Rituximab Surveillance Registry in Vasculitis (RIVAS)

Annual Report 2021

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1 Research question and objectives

RIVAS is a secondary use of data study aiming to provide long-term safety data from the use of rituximab (MabThera®) and other available therapies for patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA).

The primary objective of this study is:

- To provide long-term safety data on rituximab (MabThera®)-treated patients with GPA/MPA.

The secondary objectives are:

- To estimate the incidence of serious adverse events (SAEs), including infections, cardiovascular events and malignancy, following rituximab (MabThera®) or other available treatments in patients with GPA/MPA

- To compare the incidence of each safety event over time between the rituximab (MabThera®)-treated GPA/MPA cohort and a GPA/MPA cohort treated with other available therapies

2 Study design and population

The RIVAS study aims to provide long-term safety data in patients with GPA/MPA exposed to rituximab (MabThera®). Occurrences of serious adverse events (SAEs) and medically significant events, e.g. hypogammaglobulinemia, malignancies or neutropenia will be recorded in patients who received MabThera® and compared to a control cohort treated with other available therapies.

RIVAS is a non-interventional secondary data study designed to evaluate the long-term safety of rituximab (MabThera®) in a real-world setting. The initial study design (Protocol Version 1.2, March 2016) aimed to follow 500 patients with GPA/MPA who received rituximab (MabThera) (rituximab cohort) or other available treatments (control cohort) as part of their standard clinical care over a period of five years (2016 to 2021). Following the introduction of the rituximab biosimilar (Truxima) at Cambridge University Hospitals in September 2017, the study was changed from prospective to retrospective design in a substantial amendment (July 2018).

For the retrospective study design, 400 patients were to be recruited and based on rituximab (MabThera®) exposure status assigned to the rituximab or the control cohort. Patients in the rituximab cohort will have received ≥ 1 MabThera® course, whereas patients in the control cohort will have never received MabThera®. Baseline/entry point is the date of first MabThera® treatment since 2003 (year of first use of rituximab in CUH, rituximab cohort), and time of first disease flare/diagnosis since 2003 for the control cohort. Study data were collected at baseline and at least every 12 months thereafter until September 2018. Follow-up periods include the entire study period, even after rituximab discontinuation or start of another therapeutic agent. Data collection focused on serious adverse events and targeted medically significant events.

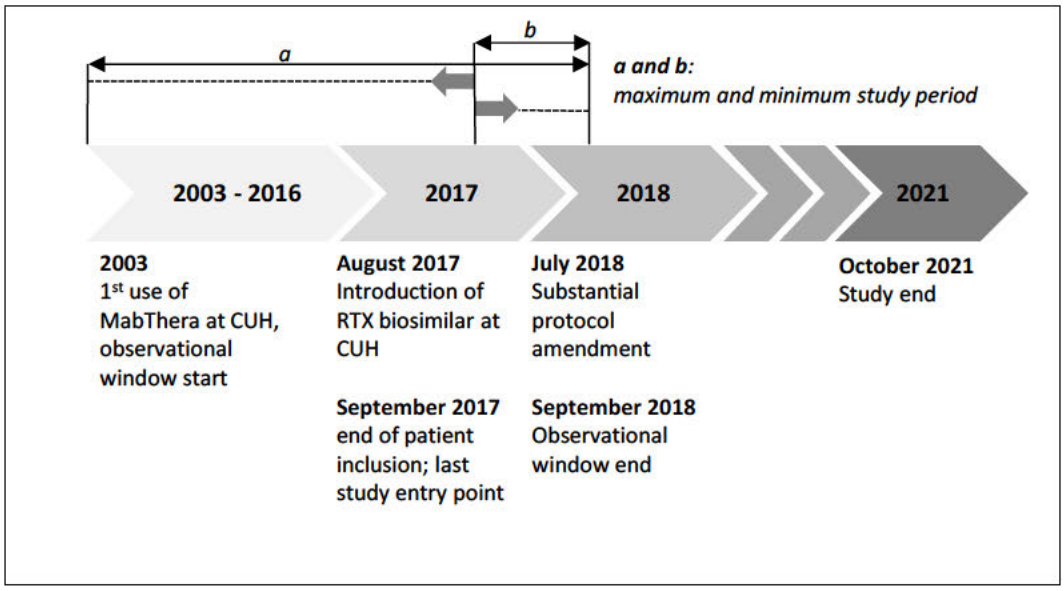

***Figure 1**: Timeline RIVAS. Entry point for the rituximab cohort is defined as the date of first MabThera® treatment since 2003 whereas the control group patients enter the study at a time of first disease flare/diagnosis since 2003. September 2017 and 2018 defined as the latest study entry and end points respectively, the observational windows span a treatment period between one and 15 years.*

