

**NIHR Innovation Observatory  
Evidence Briefing: August 2017**

**Rituximab (MabThera) maintenance therapy for  
granulomatosis with polyangiitis (GPA) and  
microscopic polyangiitis (MPA)**

NIHRIO (HSRIC) ID: 12979

NICE ID: 9284

**LAY SUMMARY**

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis is a rare condition in which abnormal antibodies attack the body's own cells, causing inflammation. Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are two different types of ANCA-associated vasculitis. These conditions can cause serious organ damage and severely impact quality of life. Following initial treatment, these conditions frequently return.

Rituximab is a medicine, delivered as an infusion into the vein. It destroys B cells, the part of the immune system thought to be involved in this type of vasculitis. It is already licensed for use (and recommended by NICE) as a treatment for people with GPA or MPA. There has however not been sufficient evidence to consider the continued use of rituximab as maintenance therapy, although this is already commissioned by NHS England in some instances. The current clinical trial examines the use of rituximab as a maintenance treatment in patients with GPA or MPA. If licensed, rituximab would offer another option for maintenance therapy in this patient cohort.

*This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.*

*This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.*

## TARGET GROUP

Granulomatosis with polyangiitis (GPA; Wegener's granulomatosis) or microscopic polyangiitis (MPA); maintenance therapy

## TECHNOLOGY

## DESCRIPTION

Rituximab (MabThera) is an anti-neoplastic agent. It is a monoclonal antibody that binds to a specific protein, the CD20 marker found on the surface of some B-cells. Following binding, rituximab triggers a host cytotoxic immune response against CD20-positive cells.<sup>1</sup>

Rituximab already has a marketing authorisation (in combination with glucocorticoids) for the induction of remission in adult patients with severely active granulomatosis with polyangiitis (GPA; Wegener's granulomatosis) and microscopic polyangiitis (MPA). It was recommended by NICE in 2014 as a possible treatment for these indications if the following conditions were met:

- More treatment with cyclophosphamide would exceed the maximum amount of cyclophosphamide they can have; or
- Cyclophosphamide is not suitable for them or they cannot take it; or
- They want to have children and treatment with cyclophosphamide may affect their fertility; or
- The disease has stayed active or got worse after a course of cyclophosphamide lasting 3 to 6 months; or
- The person has had cancer affecting the lining of the bladder and other parts of the urinary system.<sup>2</sup>

Truxima, a biosimilar of rituximab has also been launched in the UK in 2017 and is licensed for use in GPA and MPA similarly to the previous approval for rituximab by EMA.<sup>3</sup>

European Vasculitis Study Group guidelines recommend maintenance treatment after remission to prevent relapse, but limited data has precluded any conclusions about the efficacy and safety of subsequent courses of rituximab as maintenance therapy for people with GPA and MPA. The EMA marketing authorisation did not include rituximab use as a maintenance treatment. This assessment was therefore outside the scope of the 2014 NICE appraisal.<sup>2</sup>

Maintenance therapy with rituximab is not routinely commissioned in England. However, NHS England recognised that there is a subgroup of patients for whom maintenance with rituximab is required, and will (according to its 2015 policy) commission the use of rituximab as maintenance therapy when one of the following three clinical criteria, and all three additional centre criteria, is met:

1. The person is enrolled in a randomised trial that includes B cell suppression as maintenance therapy (e.g. RITAZAREM); or
2. Relapse requiring re-induction therapy has occurred after a previous rituximab induced remission; or
3. Rituximab has been required to induce remission in Cyclophosphamide-refractory disease and future relapse would have a high risk of organ damage.<sup>4</sup>

In addition NHS England requires that:

- The decision regarding rituximab maintenance has been made at, or in conjunction with, a specialised centre; and
- The person has been provided with the opportunity to be considered for any suitable clinical trials; and
- The person is registered on the UKIVAS database, to enable identification of use and outcome of treatment.

