Pemphigus vulgaris (PV) is a rare autoimmune disease, where the immune system attacks cells found in the outer layer of the skin, as well as cells in the protective lining (mucous membrane) of the mouth, nose, throat, and genitals. This causes blisters to form in the affected tissue. It is unclear what causes these disturbances in the immune system, however certain genes have been linked to an increased risk of PV. The condition mainly affects middle-aged and older people and can lead to problems with sleeping, eating and drinking and weight loss. There is currently no cure for PV, however, treatments can help to keep the disease under control.

Corticosteroids (anti-inflammatory medicines) are usually used for the treatment of PV. Most people will need to take corticosteroids in addition to another medication to help improve the effectiveness and minimise the doses and side effects of corticosteroids. Rituximab is currently being investigated as a treatment option for PV. Rituximab binds specifically to a protein called CD20 located on pre-B and mature B lymphocytes inducing death of these cells. If licensed, rituximab may offer an additional treatment option for patients with PV after failure of systemic steroids and steroid sparing agents to control the disease.
TARGET GROUP

Pemphigus vulgaris (moderate to severely active) - treatment option after failure of systemic steroids and steroid sparing agents to control the disease

TECHNOLOGY

DESCRIPTION

Rituximab (MabThera; Rituxan; RG105) is an antineoplastic agent (monoclonal antibody). Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. CD20 is found on both normal and malignant B cells, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue. This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding. The antigen-binding fragments (Fab) domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fragment crystallisable (Fc) domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fc gamma (Fcy) receptors on the surface of granulocytes, macrophages and Natural killer (NK) cells. Rituximab binding to CD20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.1

Rituximab is currently in development for the treatment of pemphigus vulgaris when other treatments, including systemic steroids and steroid sparing agents have failed to control the disease. In the phase III clinical trial (NCT02383589), rituximab was administered at a dose of 1000 milligrams (mg) by intravenous (IV) infusion on days 1 and 15 with repeat administration on days 168 and 182 provided specific safety criteria have been met.2

Rituximab is currently licensed in the UK for:3

- Treatment of severe active rheumatoid arthritis in patients whose condition has not responded adequately to other disease-modifying antirheumatic drugs (including one or more tumour necrosis factor inhibitors) or who are intolerant of them (in combination with methotrexate)
- Treatment of previously untreated stage III–IV follicular lymphoma (in combination with other chemotherapy)
- Maintenance therapy in patients with follicular non-Hodgkin’s lymphoma that has responded to induction therapy (in combination with other chemotherapy)
- Treatment of diffuse large B-cell non-Hodgkin’s lymphoma (in combination with other chemotherapy)
- Treatment of chemotherapy-resistant or relapsed stage III–IV follicular non-Hodgkin’s lymphoma,
- Previously untreated or relapsed chronic lymphocytic leukaemia
- Induction of remission in patients with severe, active granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis (in combination with glucocorticoids)

The most common side effects (affecting more than 1 in 10 people) with rituximab intravenous infusions are reactions related to the infusion (such as fever, chills and shivering) while most common serious side effects are infusion reactions, infections and heart-related problems. Similar side effects are seen when rituximab is injected under the skin, with the exception of reactions around the injections site (pain, swelling and rash), which occur more frequently with the skin injections.4 For further details about adverse drug reactions, see the summary of product characteristics (smPC).1
Rituximab is in phase II stage of development for the treatment of glomerulonephritis.\textsuperscript{5,6,7,8}

**INNOVATION and/or ADVANTAGES**

There is currently no curative therapy for pemphigus vulgaris, but treatment can help keep the symptoms under control. Most people require corticosteroids in the adjuvant setting to help control the condition.\textsuperscript{9} This allows for improved efficacy, minimised dosing and reduces the side effects associated with corticosteroids.\textsuperscript{10} Rituximab can currently be used as a second line adjuvant in the treatment of PV.\textsuperscript{11} Clinical evidence has suggested that first-line use of rituximab in addition to short-term prednisone for patients with pemphigus can be more effective than using prednisone monotherapy and is associated with fewer adverse events.\textsuperscript{12} If licensed, rituximab may offer an additional treatment option for patients with PV after failure of systemic steroids and steroid sparing agents to control the disease.

