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ORIGINAL RESEARCH

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A non-interventional, post-marketing surveillance study evaluating the safety and effectiveness of biosimilar rituximab (CT-P10) during routine clinical practice in the Republic of Korea

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ABSTRACT

Background: CT-P10 was the first licensed rituximab biosimilar. This Korean post-marketing surveillance study evaluated CT-P10 safety and effectiveness in approved indications.

Research design and methods: This prospective, open-label, observational, phase 4 study collected routine clinical practice data across 27 centers in the Republic of Korea. Patients received their first CT-P10 treatment, per prescribing information, for non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA), or microscopic polyangiitis (MPA) during the surveillance period (16 November 2016–15 November 2020). Safety (including adverse events [AEs] and adverse drug reactions [ADRs]) and disease-specific clinical response (by best overall response [NHL/CLL], Disease Activity Score in 28-joints [RA], or Birmingham Vasculitis Activity Score for Wegener's Granulomatosis [GPA/MPA]) were assessed for ≤1 year (NHL/CLL) or ≤24 weeks (RA/GPA/MPA).

Results: The safety population comprised 677 patients (604 NHL, 16 CLL, 42 RA, 7 GPA, 8 MPA). AEs/ADRs were reported for 68.4%/27.7% (NHL/CLL), 31.0%/14.3% (RA), and 86.7%/13.3% (GPA/MPA) of patients. Serious AEs and unexpected ADRs did not raise new safety signals. Pneumonia was the most frequent serious ADR overall. Positive effectiveness outcomes were observed.

Conclusions: Findings were consistent with the known CT-P10/reference rituximab safety profile, with high effectiveness observed in NHL/CLL and RA.

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Chronic lymphocytic leukemia; CT-P10; granulomatosis with polyangiitis; microscopic polyangiitis; non-Hodgkin's lymphoma; rheumatoid arthritis; rituximab

1. Introduction

Rituximab was the first monoclonal antibody to receive regulatory approval for use in oncology and became a best-selling oncology drug with worldwide sales exceeding $8 billion in 2016 [1]. Reference rituximab (Rituxan®; Genentech, South San Francisco, CA, US) received US Food and Drug Administration (FDA) regulatory approval in 1997 for the treatment of relapsed/refractory low-grade or follicular, CD20-positive B-cell non-Hodgkin's lymphoma (NHL) [2,3]; European Medicines Agency (EMA) regulatory approval (for MabThera®; Roche, Basel, Switzerland) was granted in 1998 for the treatment of relapsed/refractory follicular lymphoma (FL) [4]. The FDA and EMA subsequently extended the approval within the NHL indication, and several additional indications were added. These include chronic lymphocytic leukemia (CLL), rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and pemphigus vulgaris [3,5]. Rituximab is used extensively across a broad range of indications in routine clinical practice, particularly in NHL [1], for which it is a component of combination therapy in first- and later-line treatment settings [6,7].

CT-P10 (Truxima®; Celltrion, Inc., Incheon, Republic of Korea) was the first rituximab biosimilar to receive regulatory approval from the Ministry of Food and Drug Safety (Republic of Korea), as well as the EMA and FDA [8–10], and currently possesses a high

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market share, particularly in the European Union (EU) [11]. Currently, approved indications for CT-P10 include NHL, CLL, RA, GPA, MPA, and pemphigus vulgaris (the latter is approved for use in some territories, including the EU) [8–10]. Other approved rituximab biosimilars include GP2013 (Rixathon®; Sandoz, Basel, Switzerland) and PF-05280586 (Ruxience®; Pfizer, NY, USA), which are EMA approved [12]; however, CT-P10 is the only biosimilar approved in the Republic of Korea. The approval of CT-P10 was supported by the demonstration of analytical similarity between CT-P10 and both EU- and US-sourced reference rituximab [13]. Clinical studies demonstrated the equivalence or similarity of CT-P10 to reference rituximab in terms of pharmacokinetics, efficacy, safety, and immunogenicity in patients with RA or FL [14–17], and follow-up studies of patients enrolled in the pivotal clinical trials further supported the comparable long-term efficacy and overall safety between CT-P10 and reference rituximab [18–20]. A recent systematic review and meta-analysis of 29 randomized controlled clinical trials in patients with cancer has demonstrated that rituximab biosimilars, including CT-P10, have comparable safety and efficacy profiles to reference rituximab in treatment-naïve patients [21]. Budget impact analyses have also shown that the introduction of CT-P10 offers substantial potential cost savings relative to continued use of the reference product [22,23]. Reallocation of these savings could enable more patients to access rituximab treatment with CT-P10 [22,23].

Post-marketing surveillance (PMS) studies are an important component of ongoing safety monitoring following regulatory approval [24,25]. Following launch of a drug product, a broad spectrum of patients with a range of comorbidities, and those taking various concomitant medications, are exposed to the drug during routine clinical practice, including patients who may not have been eligible for inclusion in clinical trials [25]. Thus, PMS studies provide important information on the benefit/risk profile of the drug in the real-world patient population [26]. In addition, real-world safety evaluation has the potential to detect rare adverse effects or variability in responses, due to biological or behavioral factors, which were not detected in trial populations [25,26]. In the context of biosimilar development, PMS studies can provide evidence for the safety and effectiveness of a product in indications where approval was based on extrapolation of comparative data in other indications [27,28]. In the case of CT-P10, the biosimilarity of CT-P10 to reference rituximab comprehensively demonstrated in patients with RA and FL during the clinical development program formed the basis of CT-P10 approval in other indications licensed for reference rituximab [29], in accordance with regulatory guidelines [30,31]. This included the indications of diffuse large B-cell lymphoma (DLBCL), CLL, GPA, and MPA [29].

The present PMS study evaluated the safety and effectiveness of CT-P10 in patients with NHL (including DLBCL and FL), CLL, RA, GPA, and MPA during routine clinical practice in the Republic of Korea. The objective was to investigate the type and frequency of unexpected adverse events (AEs), adverse drug reactions (ADRs), and serious AEs, and to identify factors that affect safety and effectiveness.