Maintenance therapy will be stopped after 2 years, or earlier if either treatment intolerance, a contraindication, or a major relapse occurs.<sup>4</sup>

The ongoing programme of clinical trials explores the role of rituximab specifically as maintenance therapy in people with GPA or MPA. In the phase III clinical trial, a rituximab IV infusion of 1,000 mg is delivered at months 4, 8, 12, 16 and 20 with glucocorticoids, with rituximab treatment stopping at month 20.<sup>5</sup>

The summary of product characteristics lists the following adverse events occurring at a rate of  $\geq 10\%$  in patients receiving rituximab to treat GPA and MPA: diarrhoea, peripheral oedema, muscle spasms, arthralgia, back pain, dizziness, tremor, insomnia, cough, dyspnoea, epistaxis and hypertension.<sup>2</sup> A recent interim analysis of rituximab use in an ANCA-associated vasculitis registry reported that serious adverse events were not increased compared with comparable cohorts of patients with renal involvement, and safety events did not increase with rituximab retreatment.<sup>6</sup>

In addition to induction of remission in GPA and MPA, rituximab is also licensed for use in non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, as subcutaneous formulation for untreated follicular non-Hodgkin's lymphoma. Rituximab is under development for fibrillary glomerulonephritis, pemphigus vulgaris (PV), follicular lymphoma, and for idiopathic thrombocytopenic purpura (immune thrombocytopenic purpura) in Japan.<sup>1</sup>

## **INNOVATION and/or ADVANTAGES**

Long-term therapy with cyclophosphamide has been used to maintain remission in patients with AAV, however the toxicity associated with its long-term use makes it a less optimal treatment option.<sup>7</sup> If licensed as maintenance treatment, rituximab may provide a potentially less toxic maintenance therapy option to patients, and would offer an alternative to those patients for whom current maintenance therapy options are not suitable.

## **DEVELOPER**

Roche Products Ltd

## **AVAILABILITY, LAUNCH or MARKETING**

Rituximab is currently in phase III clinical trials for maintenance therapy in GPA and MPA.

## PATIENT GROUP

### BACKGROUND

Anti-Neutrophil Cytoplasmic Autoantibody (ANCA) vasculitis is a type of autoimmune swelling caused by autoantibodies. Normal antibodies are produced by the immune system to fight germs, while autoantibodies are abnormal antibodies that attack one's own cells and tissues. ANCAs are autoantibodies that attack the inside (cytoplasm) of neutrophils (a type of white blood cell). GPA and MPA are both types of ANCA vasculitis (AAV), which also includes eosinophilic granulomatosis with polyangiitis (EPGA).<sup>8</sup>

AAV is a controllable but currently incurable lifelong illness, as it is a characteristically relapsing disease. AAV is a systemic disease with the potential to affect and permanently damage almost any organ. People with GPA or MPA may lose digits or limbs or be left with facial disfigurement or severe skin scarring. Severe fatigue, muscle weakness and chronic pain are frequent direct consequences of AAV, and treatment of the condition often results in serious side effects, contributing to depression as a secondary consequence of AAV.<sup>7</sup>

Maintenance therapy significantly reduces the risk of relapse in people with AAV. Each relapse carries a risk that additional critical organ damage will occur, leading to an irreversible deterioration in health. Relapse is also associated with significantly increased NHS costs. Prevention of relapse is a key priority, improving long-term outcomes for people living with AAV and directly impacting NHS activity and costs. NHS England states that the cost of each year of maintenance therapy with rituximab is identical to the cost of treating a relapse with rituximab re-induction therapy, yet avoids the additional cost of managing the relapse (e.g. adjunctive steroid, hospitalisation, and the costs of managing any resultant organ damage).<sup>4</sup>