**DEVELOPER**

Roche Products Ltd

**REGULATORY INFORMATION/ MARKETING PLANS**

Rituximab received Orphan Drug designation in the USA for the treatment of pemphigus vulgaris in February 2015.\textsuperscript{13}

Rituximab received Breakthrough Therapy designation for pemphigus vulgaris by FDA in March 2017.\textsuperscript{14}

Rituximab was granted Priority review designation for pemphigus vulgaris by FDA in February 2018.\textsuperscript{15}

**PATIENT GROUP**

**BACKGROUND**

Pemphigus is a group of rare autoimmune diseases that cause blistering of the skin and mucous membranes. Pemphigus types include pemphigus vulgaris (PV), pemphigus foliaceus, pemphigus vegetans, IgA pemphigus and paraneoplastic pemphigus. These classifications are based on the location of where the blisters form. PV is a rare and serious condition that causes painful blisters to develop on the skin and the mucous membrane lining of the mouth, nose, throat and genitals. It is an autoimmune disease where Immunoglobulin G (IgG) antibodies target desmogleins. Desmogleins are found in the cells in epidermis and they function as an adhesive, helping the cells join together. When desmogleins are attacked by autoantibodies, the cells in the skin and mucous membranes begin to separate from the epidermis causing acantholysis. This causes the blisters and erosions that characterise PV. It is unclear what causes the immune system to act in this way, however certain genes have been linked to an increased risk of PV, although it doesn’t tend to run in families.\textsuperscript{9,16,17,18,19,20}

The blisters associated with PV are fragile and can easily erupt, leaving areas of raw unhealed skin that are very painful and can increase the risk of infections. PV is a relapse-remitting condition where there are periods of severe blistering, known as “flare-ups” followed by periods when they heal and begin to fade, when the disease is in remission. The sores on the skin can join together to form large areas of painful, raw-looking skin, before crusting over and forming scabs. They do not usually leave any scars, although the affected skin can occasionally become permanently discoloured. Blisters in the mouth are usually painful and interfere with eating and drinking which can lead to weight loss.\textsuperscript{9,16}
There is currently no cure for PV. It cannot be predicted when and how severe the flares up of the sores will be. However, treatment can help keep the symptoms under control. PV has been associated with debilitating morbidity caused by anxiety, depression and impaired quality of life. Infection and sepsis are a significant risk and a major cause of mortality in PV.

**CLINICAL NEED and BURDEN OF DISEASE**

A retrospective historical cohort study investigated the incidence and mortality of PV in the UK. Patients with a diagnosis of PV between 1996 and 2006 were identified from the health improvement network database. The crude incidence of PV was 0.68 (range: 0.58 to 0.80) per 100,000 person years. Incidence was higher in women and in older age groups. Applying these data to the UK population between 2001 and 2005 gave an average of 467 (range: 297 to 643) new cases of PV a year. The overall crude mortality was 94.64 (range: 68.268 to 131.205) per 1000 person years for PV. Applying the mortality data to the UK population data between 2001 and 2005 gave 221 deaths in PV cases. This is a much higher figure than the 36 deaths attributed to this diseases in the Office for National Statistics dataset.

In 2016-17 there were 216 hospital admissions for pemphigus vulgaris (ICD 10 code: L10.0) in England, which resulted in 251 finished consultant episodes (FCE), and 847 FCE bed days.

PV affects all races and both sexes. It most commonly presents between the ages of 50-60 years, but can affect any age, although rarely children. Pemphigus is estimated to affect anywhere from 0.7-5 people per 1,000,000 per year in the general population. PV is the most common form of pemphigus and is the most common form in Europe and the United States. In the EU, pemphigus affects 1.4 in 10,000 which equates to 14 per 100,000. Applying this to England and Wales population taken from the UK 2016 mid-year population estimates, gives approximately 8,173 cases of pemphigus in England and Wales.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE GUIDANCE**

No relevant guidance could be identified.