2. Patients and methods

2.1. Study design

A prospective, open-label, observational, phase 4, post-marketing cohort study was conducted at 27 medical centers or hospitals in the Republic of Korea (**Supplementary Tables 1 and 2**). Surveys were completed by physicians at the institutions to capture information about CT-P10 treatment during the surveillance period of 16 November 2016 to 15 November 2020. Patients with NHL or CLL were followed for up to 1 year after the first administration of CT-P10, while patients with RA, GPA, or MPA were followed for up to 24 weeks after the first administration of CT-P10.

The study adhered to the ethical principles of the Declaration of Helsinki for the conduct of medical research involving human subjects, and ethical approval was obtained from appropriate local Institutional Review Boards at each of the 27 study sites (**Supplementary Table 1**). All participants provided written informed consent.

2.2. Patients

The study enrolled patients eligible to receive CT-P10 for the first time for the approved indications of NHL, CLL, RA, GPA, or MPA in the Republic of Korea [32]. Eligible patients had not received CT-P10 treatment prior to the surveillance period; however, patients were permitted to have previously received treatment with other rituximab products (termed 'switched' patients), or to have initiated rituximab treatment with CT-P10 during the surveillance period (termed 'rituximab-naïve' patients). Specifically, relevant approved indications for CT-P10 in NHL were the treatment of previously untreated patients with Stage III/IV FL, in combination with chemotherapy; maintenance therapy for patients with previously untreated Stage III/IV FL who had responded to induction therapy; treatment of patients with Stage III/IV FL who had relapsed or were chemo-resistant; and treatment of patients with CD20-positive DLBCL NHL, in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy. In CLL, the relevant approved indication was the treatment of patients with previously untreated and relapsed/refractory CLL. For RA, the approved indication was for use of CT-P10, in combination with methotrexate, for the treatment of adult patients with severe active RA who had an inadequate response or intolerance to other disease-modifying antirheumatic medicinal products, including one or more tumor necrosis factor inhibitor therapies. For patients with severely active GPA and MPA, the relevant indication for CT-P10 was for the treatment of adult patients in combination with glucocorticoids. Patients prohibited from receiving CT-P10 according to the prescribing information, patients using CT-P10 for non-approved indications, and patients considered by the investigator to be unsuitable for participation were excluded from the study.

2.3. Treatment

CT-P10 was recommended to be administered as an intravenous infusion according to the Korean Ministry of Food and Drug Safety prescribing information [32]. For patients with FL, CT-P10 was administered at a dosage of 375 mg/m^2 body surface area (BSA) per cycle of chemotherapy, for up to 8 cycles as induction therapy, followed by maintenance treatment once every 2 months or once every 3 months for patients with previously untreated FL or relapsed/refractory FL, respectively, until disease progression or a maximum of 2 years. For patients with chemo-resistant FL or in the second or subsequent relapse after chemotherapy, CT-P10 was administered at a dosage of 375 mg/m^2 BSA once weekly for 4 weeks. For patients with DLBCL, CT-P10 was administered at a dosage of 375 mg/m^2 BSA per cycle of CHOP chemotherapy. For patients with CLL, CT-P10 was administered at a dosage of 375 mg/m^2 BSA for the first fludarabine and cyclophosphamide chemotherapy cycle, followed by 500 mg/m^2 BSA for Cycles 2–6. For patients with RA, CT-P10 was administered as a 1,000 mg dose followed by a second 1,000 mg dose after 2 weeks. For patients with GPA or MPA, CT-P10 was administered at a dosage of 375 mg/m^2 BSA once weekly for 4 weeks, with maintenance therapy administered as two 500 mg infusions separated by 2 weeks (with subsequent 500 mg infusions administered at Months 6, 12, 18, and every 6 months thereafter based on clinical evaluation).

2.4. Endpoints and assessments

Safety and effectiveness were assessed during a 1-year (NHL and CLL) or 24-week (RA and GPA/MPA) follow-up period after the first administration of CT-P10.

2.4.1. Safety

All AEs, serious AEs, unexpected AEs, AEs leading to discontinuation of CT-P10, and deaths were recorded regardless of their causality or relationship to CT-P10. AEs were deemed to be ADRs (i.e. causally related to CT-P10) if the relationship to CT-P10 was deemed by the investigator to be 'certain,' 'probable/likely,' 'possible,' 'conditional/unclassified,' or 'unassessable/unclassifiable.' Unexpected AEs and ADRs were events not listed in the reference safety information for the relevant indication in the Korean prescribing information for CT-P10 [32], or events observed at a higher frequency than expected. Protocol-defined AEs of special interest comprised infusion-related reactions (IRRs; defined as cytokine release syndrome or the Preferred Term tumor lysis syndrome), infections (based on the infections and infestations System Organ Class [SOC]), and cardiovascular disorders (based on the cardiac disorders and vascular disorders SOCs). AEs were coded using the Medical Dictionary for Regulatory Activities, version 23.0.

2.4.2. Effectiveness

For patients with NHL or CLL, effectiveness was assessed according to the best overall response (BOR) during treatment with CT-P10. Rituximab-naïve patients were considered responders if the BOR was complete response (CR) or partial response (PR), as reported by the treating physician. Switched patients were considered responders if the BOR was the same or better than that achieved with the previous rituximab product, comprising new or sustained CR or PR responses.

For patients with RA, response was assessed according to the reduction in Disease Activity Score in 28 joints (DAS28) score following administration of CT-P10. In rituximab-naïve patients, DAS28 was assessed prior to CT-P10 administration (Week 0) and 16–24 weeks after the first CT-P10 administration; patients were considered responders if the reduction in DAS28 was ≥1.2 (post-CT-P10 administration versus pre-CT-P10 administration). For switched patients, response was assessed by DAS28 evaluation prior to CT-P10 administration (Week 0) and 24 weeks after the first administration of CT-P10. Response was considered to have been maintained if the DAS28 did not increase by ≥0.6 compared to baseline.