Patients must meet the following criteria for study entry:

1. A clinical diagnosis of GPA/MPA through use of the consensus algorithm for the classification of ANCA vasculitis and polyarteritis nodosa (European Medicines Agency, Abdulkader et al 2013)

2. Age ≥ 18 years

3. Have given informed consent to participate in the UKIVAS registry

4. Have given informed consent to participate in the RIVAS study

5. Any patient with GPA/MPA who has received rituximab (MabThera®) for vasculitis since 2003 (rituximab (MabThera®) group)

6. Any GPA/MPA patient with disease flare since 2003 who has not received rituximab (disease control group)

Patients who meet any of the following criteria will be excluded from study entry:

- Patients with eosinophilic granulomatosis with polyangitis (EGPA/Churg-Strauss)
- Unwilling or unable to provide written informed consent for the UKIVAS registry
- Unwilling or unable to provide written informed consent for the RIVAS study

Patients with significant concomitant disease (e.g. cancer, HIV/AIDS) will not be excluded from the study. Significant concomitant diseases will be considered at the analysis stage. All patients provided written informed consent.

3 Data sources and management

All data included in RIVAS are obtained by the investigational site and entered in the UKIVAS registry based in Oxford, UK. The Marketing authorisation holder (MAH, Roche) does not have any influence in the data collection nor the registry design. MAH will not receive any patient-level data nor have direct access to registry data. RIVAS will include data from all consented GPA/MPA patients who have received rituximab (MabThera®) in Cambridge at any time since 2003 and all consented GPA/MPA patients treated with other agents. The total target study sample size is 400.

The recorded observational data window (data extraction period) will be from the participant's first exposure to rituximab (MabThera®) or flare of vasculitis/diagnosis requiring an alternative immunosuppressive to rituximab (MabThera®), up to the last recorded encounter date before 30th September 2018.

All baseline data and event data between assessment time points, will be derived from information routinely collected from the Hospital Patient Record. The investigational site will be responsible for management of the extracted data, including quality checking of the individual data points. Aggregate data reports will be transferred to the MAH at annual intervals as specified in the Statistical Analysis Plan. Patient confidentiality will be respected and all data transmitted to the study database will be anonymous. Quality control will be achieved by back checking periodically from the UKIVAS registry against a sample of primary data sheets.

A weakness of any retrospective study format is that original data were part of a clinical database and not collected in the required study format, and some data may be missing or were inconsistently measured between patients.

4 Bias

This observational, longitudinal, non-interventional study design aims to evaluate the risk profile of rituximab and other available treatment regimens in patients with either GPA or MPA in a real-world setting. As an observational cohort study there are risks of selection biases. There may be unobserved

confounders that influence both a participant's future event rate and the choice to prescribe rituximab (MabThera®).

The observational study window starts for both cohorts at a time of diagnosis/disease flare. The rituximab cohort received MabThera® as a first treatment option for newly diagnosed patients, or at a time of disease flare after alternative treatment options had failed. Hence the rituximab cohort may possibly be composed of a sicker patient population who are later on in their disease course; the direction of biases thus may favour the control cohort and the comparison between the cohorts could be viewed as conservative. However, this will remain as an assumption, as the data cannot provide any further information on the magnitude of such potential biases.

It is possible that patients with GPA/MPA who participate in this single-center study may not be representative of the population as a whole, however, both indications are relatively rare and this may mitigate any lack of representativeness. The statistical methods used in the generation of the cumulative and final report provided to the MAH are intended to reduce the possibility of the introduction of bias or error into the findings by adjusting for baseline covariates and potential confounders. Nevertheless, residual bias could still persist due to unmeasured or imprecisely measured confounding factors.

