and pooling of outcome data which was incomplete, limit the applicability of the findings from the study.

The studies included in the evidence summary used a variety of dosing regimens for rituximab administration. The 2 studies that assessed the efficacy of single-dose rituximab (Spinner et al. 2015 and Sugiura et al. 2011) administered an additional dose of rituximab to participants who had not responded to treatment or were steroid-dependent. Spinner et al. 2015 reported that half the participants who received an additional rituximab dose achieved partial response, suggesting that single dose of rituximab may not be as effective as a multi-dose approach. However on the small number of participants limits the applicability of this interpretation of the data. Specialists involved in the production of this evidence summary highlighted that most treatment protocols for MCD or FSGS in UK practice include the use of 2 doses of rituximab. The studies by Spinner et al. (2015) and

Sugiura et al. (2011) combined people with different forms of glomerulonephritis, which made it difficult to determine which of the participants with MCD or FSGS received an additional dose of rituximab.

Little data on adverse effects other than infusion-related reactions were reported in the included studies. Most of the studies did not report which indications the people who experienced adverse effects were being treated for, making it difficult to establish the safety of rituximab for treating MCD and FSGS from the available data.

The limitations highlighted in this evidence review make it difficult to compare the reported response rates and other outcomes in the studies, or to draw any firm conclusions from the evidence on the efficacy and safety of rituximab for treating MCD and FSGS in adults.

Context and estimated impact for the NHS

Cost effectiveness

No cost-effectiveness studies of rituximab for treating MCD or FSGS in adults were identified.

People with MCD or FSGS undergoing treatment with corticosteroids may exhibit steroid resistance, steroid dependence or complications of steroid therapy such as cataracts, diabetes and osteoporosis. Immunosuppressants such as ciclosporin also have significant adverse effects, which limit their long-term use in people presenting with nephrotic syndrome. Low quality evidence suggests that rituximab could be considered for use in people who experience these complications.

Comparing the cost of rituximab with other therapies for MCD or FSGS is difficult because there is a lack of evidence to establish an optimal dose and drug regimen (including using either a fixed or multiple dosage, and combination with other treatments).

Most of the studies in this evidence summary used rituximab as a single dose or multiple doses ranging from 375 mg/m^2 to a fixed administration of 100–1000 mg or consecutive infusions (no more than 4) of 375 mg/m^2. Costs would vary depending on the height and weight of a person. Specialists involved in the production of this evidence summary commented that, based on clinical experience, most people with MCD or FSGS would require more than 1 dose of rituximab and that protocols often include using 2 doses of

rituximab.

As an approximate guide, the cost for 1, 2, 3 or 4 doses of intravenous rituximab 375 mg/m^2 based on an adult with a body surface area of 1.86 m^2 is estimated to be £1222.40, £2444.80, £3667.20 and £4889.60, respectively (assuming wastage and excluding VAT; MIMS September 2016).

Specialists who commented on this evidence summary highlighted additional costs associated with the use of rituximab that would need to be considered. These include costs of premedication with paracetamol and an antihistamine administered before rituximab infusion and attendance for day case treatment.

Current drug usage

Estimating current drug usage of rituximab for treating MCD or FSGS is difficult because rituximab is used to treat various conditions. No information on prescribing rituximab for MCD and FSGS was available at the time this evidence summary was prepared.

Information for the public

A plain English summary is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with minimal change disease or focal segmental glomerulosclerosis who are thinking about trying rituximab.

Relevance to NICE guidance programmes

NICE has published several technology appraisals relating to licensed indications for the intravenous formulation of rituximab. This use of rituximab for MCD or FSGS is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

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Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

Expert advisers

Elizabeth Lamerton, Principal Clinical Pharmacist & Independent Prescriber (Renal Medicine), Salford Royal Hospital NHS Foundation Trust

Professor Neil Sheerin, Professor of Nephrology, Institute of Cellular Medicine, Newcastle University

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About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance**.

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