For patients with GPA/MPA, response was assessed according to the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis criteria [33] during the 24 weeks after first administration of CT-P10. Rituximab-naïve and switched patients were assessed in the same way, with response categorized as improvement (symptoms improved or effect maintained), no change, or deterioration.

2.5. Statistical analyses

The total population comprised all patients with a completed and submitted survey form. The safety population comprised all patients in the total population who received ≥1 dose of CT-P10 and had ≥1 safety follow-up meeting, carried out via an in-person visit or phone call, following administration of CT-P10. The effectiveness population comprised all patients in the safety population who completed ≥1 effectiveness evaluation following administration of CT-P10.

Quantitative variables, such as patient characteristics, were reported using descriptive statistics (n; mean, standard deviation [SD]; or median, range). The frequency and percentage were reported for qualitative variables, such as AEs.

Subgroup analyses for safety and effectiveness outcomes were conducted based on baseline and demographic parameters. For safety analyses, these parameters included sex, age, Ann Arbor stage at the time of first dose (for NHL), FL grade at the time of first dose (for FL), Rai system stage at the time of first dose (for CLL), disease duration (for RA and GPA/MPA), patients receiving treatments for the indication in addition to CT-P10 (for NHL/CLL), and the total number of cycles of CT-P10 treatment received. Safety analyses were also conducted for the special populations of pediatric patients (aged <19 years), elderly patients (aged ≥65 years), pregnant women, individuals with hepatic disorders, and individuals with renal disorders. For effectiveness analyses, parameters for subgroup analyses comprised sex, age, Ann Arbor stage at the time of first dose (for NHL), FL grade at the time of first dose (for FL), Rai system stage at the time of first dose (for CLL), disease duration (for RA and GPA/MPA), patient classification (rituximab-naïve versus switched [for NHL/CLL and RA]), and surgical history prior to first dose (for NHL). All statistical analyses were performed using SAS software, version 9.4 or later (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient disposition and baseline characteristics

The patient disposition is presented in Figure 1. Overall, 677 patients were included in the safety population, comprising patients with NHL (n = 604), CLL (n = 16), RA (n = 42), GPA (n = 7), and MPA (n = 8). Of the 604 patients with NHL, 108 had FL and 496 had DLBCL. In total, 611 patients were included in the effectiveness population, comprising patients with NHL (n = 549), CLL (n = 15), RA (n = 32), GPA (n = 7), and MPA (n = 8).

Patient demographics and baseline characteristics for the safety population are presented in Table 1. In the combined population of patients with NHL and CLL, a minority (69 [11.1%]) had switched from another rituximab product. Overall, 266 (42.9%) patients were aged ≥65 years, 67 (10.8%) patients had hepatic disorders, and 12 (1.9%) patients had renal disorders. In the RA cohort, the majority of patients (32 [76.2%]) had a history of rituximab treatment. Fourteen (33.3%) patients were aged ≥65 years, 3 (7.1%) patients had hepatic disorders, and no patients had renal disorders. In the GPA/MPA cohort, a low proportion of patients (2 [13.3%]) had a history of rituximab treatment. Five (33.3%) patients were aged ≥65 years, 4 (26.7%) patients had hepatic disorders, and 9 (60.0%) patients had renal disorders. Across indications, no female patients were pregnant and there was only 1 patient aged <19 years, who had DLBCL.

3.2. Exposure to CT-P10 and other treatments

Patients with FL, DLBCL, and CLL received a median (range) of 6 (1–18), 6 (1–8), and 6 (2–6) doses of CT-P10 over a 1-year period, respectively; corresponding mean (SD) doses per administration were 645 (78) mg, 631 (75) mg, and 822 (70) mg. Two of 108 (1.9%) patients with FL, 14 of 496 (2.8%) patients with DLBCL, and all 16 (100.0%) patients with CLL received dosage modifications. Dosage modifications were due to AEs for 1 (0.9%), 7 (1.4%), and 1 (6.3%) patients with FL, DLBCL, and CLL, respectively. Patients with RA received a median (range) of 2 (1–2) doses over a 24-week period. All administered doses were 1,000 mg; thus, no patients received a dosage modification. Patients with GPA/MPA received a median (range) of 4 (2–4) doses over a 24-week period. The mean (SD) administered dose was 554 (76) mg, with 1 of 15 (6.7%) patients receiving a dosage modification. The dosage modification was not due to an AE but made due to an incorrect dose set at the first administration.

Most patients (615/620; 99.2%) with NHL and CLL were receiving anticancer chemotherapy; 504 (81.3%) patients