5 Results

5.1 Patients

Of 420 patients enrolled in the study, 247 patients received at least one dose of MabThera® and entered the rituximab group, 145 entered the control group. 28 patients were excluded from the retrospective study due to death, study withdrawal by patient, loss to follow-up or not meeting inclusion criteria (Figure 2, patient disposition). 5 patients who provided written consent to the prospective study design died before reconsent and were excluded from the retrospective study. None of the deaths were considered to be treatment-related. 50% of the rituximab and 56% of the control cohort were female, with the majority (93%) being white British. With a mean ± SD age of 58.2 ± 17.1 years, the MabThera® group was slightly younger than the control group (65.6 ± 13.6 years). In particular, patients under the age of 50 were three times more likely to be in the MabThera® group. The predominant diagnosis was GPA (82% in the rituximab group and 69% in the control group) and ANCA serotype PR3-ANCA. Considerable baseline differences between both groups were observed for the mean disease duration (55.3 months for the rituximab and 33.2 months for control patients), items in the Vasculitis Damage Index (VDI) (mean, 1.5 for the rituximab and 0.5 for the control group) and immunoglobulin IgG level (9.1, 95% CI 8.6 – 9.5 (rituximab) and 11.8, 95% CI 11.0 – 12.6 (control)) (Table 1).

The baseline imbalances reflect the predominant use of MabThera® for relapsing or refractory disease in line with NHS guidelines, where there is a longer disease course, with more diagnoses of GPA and PR3-ANCA, both factors associated with relapse risk. Also, GPA has a mean age at diagnosis of 58 years compared to 65 years for MPA, so a younger preponderance of MabThera® exposed. The higher VDI reflects more items of irreversible disease or treatment related damage in the MabThera® group consistent with a longer disease course with more episodes of vasculitic activity. This treatment group will also have had a higher exposure to glucocorticoids and non-rituximab therapies. Conversely, older patients with MPA are more likely to have severe kidney disease, and this is reflected in the lower baseline GFR in the control group.

