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STUDY INFORMATION

TITLE:	**MABTHERA DRUG UTILISATION STUDY AND PATIENT ALERT CARD EVALUATION IN NON-ONCOLOGY PATIENTS IN EUROPE: AN INFUSION CENTRE-BASED APPROACH**
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STUDIED MEDICINAL PRODUCT:	MabThera® (rituximab)
COUNTRIES OF STUDY POPULATION:	France, Germany, Italy, Spain and the United Kingdom
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DATE FINAL:	See electronic date stamp below
MARKETING AUTHORISATION HOLDER:	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom

CLINICAL STUDY REPORT APPROVAL

Clinical Study Report Version 1.0
Protocol BA28478

Based on primary data collection with studied medicinal product CSR template Version 1.0 released on 16-Feb-2016

Clinical Study Report Version 1.0
Protocol BA28478

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1. SYNOPSIS/ABSTRACT

Title

MABTHERA DRUG UTILISATION STUDY AND PATIENT ALERT CARD EVALUATION IN NON-ONCOLOGY PATIENTS IN EUROPE: AN INFUSION CENTRE-BASED APPROACH

Date of abstract: February 2018

NIS Data Science Responsible: [redacted]

Keywords

Non-interventional; drug utilisation study; patient survey; MabThera; rituximab; non-oncology indications

Research Question and Objectives

Study Objectives

- Specific Aim 1: To quantify and characterize off-label use through an evaluation of the disease and characteristics of patients treated with MabThera for non-oncology conditions.
- Specific Aim 2: To evaluate the extent to which patients receive and read the Patient Alert Card (PAC), knowledge of the PAC content among patients receiving MabThera for non-oncology conditions at infusion centres, and whether distribution of the PAC may influence patient actions.

Off-label non-oncology indications include conditions other than rheumatoid arthritis (RA) and granulomatosis polyangiitis (GPA)/microscopic polyangiitis (MPA), which are the two approved autoimmune (AI) indications for MabThera.

Study Design

This drug utilisation study (DUS) was a multinational, multicentre study involving the retrospective chart review of MabThera patients' medical records in non-oncology indications.

At each participating centre, de-identified data were retrospectively abstracted from medical records per treatment indication (RA, systemic lupus erythematosus/lupus nephritis [SLE/LN], other), and selected patient and disease characteristics for all patients receiving MabThera for a non-oncology condition. A cross-sectional survey was conducted during the same time period, and prospectively collected information on patient characteristics, including questions about patient knowledge on the risk of infections, including progressive multi-focal leukoencephalopathy (PML), patient receipt and review of the PAC, and any actions the patient has taken as a result of receiving the PAC.

Target Population

Patients receiving MabThera for non-oncology indications at infusion centres in France, Germany, Italy, Spain, and the United Kingdom (UK).

Inclusion Criteria:

1. Patient is in the centre to receive an infusion for MabThera for a non-oncology indication during the study period;
2. Patient is aged 18 years or older;
3. Patient provides informed consent for medical record abstraction (MRA) and/or survey participation; and
4. Patient participating in the survey can read and understand English, French, German, Italian, or Spanish, according to the country.

Exclusion criteria (applicable only to patients participating in the survey):

1. Patient has previously completed the MabThera survey; and
2. Patient has participated in the past 12 months in a clinical trial in which MabThera was one of the treatments being evaluated.

Study Size

In this study, 1012 patients were enrolled for the MRA, and 524 patients were enrolled for the survey, across 47 sites.

Studied Medicinal Product

MabThera (rituximab).

Variables

Medical Record Data

The sites abstracted information from the medical records for each of the DUS consenting patients, and entered the abstracted information in an electronic Case Report Form (eCRF):

- Study ID (identification), age, gender
- Condition for which MabThera has been prescribed (via checklist)
- Reason for MabThera prescription
- Date of first diagnosis of the condition
- For patients with RA, severity of RA was measured using the 28-joint Disease Activity Score-erythrocyte sedimentation rate (DAS28-ESR).
- Presence of extra-articular involvement
- C-reactive protein level (CRP)
- MabThera dosage for the most recent infusion and number of MabThera infusions in the past 2 years
- Other current and previous anti-inflammatory medication, including biological agents other than MabThera

Patient Survey Data

The questionnaire collected information on patient demographics, disease history, previous treatment with MabThera, receipt of MabThera PAC and patient information leaflet (PIL), patient understanding and awareness of the content of the PAC, and patient actions and changes of behaviour triggered by the PAC.

Data Sources

Medical Record Data

Data on drug utilisation were obtained via retrospective medical chart review. Local site staff reviewed the medical chart of each enrolled patient and extracted the data already collected as routine practice.

Patient Survey Data

The questionnaire was completed after the patient arrived at the centre and before the start of the infusion, to make sure the questionnaire was completed before any additional counselling regarding the content of the PAC was provided by the site. The patient questionnaire underwent cognitive pre-testing, and was self-administered (close-ended questions [Qs] with predefined answers) on a hard-copy form at the site.

Statistical and Epidemiological Methods

Analysis of MabThera off-label use and the evaluation of PAC knowledge and utilisation were descriptive in nature, and entailed the tabular display of summary statistics and the frequency distribution of item responses. Therefore, no statistical testing was performed. Nevertheless, the 95% confidence intervals (CIs) of MabThera approved and off-label use proportions were calculated in order to assess precision of the prevalence estimates. All analyses were performed using SAS 9.4 statistical software (SAS Institute Inc., Cary, North Carolina, USA).

Results

MRA patient population

A total of 1012 patients, predominantly female (75.5%) and mainly falling within the age categories 46 to 55 years (21.6%), 56 to 65 years (26.1%) and 66 to 75 years (26.5%), participated in the MRA part of the study.