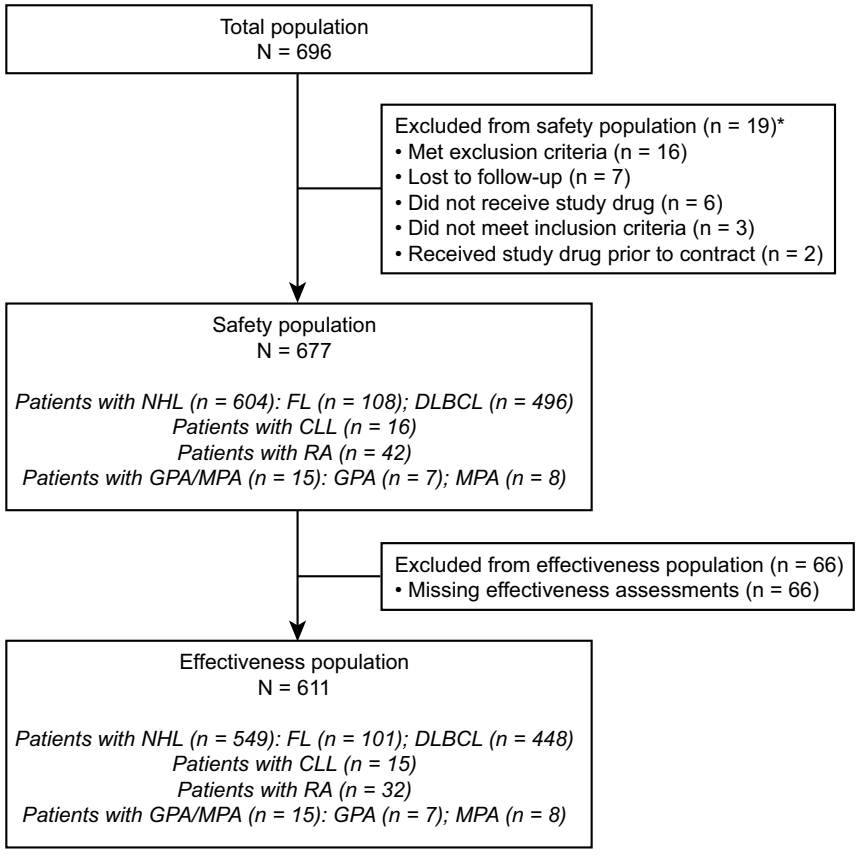

Figure 1. Study flow diagram.

*Multiple reasons for exclusion from the safety population were present for 8 patients. Five patients were excluded due to meeting exclusion criteria, loss to follow-up, and not receiving study drug. One patient was excluded due to not meeting inclusion criteria, not receiving study drug, receiving study drug prior to contract, and loss to follow-up. One patient was excluded due to meeting exclusion criteria and loss to follow-up. One patient was excluded due to not meeting inclusion criteria and receiving study drug prior to contract.

CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; NHL, non-Hodgkin's lymphoma; RA, rheumatoid arthritis.

Table 1. Patient demographics and baseline characteristics (safety population).

Characteristic	NHL (n = 604)*	CLL (n = 16)	RA (n = 42)	GPA/MPA (n = 15)†
Age, median (range), years	62.0 (18.0–91.0)	62.0 (50.0–69.0)	57.5 (31.0–77.0)	59.0 (22.0–79.0)
Male, n (%)	356 (58.9)	13 (81.3)	2 (4.8)	6 (40.0)
Weight, mean (SD), kg	64.2 (12.9)	64.5 (9.7)	57.2 (9.8)	58.8 (11.5)
Prior rituximab use, n (%)	68 (11.3)	1 (6.3)	32 (76.2)	2 (13.3)
Disease duration, median (range), years	0.04 (0–24.0)	0.13 (0–6.0)	14.75 (1.4–30.0)	0.08 (0–4.0)
Ann Arbor stage,‡ n (%)				
I	110 (18.2)			
II	131 (21.7)			
III	135 (22.4)			
IV	211 (34.9)			
Rai stage,‡ n (%)				
0		2 (12.5)		
I		1 (6.3)		
II		3 (18.8)		
III		3 (18.8)		
IV		6 (37.5)		

*FL, n = 108 (17.88%) and DLBCL, n = 496 (82.12%).
†GPA, n = 7 (46.67%) and MPA, n = 8 (53.33%).
‡At baseline.
CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; NHL, non-Hodgkin's lymphoma; RA, rheumatoid arthritis; SD, standard deviation.

were receiving rituximab-CHOP. Low proportions of patients were receiving hormone therapy (1/620; 0.2%), radiotherapy (4/620; 0.6%), or surgery (4/620; 0.6%). Most patients with NHL or CLL received concomitant analgesics (556/620; 89.7%), systemic antihistamines (555/620; 89.5%), antiemetics or antinauseants (518/620; 83.5%), or drugs for acid-related disorders (439/620; 70.8%). Over half of patients used concomitant systemic corticosteroids (407/620; 65.6%), systemic antibacterial agents (349/620; 56.3%), or immunostimulants (334/620; 53.9%).

Most patients with RA received concomitant systemic antihistamines (40/42; 95.2%), systemic corticosteroids (39/42; 92.9%), immunosuppressants (35/42; 83.3%), analgesics (34/42; 81.0%), or anti-inflammatory or antirheumatic products (32/42; 76.2%). All (15/15; 100.0%) patients with GPA/MPA received concomitant systemic antihistamines and systemic corticosteroids, and most received analgesics (14/15; 93.3%), systemic antibacterial agents (13/15; 86.7%), or immunosuppressants (9/15; 60.0%).

3.3. Safety

A summary of the safety findings is shown in Table 2. Of the 620 patients with NHL or CLL, 424 (68.4%) experienced a total of 1,717 AEs. The most common AE was nausea, reported by 69 (11.1%) patients with NHL or CLL (**Supplementary Table 3**). The majority of AEs were mild (1,152 [67.1%] events) or moderate (424 [24.7%] events) in severity, with the remaining AEs classified as severe (125 [7.3%] events), life-threatening (2 [0.1%] events), or leading to death (14 [0.8%] events). The life-threatening AEs were one case of neutrophil count decreased and one case of respiratory arrest. Deaths were predominantly due to infections (pneumonia [n = 4], sepsis/septic shock [n = 4], pseudomembranous colitis [n = 1], and pneumonia cytomegaloviral [n = 1]). The remaining cases were due to cardiomyopathy (n = 1) or were of unknown cause (n = 3). Two of the 14 deaths were considered to be possibly related to CT-P10 treatment, comprising one of the deaths due to pneumonia, reported in a 66-year-old female patient with DLBCL, and one of the deaths due to sepsis,

Table 2. Summary of safety, by indication (safety population).