**NHS ENGLAND and POLICY GUIDANCE**


**OTHER GUIDANCE**


- The European Dermatology Forum (EDF) and the European Academy of Dermatology and Venereology (EADV). Pemphigus. S2 Guideline for diagnosis and treatment--guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). 2015.
CURRENT TREATMENT OPTIONS

According to the British Association of Dermatologists’ guidelines for the management of pemphigus vulgaris, treatment of PV consists of two phases.\(^\text{10}\)

- **Remission induction:** this is to induce disease control in terms of cessation of new lesions formation and the start of healing of established lesions. Corticosteroids are critical in this phase as they are the most effective and rapidly acting treatment for PV. Adjuvant drugs are usually initiated during this phase. When disease control is achieved the consolidation phase begins when approximately 80\% of the lesions (both mucosal and skin) have healed and no new lesion have developed for at least 2 weeks. At the end of the consolidation phase, tapering of treatment starts, usually involving corticosteroid dose.

- **Remission maintenance:** during this phase, treatment is gradually reduced, to minimise the side effects, to the lowest dose required to maintain disease control. The ultimate goal of treatment should be to maintain remission on prednisolone 10 mg daily or less, with 10 mg being the dose designated arbitrarily as ‘minimal therapy’ by international consensus. Systemic corticosteroids are the core elements of the remission induction and consolidation. Adjuvant drugs are usually combined with corticosteroids to improve the efficacy and minimising the doses and side effects of corticosteroids.

Until 2017 there had been no prospective, high-quality controlled studies that demonstrated conclusively the presumed benefits of adjuvant drugs in PV. Therefore, some authorities have not used adjuvant drugs unless there were contraindications or side-effects of corticosteroids, or if tapering the corticosteroids dose was associated with repeated relapses.\(^\text{10}\)

Adjuvant drugs used in PV treatment include:\\(^\text{11}\)

- **First line adjuvants:**
  - Azathioprine (1–3 mg/kg/day)
  - Mycophenolate mofetil (2 g/day) or mycophenolic acid (1440 mg/day).