Patient questionnaire (PQ) population

A total of 524 patients, predominantly female (73.6%) and mainly falling within the age categories 46 to 55 years (21.8%), 56 to 65 years (28.3%) and 66 to 75 years (23.9%), participated in the PQ part of the study.

Results addressing the Specific Aim 1:

MabThera off-label use: 29.8% (95% CI: 27.0, 32.7) of MRA patients (N=1012) were prescribed MabThera for off-label non-oncology indications, comprising 58 SLE/LN patients (5.7%), 49 Sjögren syndrome patients (4.8%), and 195 patients (19.3%) with other off-label indications. Furthermore, 70.2% (95% CI: 67.3, 73.0) of MRA patients received MabThera for approved non-oncology indications, comprising 618 RA patients (61.1%) and 92 GPA/MPA patients (9.1%). The proportion of patients treated with MabThera off-label was 16.5% (95% CI: 11.4, 21.6) in the UK (N=200), 25.0% (95% CI: 19.2, 30.8) in Germany (N=212), 29.9% (95% CI: 23.6, 36.2) in France (N=204), 34.8% (95% CI: 28.2, 41.5) in Spain (N=198) and 43.4% (95% CI: 36.5, 50.3) in Italy (N=198).

Results addressing the Specific Aim 2:

Use of the PAC was assessed in terms of its distribution to patients, knowledge among patients of its content, and action taken/that would be taken by the patient if they had symptoms of an infection or PML.

Receipt and Review of the PAC: Key Questions

Receipt of the PAC (Q14); N=509: In total, 167 patients (32.8%) reported to have received the PAC, 302 patients (59.3%) reported they did not receive the PAC, and 40 patients (7.9%) did not know whether they had received the PAC. Among patients who visited the centre to receive their first-ever MabThera infusion (N=67) and second/subsequent infusion (N=438), 80.6% and 56.4% respectively reported they did not receive the PAC.

How often patients received the PAC (Q15); N=155: Most patients who reported receipt of the PAC responded that they received the PAC “only the first time I received a MabThera infusion” (71.6%).

Review of the PAC (Q18); N=157: Most patients who received the PAC reported they had read the PAC (79.6%).

Additional explanation of the PAC (Q20); N=157: Approximately half of the patients who received the PAC, reported that they received an explanation of the PAC content from a doctor/nurse other than the doctor who prescribed MabThera (51.6%), while 43.3% reported that they had not received additional explanation regarding the PAC.

Patient Knowledge of PAC Content: Key Questions

Awareness of PML (Q8); N=497: Most patients (72.4%) reported that they were not aware that, very rarely, some patients being treated with MabThera have had PML, while 24.9% were aware of it. Patients who received the PAC correctly identified PML as a potential side effect of MabThera in a greater proportion, compared with patients who did not receive the PAC (37.8% vs. 19.9%, respectively). PAC recipients also had a poor awareness of PML, with the majority answering “I don’t know” (58.3%).

Symptoms of PML (Q9): There were four correct options, “memory loss” (N=495), “problems thinking” (N=491), “change in the way of walking” (N=492) and “loss of vision”

(N=494). The proportion of patients who correctly identified these as possible symptoms of PML were 23.0% (“memory loss”), 23.0% (“problems thinking”), 18.3% (“change in the way of walking”) and 23.1% (“loss of vision”), respectively. The proportion of patients who correctly identified each PML symptom was higher among PAC recipients compared with PAC non-recipients.

Action that would be taken if experiencing symptoms suggestive of infection (Q11); N=481: The majority of patients answered correctly “seek medical attention immediately” (85.2%). Among PAC recipients and PAC non-recipients, the correct answer was selected by 90.0% and 85.5% of patients, respectively.

Action Taken by the Patient During an Infection: Key Question

Action taken when the patient experienced their most recent infection (Q31); N=70: Most patients answered “when I noticed symptoms, I talked to my doctor” (70.0%); the next most common response was “I told the doctor who treated me for the infection that I was taking MabThera” (40.0%). Patients who received the PAC reported “when I noticed symptoms, I talked to my doctor” in greater proportion compared with patients who did not receive the PAC (78.6% vs. 64.1%).

Conclusions

The results of Study BA28478 indicate that MabThera treatment in non-oncology conditions was predominantly in the approved indications of RA and GPA/MPA (~70.0%). Treatment of off-label conditions (~30.0%) mainly included SLE (5.7%) and Sjögren syndrome (4.8%), in addition to over 12 other individual conditions (<2% for each specified condition). Due to the focus of the infusion centres which were selected as study sites, these findings largely pertain to treatment in routine rheumatological practice. These results are in line with findings from previous research which indicate that, despite the absence of approval in these indications, rituximab is used to treat a range of systemic AI diseases in routine rheumatological practice due to the perceived efficacy and tolerability in the broad therapeutic field of AI disease (Gottenberg et al 2005).

The survey found that most patients reported that they did not receive the PAC (~60%). The majority of patients who received the PAC also read the PAC, suggesting that the PAC is accepted by patients as an educational tool. The results indicate slightly better knowledge scores among patients who received the PAC compared to those who did not receive the PAC. Furthermore, receipt of the PAC may be linked with a beneficial impact on patient actions, as PAC recipients were more likely to talk to their doctor when they noticed symptoms of infection compared with PAC non-recipients. These results may be explained by a positive effect of the PAC, or could have been influenced by other factors (e.g. differences in patient characteristics,

healthcare providers or infusion centres). However, the PAC may only contribute to patient knowledge to a limited extent, since PAC recipients showed poor knowledge of PML symptoms (although better knowledge than PAC non-recipients).

Overall, the AEs reported during the course of this study are consistent with the known MabThera safety profile. Based on these data, no new safety signal was identified.