Patients, n (%)	NHL/CLL (n = 620)	RA (n = 42)	GPA/MPA (n = 15)
Any AE	424 (68.4)	13 (31.0)	13 (86.7)
ADR*	172 (27.7)	6 (14.3)	2 (13.3)
Any serious AE	102 (16.5)	5 (11.9)	7 (46.7)
Serious ADR	31 (5.0)	3 (7.1)	1 (6.7)
Any unexpected AE	195 (31.5)	11 (26.2)	11 (73.3)
Unexpected ADR	29 (4.7)	4 (9.5)	1 (6.7)
Any AE leading to discontinuation of study drug	36 (5.8)	1 (2.4)	2 (13.3)
ADR leading to discontinuation of study drug	16 (2.6)	1 (2.4)	0
Death	14 (2.3)	0	2 (13.3)
Death due to ADR	5† (0.8)	0	0

*Causal relationship to treatment with CT-P10 determined as 'certain,' 'probable/likely,' 'possible,' 'conditional/unclassified,' or 'unassessable/unclassifiable.'
†Three deaths classified as 'unassessable/unclassifiable,' and 2 deaths classified as 'possible.'
ADR, adverse drug reaction; AE, adverse event; CLL, chronic lymphocytic leukemia; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; NHL, non-Hodgkin's lymphoma; RA, rheumatoid arthritis.

reported in a 79-year-old male with DLBCL. All other deaths were considered unlikely to be related to CT-P10 treatment (n = 9), except for the 3 deaths of unknown cause, which occurred in patients with DLBCL. For these cases, causality was assessed as 'unassessable/unclassifiable'; thus, a causal relationship to CT-P10 could not be ruled out and these deaths were considered ADRs, alongside the 2 deaths considered to be possibly related to CT-P10 treatment.

ADRs occurred in 172 (27.7%) patients with NHL or CLL (Table 2), which were most commonly nausea (30 [4.8%] patients), neutropenia (24 [3.9%] patients), and decreased appetite (20 [3.2%] patients) (**Supplementary Table 4**). Serious ADRs occurred in 31 (5.0%) patients with NHL or CLL (Table 3); pneumonia was the most frequent serious ADR, reported by 7 (1.1%) patients. Unexpected ADRs occurred in 29 (4.7%) patients (**Supplementary Table 4**). The most common unexpected ADRs were an increase in hepatic enzymes, erythema, death, and oropharyngeal pain, each reported by 3 (0.5%) patients, followed by dermatitis contact, dysuria, and chest discomfort, each reported by 2 (0.3%) patients. Sixteen (2.6%) patients experienced an ADR leading to discontinuation of CT-P10, most commonly due to pneumonia (4 [0.6%] patients) or death (3 [0.5%] patients).

Of the 42 patients with RA, 13 (31.0%) patients reported a total of 35 AEs. The most frequent AE was cough, experienced by 3 (7.1%) patients (**Supplementary Table 3**). All AEs were classified as mild (21 [60.0%] events) or moderate (12 [34.3%] events), with the exception of one severe case each of osteomyelitis and *Pneumocystis jirovecii* pneumonia. Eight ADRs (herpes zoster, osteomyelitis, *Pneumocystis jirovecii*

Table 3. Summary of serious ADRs by Preferred Term, by indication (safety population).

System Organ Class **Preferred Term, n (%)**	**NHL/CLL (n = 620)**
Any serious ADR	31 (5.0)
Infections and infestations	
Pneumonia	7 (1.1)
Herpes zoster	3 (0.5)
Atypical pneumonia	1 (0.2)
Cytomegalovirus infection	1 (0.2)
Fungal pneumonia	1 (0.2)
Herpes simplex	1 (0.2)
Mycobacterial infection	1 (0.2)
Sepsis	1 (0.2)
Septic shock	1 (0.2)
Blood and lymphatic system disorders	
Febrile neutropenia	5 (0.8)
Neutropenia	2 (0.3)
Pancytopenia	1 (0.2)
Thrombocytopenia	1 (0.2)
General disorders and administration site conditions	
Death*,†	3 (0.5)
Asthenia	1 (0.2)
Pyrexia	1 (0.2)
Respiratory, thoracic, and mediastinal disorders	
Interstitial lung disease	1 (0.2)
Pneumonitis*	1 (0.2)
Respiratory arrest*	1 (0.2)
Cardiac disorders	
Supraventricular tachycardia	1 (0.2)
Gastrointestinal disorders	
Vomiting	1 (0.2)
Nervous system disorders	
Dizziness	1 (0.2)
System Organ Class **Preferred Term, n (%)**	**RA (n = 42)**
Any serious ADR	3 (7.1)
Infections and infestations	
Osteomyelitis*	1 (2.4)
Pneumocystis jirovecii pneumonia*	1 (2.4)
Pneumonia*	1 (2.4)
System Organ Class **Preferred Term, n (%)**	**GPA/MPA (n = 15)**
Any serious ADR	1 (6.7)
Infections and infestations	
Atypical pneumonia	1 (6.7)

*Unexpected serious ADR.
†Event was unassessable/unclassifiable as cause of death was unknown.
ADR, adverse drug reaction; CLL, chronic lymphocytic leukemia; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; NHL, non-Hodgkin's lymphoma; RA, rheumatoid arthritis.

pneumonia, pneumonia, pain in extremity, cough, pruritus, and rash) occurred in 6 (14.3%) patients; no ADR was experienced by more than 1 patient (**Supplementary Table 4**). Serious ADRs occurred in 3 (7.1%) patients, comprising one case each of osteomyelitis, *Pneumocystis jirovecii* pneumonia, and pneumonia (Table 3). Five unexpected ADRs occurred in 4 (9.5%) patients: one case each of herpes zoster, osteomyelitis, *Pneumocystis jirovecii* pneumonia, pneumonia, and cough (**Supplementary Table 4**). One (2.4%) patient experienced an ADR leading to discontinuation of CT-P10 (*Pneumocystis jirovecii* pneumonia). There were no deaths.