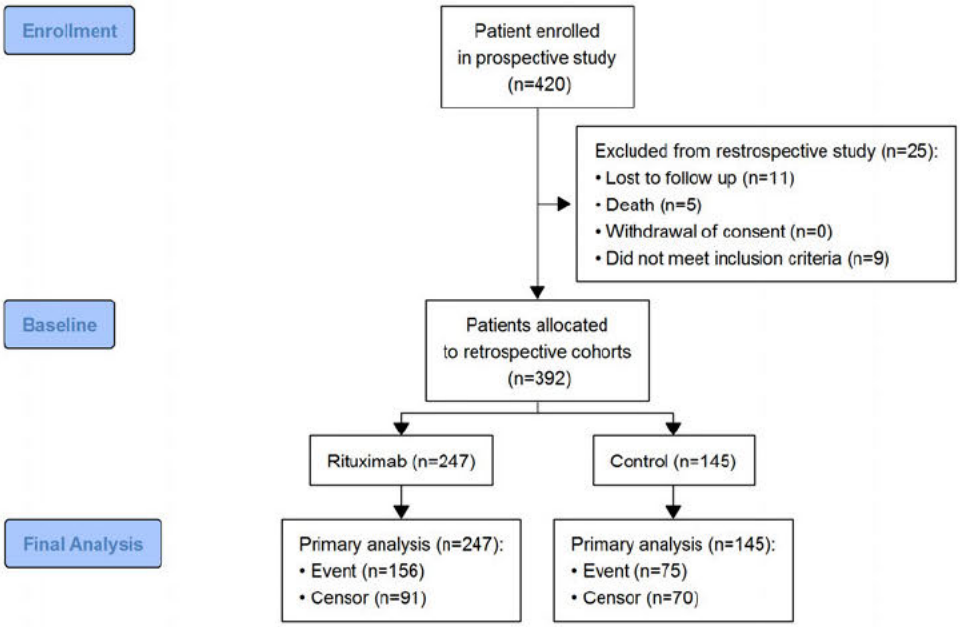

***Figure 2**: Study patient disposition*

***Table 1**: Patient demographics and baseline characteristics*

Characteristic	Safety population	
	MabThera® group (n=247)	Control group (n=145)
Total person years	1369.7	847.8
Age (years), mean ± SD years	58.3 ± 17.1	65.6 ± 13.6
Age category		
18-50 years	81 (33%)	17 (12%)
>50 years	166 (67%)	128 (89%)
Female sex	124 (50%)	81 (56%)
Ethnicity		
White British	230 (93.1%)	135 (93.1%)
other White	10 (4.0%)	6 (4.1%)
Asian	6 (2.5%)	2 (1.4%)
other	1 (0.4%)	2 (1.4%)
GPA	203 (82%)	99 (69%)
MPA	44 (18%)	46 (32%)
Disease duration at baseline, mean (SD) months	55.3 (70.2)	33.2 (63.8)
median	25	1.6
min, max	0, 393.7	0, 272.6
ANCA antigen type at diagnosis		
Myeloperoxidase	28 (11%)	45 (31%)
Proteinase 3	104 (58%)	53 (37%)
VDI score baseline mean (SD)	1.5 (1.6)	0.5 (1.1)
VDI score study end mean (SD)	2.8 (2.3)	1.7 (1.6)
IgG mean baseline (95% CI)	9.1 (8.6; 9.5)	11.8 (11.0; 12.6)
IgG median baseline (95% CI)	8.6 (8.1; 9.1)	10.9 (10; 11.7)
eGFR baseline	74.2 (69.8; 78.6)	60.7 (54.8; 66.6)

GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; ANCA = antineutrophil cytoplasmic autoantibody; VDI = Vasculitis Damage Index; eGFR = estimated glomerular filtration rate

A study duration cohort comparison showed fairly evenly-matched patient year follow-up throughout the observational window, however 20% of the control cohort patients entered the study in 2017 and had a shorter follow up of 1 to 1.5 years (Figure 3).

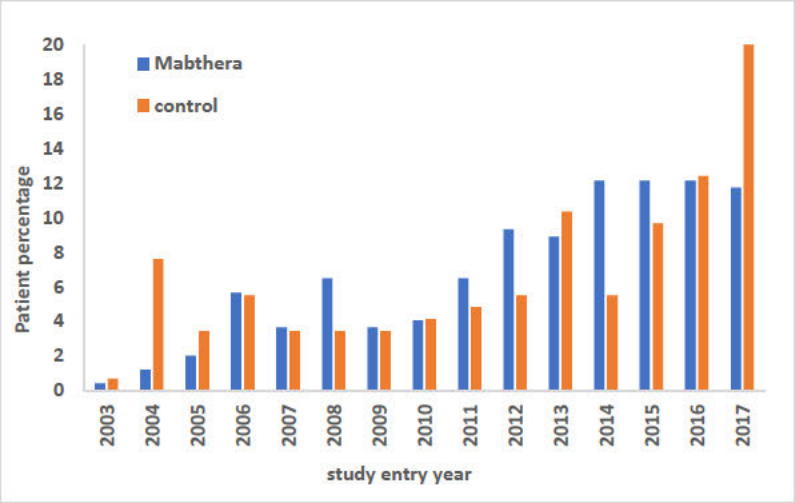

Figure 3: RIVAS study entry year by patient percentage.

The MabThera® group had a more complex immune-suppressant medication history prior to study entry (Figure 4(a)). Glucocorticoids (steroids) (96%) and cyclo-phosphamide (70%) were most widely used, followed by azathioprine (58%) and mycophenolate mofetil (MMF) (40%). Reflecting more newly diagnosed patients only 60% of the control group had received steroids before RIVAS entry, with 20% receiving azathioprine and cyclophosphamide. Baseline treatment at time of RIVAS enrolment (Figure 4(b)) involved most frequently cyclophosphamide and steroids for control patients and, as protocol-specified, MabThera® for patients in the rituximab cohort.