- **Second line adjuvants:**
  - Anti-CD20 monoclonal antibody, such as rituximab 2 x 1 g i.v. (2 weeks apart) or 4 x 375 mg/m\(^2\) (each 1 week apart)
  - Intravenous immunoglobulins (IVIG) (2 g/kg/month)
  - Immunoadsorption (two cycles a four consecutive days are performed 4 weeks apart)
  - Cyclophosphamide (500 mg as i.v. bolus or given orally at 2 mg/kg/day)
  - Methotrexate (10–20 mg/week)
  - Dapsone 100 mg/day or up to 1.5 mg/kg/day
# EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02383589, 2014-000382-41; rituximab vs mycophenolate mofetil (MMF) both in combination with a matching placebo; phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Hoffmann-La Roche.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Source of Information</td>
<td>Trial registry2</td>
</tr>
<tr>
<td>Location</td>
<td>EU (not UK), USA, Canada and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, active-comparator, double-blind, double-dummy, parallel-arm, multicentre.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=124 (planned); aged 18-75 years; males and females; confirmed diagnosis of PV within the previous 24 months; moderate-to-severely active disease; receiving standard-of-care corticosteroids consisting of 60-120 mg/day oral prednisone or equivalent.</td>
</tr>
</tbody>
</table>
| Schedule | Randomised to:  
- Rituximab by IV infusion administered at a dose of 1000 mg on days 1 and 15 with repeat administration on days 168 and 182 provided specific safety criteria have been met. Participants will also receive MMF matching placebo orally every 12 hours (Q12H) from day 1 to week 52.  
Or  
- MMF orally administered at a starting dose of 500 mg Q12H from Day 1 to week 52. Participants will also receive rituximab matching placebo by IV infusion on days 1 and 15 with repeat administration on days 168 and 182 provided specific safety criteria have been met. |
| Follow-up | Active treatment for 52 weeks, follow-up 48 weeks. |
| Primary Outcomes | Percentage of participants who achieve sustained complete remission, evaluated by the pemphigus disease area index (PDAI) activity score [time frame: from baseline up to 52 weeks] |
| Secondary Outcomes |  
- Time frame: from baseline up to 52 week:  
  - Time to Protocol Defined Disease Flare  
  - Cumulative Oral Corticosteroid Dose  
  - Duration of Sustained Complete Remission, Evaluated by the PDAI Activity Score  
  - Protocol Defined Disease Flares  
  - Time to Initial Sustained Complete Remission, Evaluated by the PDAI Activity Score  
- Time Frame: Baseline, Weeks 12, 24, 40, and 52:  
  - Change in Health-Related Quality of Life (HRQoL), as Measured by the Dermatology Life Quality Index (DLQI) Score  
  - Change in Participants Impression of PV Symptoms, as Measured by the Patients' Global Impression of Change (PGIC) Questionnaire Score  
  - Change in Clinician Impression of Participant's PV Symptoms, as Measured by the Clinician Global Impression of Change (CGIC) Questionnaire Score  
- Percentage of Participants With Adverse Events, Serious Adverse Events, and Corticosteroid-Related Adverse Events [Time Frame: Baseline up to 100 weeks] |
- Percentage of Participants With Human Anti-Chimeric Antibody (HACA) [Time Frame: Baseline; Weeks 24 and 52/early withdrawal; 48 weeks after end of treatment (end of treatment: up to Week 52)]
- Blood Lymphocyte Levels [Time Frame: Baseline; Weeks 2, 4, 8, 16, 24, 26, 40 and 52; 12, 24, 36, 48 weeks after end of treatment (end of treatment: up to Week 52)]
- Plasma Immunoglobulin (Ig) Levels [Time Frame: Baseline; Weeks 16, 24, 40 and 52; 12, 24, 36, 48 weeks after end of treatment (end of treatment: up to Week 52)]

Key Results

Adverse effects (AEs)

Expected reporting date

Study completion date is reported as November 2019.

Trial

Rituximab 3, NCT00784589; rituximab vs general corticotherapy; phase III

Sponsor

University Hospital, Rouen.

Status

Published

Source of Information

Publication; trial registry

Location

France

Design

Randomised, parallel assignment, open label.

Participants

n=90; aged 18-80 years; males and females; new case of PV or pemphigus foliaceus (PF).

Schedule

Participants were randomised in 1:1 ratio to:

- Rituximab (IV) combined with a short-term prednisone regimen
  - For patients with severe pemphigus: rituximab was given at a dose of 1mg/kg/d for 1 month, then 0.75 mg/kg/d for 1 month, then 0.5 mg/kg/d for 1 month, then 0.3 mg/kg/d for 1 month, then 0.2 mg/kg/d for 1 month, then 0.1 mg/kg/d for 1 month.
    Oral prednisone (Cortancyl) was given once per day at an initial dosage of 1.0 mg/kg per day for 1 month and thereafter gradually reduced after achievement of disease control, with the aim to stop prednisone after 6 months.

  - For patients with moderated pemphigus: prednisone was given at a dose of 0.5mg/kg/d for 1 month, then 0.30 mg/kg/d for 1 month, then 0.2 mg/kg/d for 1 month.
    Oral prednisone was given once per day at an initial dosage of 0.5 mg/kg per day for 1 month and thereafter gradually reduced after achievement of disease control, with the aim to stop prednisone after 3 months.

  Or

General Corticotherapy (prednisone) alone:

- For patients with severe pemphigus: prednisone was given at an initial dose of 1.5 mg/kg per day. The initial dose of prednisone was maintained for 1 month, and thereafter gradually tapered in patients who achieved disease control to stop prednisone after 18 months in patients.