Of the 15 patients with GPA or MPA, 13 (86.7%) patients reported a total of 45 AEs. The most frequent AE was pneumonia, which was experienced by 4 (26.7%) patients (**Supplementary Table 3**). The majority of AEs were mild (6 [13.3%] events) or moderate (33 [73.3%] events), with 4 (8.9%) AEs classified as severe. No AEs were classed as life-threatening. ADRs occurred in 2 (13.3%) patients: one case each of atypical pneumonia and laryngeal edema (**Supplementary Table 4**). The case of atypical pneumonia in 1 (6.7%) patient was considered to be a serious ADR (Table 3), while the case of laryngeal edema in 1 (6.7%) patient was considered to be an unexpected ADR (**Supplementary Table 4**). No patients experienced ADRs leading to discontinuation of CT-P10. Two deaths occurred in patients with MPA, one each as a result of pneumonia and acute kidney injury. Causality was assessed as unlikely to be related to CT-P10 treatment in both cases.

Across indications, there were no cases of IRR (defined as cytokine release syndrome or tumor lysis syndrome). One case of hepatitis B reactivation occurred in the NHL/CLL population. This was a moderate AE considered unlikely to be related to CT-P10 treatment, from which the patient was recovering, and which required CT-P10 treatment to be withdrawn.

Subgroup analyses in the NHL/CLL and RA populations did not identify statistically significant differences in the proportions of patients experiencing AEs, other than the analysis by number of CT-P10 doses received. AEs occurred in 18/37 (48.6% [95% exact confidence interval (CI): 31.9–65.6]) of patients with NHL/CLL who received CT-P10 once versus 406/583 (69.6% [95% exact CI: 65.7–73.4]) of patients with NHL/CLL who received more than one dose of CT-P10 (Chi square test; P = 0.0077). Owing to the small patient numbers in different subgroups, statistical analyses in the GPA/MPA population were not considered to be clinically meaningful.

3.4. Effectiveness

Effectiveness findings are presented in Table 4. For patients with NHL, the response rate was 96.7% and 50.8% for rituximab-naïve and switched patients, respectively. For patients with CLL, all (100.0%) rituximab-naïve patients were responders; no patients switched to CT-P10 from another rituximab product. In the RA effectiveness population, the response rate was 77.8% for rituximab-naïve patients and 100.0% for patients switched from another rituximab product. In the GPA/MPA effectiveness population, response rates were 38.5% and 100.0% for rituximab-naïve and switched patients, respectively.

4. Discussion

Within this PMS study, the safety and effectiveness of CT-P10 in patients with NHL, CLL, RA, GPA, and MPA were assessed during routine clinical practice in the Republic of Korea. As well as extending clinical trial findings regarding CT-P10 treatment in patients with FL and RA, this study provides evidence regarding the safety and effectiveness of CT-P10 in the DLBCL, CLL, GPA, and MPA indications that were not evaluated in randomized controlled trials for CT-P10, instead receiving regulatory approval through the extrapolation of biosimilarity conclusions [29]. In addition, this PMS study investigated the safety profile of CT-P10 in patients with RA and FL who switched from other rituximab products at study entry, in contrast to the patients enrolled in the clinical trials who

Table 4. Summary of effectiveness, by indication (effectiveness population).

	n	Responders, n (%)	Non-responders, n (%)	Not evaluable, n (%)
NHL				
Rituximab-naïve	484	468 (96.7)	16 (3.3)	0
Switched	65	33 (50.8)	3 (4.6)	29 (44.6)
FL				
Rituximab-naïve	78	77 (98.7)	1 (1.3)	0
Switched	23	16 (69.6)	2 (8.7)	5 (21.7)
DLBCL				
Rituximab-naïve	406	391 (96.3)	15 (3.7)	0
Switched	42	17 (40.5)	1 (2.4)	24 (57.1)
CLL				
Rituximab-naïve	15	15 (100.0)	0	0
Switched	0	0	0	0
RA				
Rituximab-naïve	9	7 (77.8)	1 (11.1)	1 (11.1)
Switched	23	23 (100.0)	0	0
GPA/MPA				
Rituximab-naïve	13	5 (38.5)	8 (61.5)*	0
Switched	2	2 (100.0)	0	0

*No change in response for 4 (30.8%) patients, and deterioration in response for 4 (30.8%) patients.
CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; NHL, non-Hodgkin's lymphoma; RA, rheumatoid arthritis.

were rituximab-naïve at baseline [15–17]. Overall, the study findings in terms of AEs, ADRs, and serious ADRs were consistent with the known safety profile of CT-P10 and other rituximab products, with ADRs reported in approximately 28% of patients with NHL or CLL, 14% of patients with RA, and 13% of patients with GPA or MPA. CT-P10 was well tolerated, and the majority of AEs were of mild or moderate severity. Many of the most common ADRs were as expected in each indication, based on those listed in the product label; for example, for patients with NHL/CLL, nausea and neutropenia are identified as 'very common' ADRs in the CT-P10 prescribing information [10].

Several unexpected ADRs occurred, as shown in **Supplementary Table 4**. Oropharyngeal pain and erythema have been described in association with IRRs in the prescribing information for patients with RA [10]; in this study, these events were reported as unexpected ADRs in patients with NHL/CLL, alongside chest discomfort, for example. Chest discomfort and erythema have been reported as ADRs associated with CT-P10 treatment in a hospital-based intensive safety monitoring study for patients with NHL/CLL [34]. Pneumonia and cough, reported as unexpected ADRs in patients with RA in the current study, are mentioned in relation to serious infections and manifestations of IRRs in the US prescribing information [3], and reported as ADRs in patients with NHL/CLL in the Korean prescribing information [32]. Of the other unexpected ADRs reported by patients with RA, herpes zoster is identified as an ADR in other indications in the prescribing information [10], while several real-world reports in patients with RA describe herpes zoster occurrence with rituximab treatment [35–39]. In addition, *Pneumocystis jirovecii* infection is categorized as a rare ADR in the prescribing information for NHL/CLL indications [10], while *Pneumocystis jirovecii* pneumonia has been associated with rituximab treatment in an RA registry study [39]. A retrospective study has also reported osteomyelitis associated with rituximab treatment in a patient with pemphigus foliaceus [40]. Laryngeal edema, the only unexpected ADR in the GPA/MPA indication, is identified as an uncommon ADR for rituximab-treated patients with RA in the prescribing information [10]. In summary, many of the unexpected ADRs reported in the current PMS study have been described previously with rituximab treatment. Overall, there were limited numbers of unexpected serious ADRs in this study, none of which raised new safety concerns. While a number of unexpected AEs were reported during the surveillance period for patients with NHL or CLL, the majority of those considered possibly or probably drug related occurred in only a single patient and did not raise a new safety signal. The number of unexpected AEs reported in patients with RA or GPA/MPA was lower, none of which raised concerns.