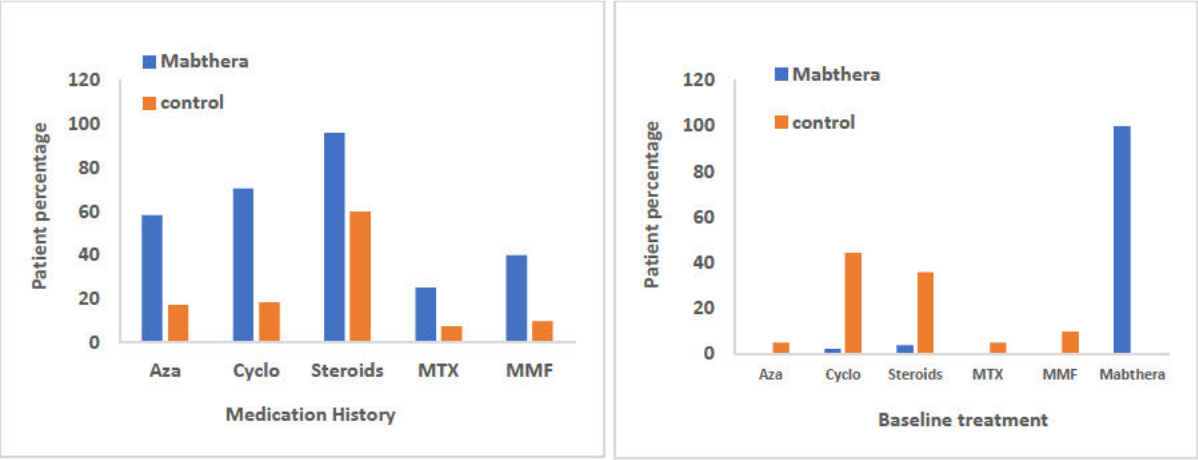

Figure 4 (a) and (b): Cohort comparison of medication history and baseline treatment

Co-morbidities in the two groups are shown in Figure 5. The most frequently reported comorbidities were hypertension (40% across both groups), pulmonary and kidney disease (18% and 16% in the MabThera® and control groups). Venous thrombotic events (DVT, PE) were three times higher in the control group.

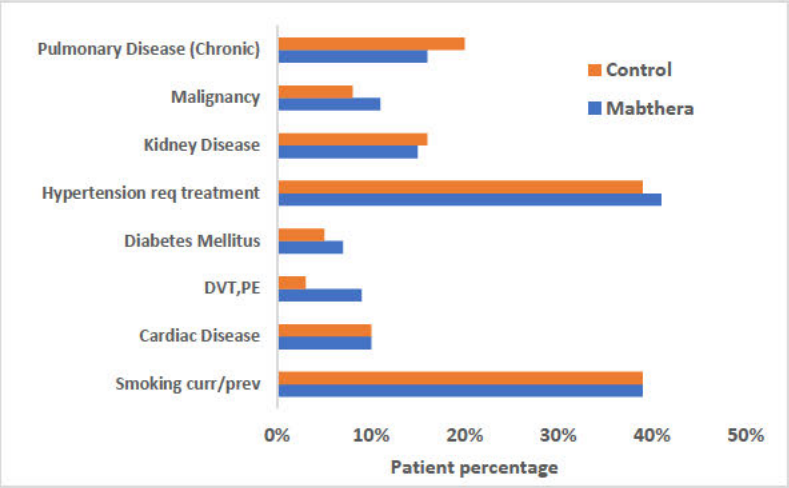

Figure 5: Co-morbidities at baseline

5.2 Rituximab Treatment

247 patients received ≥1 dose of MabThera®. The mean MabThera® treatment duration was 5.5 years for a total of 1369.7 patient years (PY); patients received a mean of 7 (range 1 to 23) infusions during the entire study follow-up period. Overall, 97% of patients received ≥ 2 doses of MabThera®, 87% ≥ 3 doses and 28% 10 doses or more. From 2003 to 2007 rituximab was given at time of disease flare only, with both 375 mg/m^2/week x 4 and 1000mg x 2 regimens employed, while from 2007 a 2-year regimen of 1000 mg x 2 induction at time of relapse followed by 1000 mg / 6 months x 4 was used to prevent relapse. After this two year period rituximab was recommenced at the time of further relapse with a subsequent relapse prevention rituximab interval of 6-12 months, tailored to individual patient responses. Rituximab was increasingly used after 2007 for remission induction of newly diagnosed patients in whom cyclophosphamide was contra-indicated. Steroids were continued for 4-6 months after first rituximab and then steroid withdrawal was typically attempted. As a routine oral immunosuppressives, such as azathioprine or methotrexate were stopped at the time of first rituximab treatment. Some patients presenting with a new diagnosis of severe renal vasculitis were treated with the combination of rituximab and short course IV cyclophosphamide (as defined in the RITUXVAS trial), otherwise rituximab induction was accompanied by steroids but not an immune suppressive.