- For patients with moderated pemphigus: prednisone was given at an initial dose of 1.0 mg/kg per day. The initial dose of prednisone was maintained for 1 month.
month, and thereafter gradually tapered in patients who achieved disease control to stop prednisone after 12 months.12

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Active treatment for 6 months (for patients with severe pemphigus) and 3 months (for patients with moderate pemphigus) Follow-up for 3 years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcomes</td>
<td>The proportion of patients who achieved complete remission off-therapy at month 24.</td>
</tr>
</tbody>
</table>
| Secondary Outcomes | • The proportion of patients who achieved complete remission on minimum therapy at month 24  
• Delay to achievement of complete  
• Remission off-therapy  
• Cumulative duration of complete remission off-therapy during the study;  
• Relapse occurrence;  
• Cumulative dose of prednisone during the study  
• Time change of DLQI and skindex quality of life scores  
• Concentration of desmoglein-specific B-lymphocytes and desmoglein-specific antibodies at months 12 and 24; occurrence of severe treatment  
• Adverse events (grade 3 or 4, or death from any cause).12 |
| Key Results | Between May 10, 2010, and Dec 7, 2012, we enrolled 91 patients and randomly assigned 90 to treatment (90 were analysed; 1 patient withdrew consent before the random assignment). At month 24, 41 (89%) of 46 patients assigned to rituximab plus short-term prednisone were in complete remission off-therapy versus 15 (34%) of 44 assigned to prednisone alone (absolute difference 55 percentage points, 95% CI 38·4–71·7; p<0·0001). This difference corresponded to a relative risk of success of 2·61 (95% CI 1·71–3·99, p<0·0001), corresponding to 1·82 patients (95% CI 1·39–2·60) who would need to be treated with rituximab plus prednisone (rather than prednisone alone) for one additional success. Data from the trial suggest that first-line use of rituximab plus short-term prednisone for patients with pemphigus is more effective than using prednisone alone, with fewer adverse events.12 |
| Adverse effects (AEs) | More severe adverse events of grade 3–4 were reported in the prednisone-alone group (53 events in 29 patients; mean 1·20 [SD 1·25]) than in the rituximab plus prednisone group (27 events in 16 patients; mean 0·59 [1·15]; p=0·0021). The most common of these events in both groups were diabetes and endocrine disorder (11 [21%] with prednisone alone vs six [22%] with rituximab plus prednisone), myopathy (ten [19%] vs three [11%]), and bone disorders (five [9%] vs five [19%]).12 |
| Expected reporting date | - |
**ESTIMATED COST and IMPACT**

### COST

Rituximab is already marketed in the UK for a variety of indications. The NHS indicative price for rituximab solution for infusion vials is as follows:\(^\text{28}\)

- MabThera 100mg/10ml concentrate for solution for infusion vials (2 vials) (Roche Products Ltd) costs £349.25
- MabThera 500mg/50ml concentrate for solution for infusion vials (Roche Products Ltd) (1 vial) costs £873.15
- Rixathon 100mg/10ml concentrate for solution for infusion vials (2 vials) (Sandoz Ltd) costs £314.33
- Rixathon 500mg/50ml concentrate for solution for infusion vials (1 vial) (Sandoz Ltd) costs £785.84
- Truxima 100mg/10ml concentrate for solution for infusion vials (2 vials) (Napp Pharmaceuticals Ltd) costs £314.33
- Truxima 500mg/50ml concentrate for solution for infusion vials (1 vial) (Napp Pharmaceuticals Ltd) costs £785.84

### IMPACT – SPECULATIVE

#### IMPACT ON PATIENTS AND CARERS

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

#### 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
- None identified

#### IMPACT ON COSTS and OTHER RESOURCE USE

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs: \textit{additional costs for IV administration in clinic}
- Other reduction in costs
OTHER ISSUES

☐ Clinical uncertainty or other research question identified  ☒ None identified

REFERENCES