### CLINICAL NEED and BURDEN OF DISEASE

GPA and MPA have respective annual incidence rates of 2.1 to 14.4 and 2.4 to 10.1 per million in Europe. The overall prevalence of AAV is estimated to be 46 to 184 per million.<sup>7</sup> The company estimates an eligible patient population of 11,371 in the UK,<sup>9</sup> while NHS England has estimated that approximately *"40 to 70 people in each senate region will need rituximab (including maintenance treatment each year"*.<sup>4</sup>

The peak age of onset for AAV is at 60 to 70 years. Without treatment the condition is usually fatal, and not everyone responds to treatment. About 80% of those treated will be alive at two years, and 20% of these survivors will have significant renal disease. Increasing age and renal involvement at diagnosis are poor prognostic factors for people with AAV.<sup>4</sup>

In 2015-16, there were 2,488 and 214 hospital admissions in England for GPA (ICD-10 M31.3) and MPA (ICD-10 M31.7) respectively, accounting for 2,767 and 263 finished consultant episodes and 3,458 and 468 bed days.<sup>10</sup>

## PATIENT PATHWAY

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE technology appraisal. Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody associated vasculitis (TA308). March 2014.

## NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Rheumatology Services (Adult). A13/S/a.
- NHS England. Clinical Commissioning Policy: Rituximab for the treatment of ANCA associated vasculitis in adults. A13/P/a. January 2015.

## OTHER GUIDANCE

- Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, Hellmich B, Holle JU, Laudien M, Little MA, Luqmani RA. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Annals of the Rheumatic Diseases*. 2016 Sep 1; 75(9):1583-94.
- British Society for Rheumatology. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. 2014.

## CURRENT TREATMENT OPTIONS

The treatment of AAV consists of two phases: remission induction and maintenance of remission. The international guidelines currently recommend maintenance treatment with a combination of low-dose glucocorticoids and either azathioprine, rituximab, methotrexate or mycophenolate mofetil. Such treatment often comes with a risk of significant side effects. Full drug-free remission can be achieved but relapse is common, and AAV adversely affects quality of life even in patients thought to have clinical remission.<sup>7</sup>

## EFFICACY and SAFETY

<b>Trial</b>	<b>RITAZAREM</b> ; rituximab vs. azathioprine as maintenance therapy in relapsing AAV; NCT01697267; EudraCT Number: 2012-001102-14; phase III
<b>Sponsor</b>	Roche Pharma AG; Cambridge University Hospitals NHS Foundation Trust; Arthritis Research UK; Genentech Inc; University of Pennsylvania
<b>Status</b>	Ongoing
<b>Source of Information</b>	Trial registry, <sup>5</sup> trial website <sup>11</sup>
<b>Location</b>	30 hospital sites in EU (incl UK), USA, Australia and Mexico
<b>Design</b>	Randomised, controlled, open label trial

<b>Participants</b>	N=160-190; aged 15 years or over; diagnosis of ANCA-associated vasculitis (AAV) including granulomatosis with polyangiitis or microscopic polyangiitis; current or historical PR3/MPO ANCA positivity by ELISA; disease relapse defined by one major or three minor disease activity items on the Birmingham Vasculitis Activity Score for Wegeners (BVAS/WG), in patients that have previously achieved remission following at least 3 months of induction therapy, with a combination of glucocorticoids and an immunosuppressive agent (cyclophosphamide or methotrexate or rituximab or mycophenolate mofetil)
<b>Schedule</b>	Rituximab IV infusion 1,000 mg x 1 dose at months 4, 8, 12, 16 and 20 and glucocorticoids. Four to six hour infusion. Treatment with rituximab will cease at month 20.
<b>Follow-up</b>	4 years
<b>Primary Outcomes</b>	Time to relapse (Time Frame: Any patients who have not relapsed at up to a maximum of 4 years will be censored.) The primary endpoint is the time to disease relapse (either minor or major relapse) from randomisation.
<b>Secondary Outcomes</b>	Remission at 24 and 48 months; Combined damage assessment score; Health-related quality of life; Cumulative GC exposure; Severe adverse event rate; Infection rates
<b>Key Results</b>	-
<b>Adverse effects (AEs)</b>	-
<b>Expected reporting date</b>	Estimated Primary Completion Date: December 2018