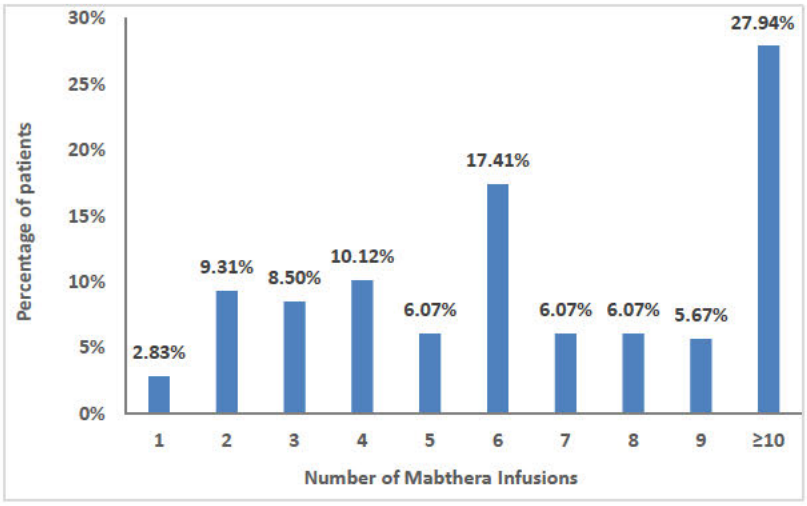

Figure 6: Number of MabThera® infusions received in the rituximab group

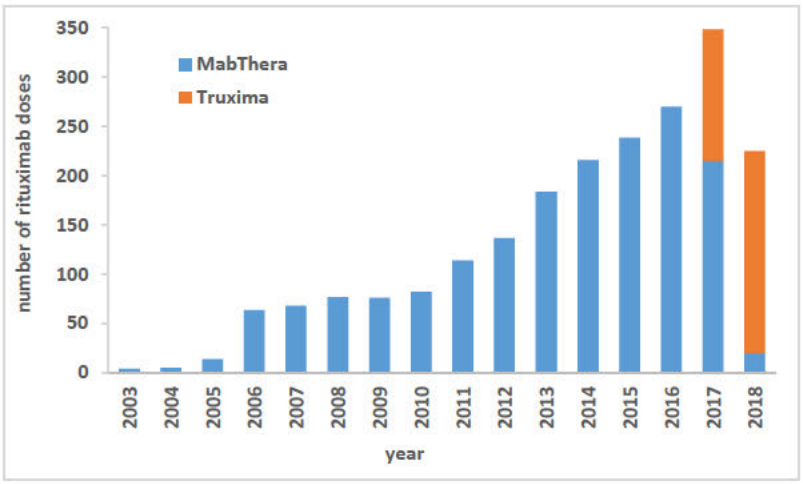

Figure 7: Annual number of rituximab doses (combined MabThera® and rituximab biosimilar Truxima) for GPA/MPA patients at CUH from 2003 to Sep 2018.

The increase in number of rituximab infusions over time is shown in Figure 7, the increase in use after 2010 reflecting the use in relapse prevention as well as for induction. GPA/MPA patients at CUH received 2,125 rituximab infusions between 2003 and September 2018, including 1,785 MabThera® doses with an average of 7 infusions per patient. With the introduction of the biosimilar Truxima in August 2017, the number of MabThera® treatments fell (Figure 7) from 270 in 2016 to 215 in 2017 and 20 infusions from January to September 2018. According to the substantial amendment in July 2018, Truxima did not affect group affiliation after original group assignment.

5.3 Safety

Serious Adverse Events

Per protocol, recorded safety events included SAEs (defined as any AEs that were life-threatening or fatal, required or prolonged hospitalization, resulted in significant disability, congenital anomaly, or a birth defect) or were medically significant in the investigator's opinion. A total of 735 SAEs and medically important events were reported, 552 events for the rituximab and 183 for the control cohort (Table 2). A brief summary of the safety event analysis with crude incidence rates (IRs) and 95% confidence intervals is given below. IRs are expressed as events per 1000 patient-years (PYs) and were calculated as the total number of events during the study period divided by the sum of PY follow-up.

Table 2. *Serious adverse events and event category for Mabthera and control groups*

		Number of events with % of patients with events	IR per 1000 PY (95% CI)
All SAEs	MabThera®	552 in 164 pts (66.4%)	403.0 (339.4-478.6)
	control	183 in 78 pts (53.8%)	215.8 (150.9-308.6)
Serious Infection	MabThera®	130 in 68 pts (27.5%)	94.9 (79.9, 112.7)
	control	30 in 20 pts (13.8%)	35.4 (24.7, 50.6)
Cardiovascular disorder	MabThera®	43 in 36 pts (14.6%)	31.4 (23.3, 42.3)
	control	23 in 19 pts (13.1%)	27.1 (18, 40.8)
Haematological events	MabThera®	38 in 33 pts (13.4%)	27.7 (20.2, 38.1)
	control	12 in 12 pts (8.3%)	14.2 (8, 24.9)
Malignant events	MabThera®	29 in 22 pts (8.9%)	21.2 (14.7, 30.5)
	control	21 in 16 pts (11.0%)	24.7 (16.1, 38)
Renal Insufficiency	MabThera®	21 in 15pts (6.1%)	15.3 (10, 23.5)
	control	27 in 18 pts (12.4%)	31.8 (21.8, 46.4)
PML	MabThera®	1 in 1 pt (0.4%)	0.7 (0.1, 5.2)
	control	0	0 (0, NaN)
Additional safety events	MabThera®	290 in 123pts (49.8%)	211.7 (188.7, 237.6)
	control	70 in 49pts (33.8%)	82.6 (65.3, 104.4)

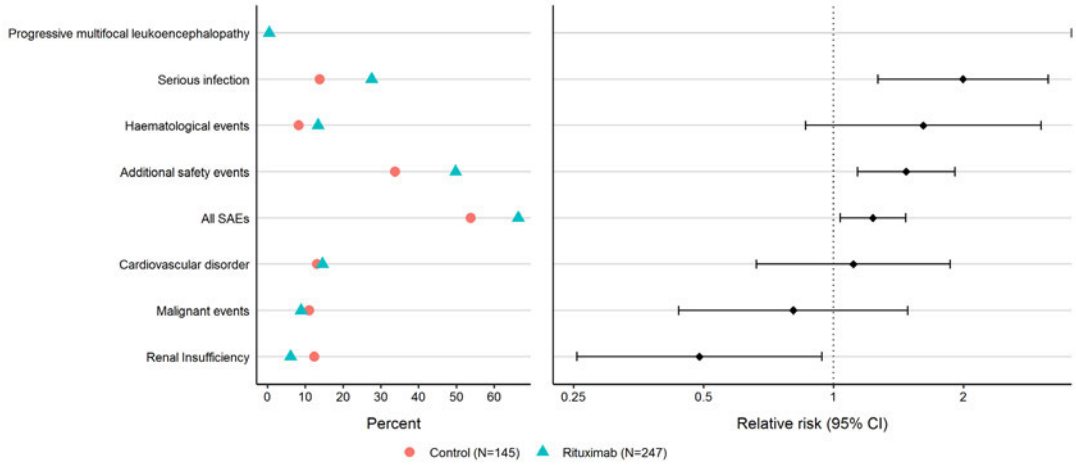

Figure 8: Incidence and Relative Risk of SAEs for Mabthera compared to control group, overall and by category

Infections

A total of 130 infection events in 68 patients (27.5%) were described for the rituximab cohort, and 30 events in 20 patients (13.8%) for the control cohort. The types of infections reported included lower respiratory tract infections (98), septicaemia (13), herpes infection (1) and other infections (48) across the whole study population. Multiple (≥2) infections were reported in 36% (90/247) of the rituximab cohort and 10% (15/145) of the control cohort population.

Progressive multifocal leucoencephalopathy

One case of Progressive Multifocal Leukoencephalopathy occurred in the rituximab group. This is a well-recognised but rare, complication of rituximab therapy although the frequency in GPA/MPA patients is not known, several cases have been reported. This case survived but with neurologic damage.