<b>Trial</b>	<b>MAINRITSAN;</b> rituximab vs. azathioprine; NCT00748644	<b>MAINRITSAN-2;</b> comparison of two rituximab regimens; NCT01731561; phase III	<b>MAINRITSAN-3;</b> NCT02433522; long-term rituximab maintenance treatment (46 months) vs. placebo; phase III extension
<b>Sponsor</b>	Assistance Publique - Hôpitaux de Paris	Assistance Publique - Hôpitaux de Paris	Assistance Publique - Hôpitaux de Paris; Roche Pharma AG
<b>Status</b>	Completed and published	Published in abstract	Ongoing
<b>Source of Information</b>	Trial registry, <sup>12</sup> journal publications <sup>13 14</sup>	Trial registry, <sup>15</sup> abstract <sup>16</sup>	Trial registry <sup>17</sup>
<b>Location</b>	France	France	France
<b>Design</b>	Randomised, controlled trial	Randomised, controlled, open label	Randomised, controlled trial
<b>Participants</b>	N=115; aged 18 to 75; GPA or MPA or kidney-limited disease with or without detectable ANCA (anti-neutrophil cytoplasmic antibodies) at the time of diagnosis	N=166; aged ≥18; GPA or MPA or kidney-limited disease with or without detectable ANCA (anti-neutrophil cytoplasmic antibodies) at the time of diagnosis or relapse, and	N=97; aged ≥18; patients must have been included in MAINRITSAN 2 and be in complete remission (BVAS 0) at 28 months of MAINRITSAN2 study

	<p>or relapse, and at remission; have achieved remission using a treatment combining corticosteroids and an immunosuppressive agent, including corticosteroids, cyclophosphamide IV or oral (the use of another immunosuppressant is allowed, according to the current French guidelines, as well as plasma exchanges and/or IV immunoglobulins); interval of 1 month between the end of the immunosuppressant treatment and the randomisation time</p>	<p>at remission; have achieved remission using a treatment combining corticosteroids and an immunosuppressive agent, including corticosteroids, cyclophosphamide IV or oral (the use of another immunosuppressant is allowed, according to the current French guidelines, as well as plasma exchanges and/or IV immunoglobulins, or rituximab); interval of 1 month between the end of the immunosuppressant treatment and the randomisation time if cyclophosphamide or methotrexate were used, interval between 4 and 6 months if rituximab was used</p>	
<b>Schedule</b>	<p>Rituximab infusion will be performed at J1, J15, M6, M12 and M18 (a total of 5 infusions), at the dose of 500 mg at a fixed dosage.</p> <p>All patients received corticosteroids, starting from induction with prednisone (or equivalent) at a dose of 1 mg/kg/day with gradual tapering according to a regimen adjusted to body weight over a mean of 18 months since diagnosis.</p>	<p>Arm 1: Rituximab infusion based on ANCA and CD19 lymphocytes. Rituximab infusion will be performed at D1 then ANCA status and CD19+ lymphocyte count will be monitored every 3 months, and patients will receive new 500 mg rituximab infusions either if CD19 are &gt; to 0/mm<sup>3</sup>, or if ANCA are positive again or if ANCA titer significantly raises.</p> <p>Arm 2: Semestrial rituximab infusion until 18 months. Rituximab infusion will be performed at D1, D15, M6, M12 and M18 (i.e. a total of 5 infusions), at the dose of 500 mg at a fixed dosage. All patients</p>	<p>500 mg rituximab infusion at the randomization visit and every 6 months for 18 months. Each infusion will be preceded by an infusion of 1000 mg paracetamol, 100 mg methylprednisolone and 5 mg dexchlorpheniramine.</p>