Cardiovascular events

66 cardiovascular events were observed during the study across the whole study population: venous thrombotic events (DVT, PE) (27), coronary artery disease (2), haemorrhagic events (2), myocardial infarction (6), and other cardiovascular events (29). Single cardiovascular events were seen in 11% (rituximab) and 10% (control) of the cohort populations, 2 events were experienced by 5.5% in each cohort. GPA/MPA patients are known to have an increased risk for cardiovascular and thromboembolic events, especially associated with periods of higher disease activity.

Malignancy

Patients with GPA/MPA have a higher incidence of malignancy, especially non-melanoma skin cancer, urothelial and lymphoproliferative malignancy. This has been attributed to the use of alkylating agents such as cyclophosphamide and anti-metabolites such as azathioprine. There has been a report of reduced malignancy rates in GPA/MPA populations treated with rituximab, presumably due to lower exposure to oncogenic agents. In view of the exposure of patients in both groups to these drugs it was unlikely that any differences in malignancy would be seen, which was confirmed in the study, indeed the frequency was relatively low for a population of those age with the duration of follow-up seen.

Haematologic events

Neutropenia was reported in 23 of the MabThera® and 3 in the control groups. Late onset neutropenia is a recognised complication of rituximab therapy, but also occurs as a complication of oral immune suppressive therapies and cyclophosphamide.

Renal events

The control group contained more patients with MPA and renal vasculitis than the MabThera® group and this was reflected in the occurrence of renal events, such as dialysis and use of plasma exchange, where there were trends to more events in the control group.

Other events

The higher number of disease flares in the rituximab group emphasises that patients in this group were more likely to have relapsing or refractory disease leading to an unstable disease course and higher requirement for medication. Of particular note was the increase in hypogammaglobulinemia (IgG<3g/L) in the MabThera® group (23 versus 3 in the control group) which led to a higher requirement for replacement immunoglobulin (19 versus 1 in the control group). While B cell depletion therapies are associated with depression of IgG levels, patients with ANCA associated vasculitis appear to be more susceptible and this has been the subject of multiple previous reports.

Deaths

The number of deaths reported in the statistical analysis report (Table 3.11) refers to patients who have died after the end of the RIVAS study follow-up (September 2018). There were no differences in mortality between treatment groups with 14 (6%) deaths in the MabThera® and 11 (6%) in the control group.

6 Conclusions

We have reported the occurrence of safety events in a retrospective observational study of GPA/MPA patients divided into those MabThera® exposed and those not MabThera® exposed, who were enrolled from 2003 through to a common follow-up stopping point in 2018. The use of rituximab evolved and became more frequent over this period. The two GPA/MPA treatment groups differed with those in the MabThera® group more likely to have GPA, PR3-ANCA, were younger and had a longer disease course with higher exposure to non-rituximab therapies and higher disease and treatment related damage score. These differences in part reflected the preferential use of rituximab for those with GPA and relapsing/refractory disease.

There was a high number of serious adverse events in both groups but this was higher in the rituximab compared to the control group, largely driven by a higher number of infections. Neutropenia was more common in the MabThera® group – a known adverse effect and there was one case of progressive multifocal leukoencephalopathy in the 247 MabThera® treated patients, and none in the control group. There was a trend to more cardiovascular events in the MabThera® group, but no differences in thrombo-embolic or malignant events or deaths between groups after study end. The increased rate of adverse events in the MabThera® group is caused in part by a longer disease duration and higher exposure to steroids and immune suppressive drugs. It is not possible in this dataset to identify the magnitude of the contribution of rituximab to most categories of adverse events. However, those known to be more common after rituximab, such as hypogammaglobulinemia, neutropenia and progressive multifocal leukoencephalopathy all appeared more frequent with rituximab in this study. Low immunoglobulin levels and neutropenia, caused by rituximab will contribute to the infective risk of this treatment.

Overall, the results from the RIVAS study are in line with the known rituximab safety profile in GPA/MPA patients, as observed in the clinical trials that led to the licensing of rituximab use for GPA/MPA patients. The type of adverse events observed in the MabThera® group are expected adverse reactions, although the longer observation of these patients, as well as their medical history and past medications are likely to have contributed to the incidence rate of certain events such as serious infections. Data from RIVAS contributes to our knowledge on the long-term safety of MabThera® in the treatment of GPA/MPA.

Further analysis will provide more insights to the safety profile of patients treated with MabThera® in the RIVAS study.

Professor [redacted]

6 h December 2021