		received corticosteroids, starting from induction with prednisone (or equivalent) at a dose of 1 mg/kg/day with gradual tapering according to a regimen adjusted to body weight over a mean of 18 months since diagnosis.	
<b>Follow-up</b>	28 months	28 months	46 months
<b>Primary Outcomes</b>	Number of major relapse (BVAS>10) in each group at the end of the maintenance treatment (18 months treatment + 10 months follow-up) [ Time Frame: 28 months ]	Number of relapses [ Time Frame: at 28 months ]	Vasculitis score 2003 (BVAS 2003 ) [ Time Frame: 28 months ] Relapse free survival rates (BVAS > 0)
<b>Secondary Outcomes</b>	Number of adverse events and their severity; Number of patients with ANCA; mortality rate; number of minor relapses; cumulated dose and the length of corticosteroid treatment in each group at 28 months	Number of adverse events and their severity; Number of patients with ANCA; mortality rate; number of minor relapses; cumulated dose and the length of corticosteroid treatment in each group at 28 months; rate of B-Lymphocytes CD-19 and the link of the clinical events; evolution of gammaglobulins; quality of life	Number of adverse events; number of patients experiencing at least one adverse event in both arms; correlation of ANCA level with the clinical events; ANCA level during follow-up; correlation B-Lymphocytes CD-19 level with the clinical events; and others (full list available in the trial registry)
<b>Key Results</b>	More patients with AAV had sustained remission at month 28 with rituximab than with azathioprine. At month 28, major relapse had occurred in 17 patients in the azathioprine group (29%) and in 3 patients in the rituximab group (5%) (hazard ratio for relapse, 6.61; 95% confidence interval, 1.56 to 27.96; P=0.002).  Azathioprine-treated patients' for AAV maintenance therapy showed a decline in	Twenty-one (13%) patients suffered 22 relapses: 14 (17.3%) in 13 experimental arm patients and 8 (9.9%) in 8 controls (P=0.20). AAV relapse rates for patients given individually tailored or systematic RTX-infusion schedules did not differ significantly. However, the experimental arm patients received fewer infusions and lower total RTX doses.	-



	physical abilities when compared to rituximab at month 24.		
<b>Adverse effects (AEs)</b>	The frequencies of severe adverse events were similar in the two groups. Twenty-five patients in each group (P=0.92) had severe adverse events; there were 44 events in the azathioprine group and 45 in the rituximab group. Eight patients in the azathioprine group and 11 in the rituximab group had severe infections, and cancer developed in 2 patients in the azathioprine group and 1 in the rituximab group. Two patients in the azathioprine group died (1 from sepsis and 1 from pancreatic cancer).	Four subjects died, one of an infectious complication.	-
<b>Expected reporting date</b>	-	-	Estimated primary completion date in the trial registry is July 2018.

## ESTIMATED COST and IMPACT

### COST

Rituximab is priced at £174.63 per 10 ml vial containing 100 mg concentrate, and £785.84 per 50 ml vial with 500 mg concentrate.<sup>a</sup> Truxima (rituximab biosimilar) is priced at £785.84 per 50 ml vial.<sup>18</sup>

### IMPACT – SPECULATIVE

#### IMPACT ON PATIENTS AND CARERS

- Reduced mortality/increased length of survival
  Reduced symptoms or disability
- Other
  No impact identified

<sup>a</sup> Information from BNF, but edited following company feedback to indicate price per concentrate amount

## IMPACT ON HEALTH and SOCIAL CARE SERVICES

- Increased use of existing services       Decreased use of existing services
- Re-organisation of existing services       Need for new services
- Other: *potential to reduce the use of existing services if relapses are prevented*       None identified

## IMPACT ON COSTS and OTHER RESOURCE USE

- Increased drug treatment costs       Reduced drug treatment costs
- Other increase in costs       Other reduction in costs
- Other: *uncertainty regarding costs*       None identified

## OTHER ISSUES

- Clinical uncertainty or other research question identified       None identified

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