The proportion of CT-P10-treated patients with NHL experiencing AEs (68%) was slightly lower than previously reported in randomized comparative studies of patients with previously untreated advanced FL (90% after up to 3 years) [18] and patients with low-tumor-burden FL (88% after up to 27 months) [41]. In the current study, the most common ADRs were nausea and neutropenia in the NHL/CLL population, which were also among the most common treatment-emergent AEs reported after long-term follow-up in the CT-P10 clinical studies in patients with FL [18,41]. Events of pneumonia and febrile neutropenia, which were also reported in the current PMS study, are listed as 'common' and 'very common' ADRs in the prescribing information for CT-P10 [10]. In patients with RA, the rate of AEs reported with CT-P10 in the present study (31%) was lower than in the phase 3 randomized clinical study (60%) after 24 weeks [14]. In total, 6 (14%) and 3 (7%) patients with RA experienced ADRs and serious ADRs, respectively, and no patient experienced multiple serious ADRs. Subgroup analyses were also conducted for the safety findings: results demonstrated a significantly lower incidence of AEs in patients with NHL/CLL who had undergone one treatment cycle compared with those who had received more than one treatment cycle (49% versus 70%, respectively; $P = 0.0077$). This suggests that the incidence of AEs increases with treatment exposure.

In terms of the effectiveness analyses, high response rates were observed with CT-P10 in the NHL/CLL population in the current study, with 97% of rituximab-naïve and 51% of switched patients categorized as responders. Given that patients with DLBCL comprised the majority (82%) of the NHL/CLL population, the response rate for rituximab-naïve patients was comparable to the overall response rate reported for previously untreated patients with DLBCL, who received CHOP in combination with reference rituximab or CT-P10 in a retrospective, single-center study in Korea (92–97%) [42]. The response rate for rituximab-naïve patients was also comparable to findings reported for patients with previously untreated NHL or CLL, who had received either reference rituximab or CT-P10 in a non-interventional, retrospective study conducted in the UK (94–98%) [43]. The lower response rate in switched patients may reflect experience that BOR is usually achieved within several months after rituximab administration for NHL/CLL [44–46]; as such, the switched patient group might have had a higher response rate following previous administration of other rituximab products, prior to the patients receiving CT-P10 and entering this PMS study. In addition, the response rate for switched patients was higher for those with FL (70%) compared with DLBCL (41%), which may reflect the more positive prognosis in indolent NHL [47].

High response rates were also reported in the RA population, with 78% and 100% of rituximab-naïve and switched patients categorized as responders, respectively. This finding is consistent with previous observations in real-world settings that repeated cycles of rituximab provide clinical improvements in patients with RA [48,49]. In addition, the response rate for switched patients demonstrates that switching from other rituximab products to CT-P10 did not result in clinically meaningful differences in DAS28 response, reflecting findings from a single-center, real-world switching study [50]. For patients with GPA/MPA, response rates of 38% and 100% for rituximab-naïve and switched patients were identified, respectively; however, few patients were evaluated in the current study and further data collection may be necessary to fully investigate the effectiveness of CT-P10 in these indications.

There are a number of strengths and limitations to the present study. The demographic and baseline disease characteristics and concomitant medication use of patients included in this

study were consistent with the approved target populations in the CT-P10 label [32]. In addition, patients received the recommended dosage and regimen of CT-P10, according to the product label [32]. A large population of patients with NHL was included in this PMS study, comprising individuals with both FL and DLBCL; however, the sizes of the study populations with CLL and GPA/MPA were relatively small. Findings in the RA population are also limited by the low proportion of male patients. As such, further studies are warranted in these populations to confirm and extend the findings of the current analysis. Overall, there was a comprehensive evaluation of the safety profile for CT-P10 in this PMS study, and effectiveness evaluations used clinically relevant disease-specific measures. Effectiveness analyses were also conducted separately for rituximab-naïve and switched patients, providing pertinent information for the use of CT-P10 in routine clinical practice. Most patients with NHL or CLL received anticancer chemotherapy alongside CT-P10, consistent with the prescribing information [32]. This gives rise to a further limitation, in that concomitant medications may present a challenge for the attribution of ADRs to CT-P10. However, this reflects the use of CT-P10 in clinical practice, and therefore provides a relevant representation of the overall treatment safety profile. Considering that this observational study drew on experience with CT-P10 treatment in routine clinical practice, we believe that our findings should be generalizable to the wider patient population.

5. Conclusions

The findings of this PMS study of CT-P10 in patients with NHL, CLL, RA, or GPA/MPA treated in routine clinical practice in the Republic of Korea are consistent with the known safety profiles of CT-P10 and reference rituximab. Tolerable safety profiles were observed for patients who switched from other rituximab products to CT-P10, as well as for rituximab-naïve patients who initiated CT-P10. Serious ADRs were reported in a small proportion of patients, but the incidence was manageable and aligned with expectations. In terms of effectiveness, a high response rate was demonstrated for rituximab-naïve patients with NHL or CLL in a real-world setting. Overall, CT-P10 was effective and well tolerated with no unexpected safety findings in patients treated during routine clinical practice in the Republic of Korea.

Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
BOR	Best overall response
BSA	Body surface area
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CR	Complete response
DAS28	Disease Activity Score in 28 joints
DLBCL	Diffuse large B-cell lymphoma
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FL	Follicular lymphoma
GPA	Granulomatosis with polyangiitis
IRR	Infusion-related reaction
MPA	Microscopic polyangiitis
NHL	Non-Hodgkin's lymphoma
PMS	Post-marketing surveillance
PR	Partial response
RA	Rheumatoid arthritis
SD	Standard deviation

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Ethical approval

The authors state that this study adhered to the ethical principles of the Declaration of Helsinki for the conduct of medical research involving human subjects, and that ethical approval was obtained from appropriate local institutional review boards at each of the 27 study sites. All participants provided written informed consent.

Author contributions

JC Jo, Y Jeon, DJ Kim, DH Yang, WS Lee, YS Choi, JH Yi, DH Yoon, JH Kong, JY Choe, and SG Cho contributed to data collection and the interpretation of study data. SH Kim and KY Ahn contributed to the design of the study and the analysis or interpretation of study data. TH Park contributed to the analysis or interpretation of study data. H Ju contributed to data collection and the analysis or interpretation of study data. S Kwon contributed to the analysis or interpretation of study data. All authors reviewed and critically revised the manuscript, approved the final draft, and are accountable for the accuracy and integrity of the research.

Data availability statement

The data that support the findings of this study are available from the corresponding author, SG Cho, upon reasonable request.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Pierpont TM, Limper CB, Richards KL. Past, present, and future of rituximab—the world's first oncology monoclonal antibody therapy. Front Oncol. 2018;8:163.
2. US Food and Drug Administration. Rituxan: BLA approval letter. 1997. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/1997/ritugen112697L.htm [accessed 29 November 2022].
3. US Food and Drug Administration. Rituxan: highlights of prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103705s5467lbl.pdf [accessed 29 November 2022].
4. European Medicines Agency. MabThera: scientific discussion. 2006. Available at: https://www.ema.europa.eu/en/documents/scientific-discussion/mabthera-epar-scientific-discussion_en.pdf [accessed 29 November 2022].
5. European Medicines Agency. MabThera: summary of product characteristics. 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/mabthera-epar-product-information_en.pdf [cited 29 November 2022].
6. Dreyling M, Ghielmini M, Rule S, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32:298–308.
7. Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(5):v116–v125.
8. Ministry of Food and Drug Safety. Biological products. 2016. Available at: https://www.mfds.go.kr/eng/brd/m_30/view.do?seq=69797 [cited 29 November 2022].
9. US Food and Drug Administration. Truxima (CT-P10): highlights of prescribing information. 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761088s018lbl.pdf [cited 29 November 2022].
10. European Medicines Agency. Truxima: summary of product characteristics. 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/truxima-epar-product-information_en.pdf [cited 29 November 2022].
11. Bloomberg. 'First mover to game changer': Celltrion announces 2020-2030 strategy at the 38th J.P. Morgan Healthcare Conference. 2020. Available at: https://www.bloomberg.com/press-releases/2020-01-16/-first-mover-to-game-changer-celltrion-announces-2020-2030-strategy-at-the-38th-j-p-morgan-healthcare-conference [cited 29 November 2022].
12. Diaz LP, Millan S, Chaban N, et al. Current state and comparison of the clinical development of bevacizumab, rituximab and trastuzumab biosimilars. Future Oncol. 2021;17(19):2529–2544.
13. Lee KH, Lee J, Bae JS, et al. Analytical similarity assessment of rituximab biosimilar CT-P10 to reference medicinal product. mAbs. 2018;10(3):380–396.
• **Study highlighting the comparable physicochemical properties, biological activity, and efficacy of CT-P10, EU-approved reference rituximab, and US-licensed reference rituximab, in preclinical analyses.**
14. Park W, Bozic-Majstorovic L, Milakovic D, et al. Comparison of biosimilar CT-P10 and innovator rituximab in patients with rheumatoid arthritis: a randomized controlled Phase 3 trial. mAbs. 2018;10(6):934–943.
•• **Study highlighting the comparable pharmacokinetics, efficacy, immunogenicity, and safety profiles for CT-P10 and reference rituximab treatment in patients with RA.**
15. Yoo DH, Suh C-H, Shim SC, et al. A multicentre randomised controlled trial to compare the pharmacokinetics, efficacy and safety of CT-P10 and innovator rituximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2017;76(3):566–570.
16. Ogura M, Sancho JM, Cho S-G, et al. Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 in comparison with rituximab in patients with previously untreated low-tumour-burden follicular lymphoma: a randomised, double-blind, parallel-group, phase 3 trial. Lancet Haematol. 2018;5(11):e543–e53.
•• **Study highlighting the comparable pharmacokinetics, efficacy, immunogenicity, and safety profiles for CT-P10 and reference rituximab treatment in patients with low-tumor-burden FL.**
17. Kim WS, Buske C, Ogura M, et al. Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 compared with rituximab in patients with previously untreated advanced-stage follicular lymphoma: a randomised, double-blind, parallel-group, non-inferiority phase 3 trial. Lancet Haematol. 2017;4:e362–e373.
•• **Study highlighting the comparable pharmacokinetics, efficacy, immunogenicity, and safety profiles for CT-P10 and reference rituximab treatment in patients with advanced FL.**
18. Buske C, Jurczak W, Sancho JM, et al. Long-term efficacy and safety of CT-P10 or rituximab in untreated advanced follicular lymphoma: a randomized phase 3 study. Blood Adv. 2021;5:3354–3361.
19. Suh CH, Yoo DH, Berrocal Kasay A, et al. Long-term efficacy and safety of biosimilar CT-P10 versus innovator rituximab in rheumatoid arthritis: 48-week results from a randomized phase III trial. BioDrugs. 2019;33:79–91.
20. Shim SC, Bozic-Majstorovic L, Berrocal Kasay A, et al. Efficacy and safety of switching from rituximab to biosimilar CT-P10 in rheumatoid arthritis: 72-week data from a randomized Phase 3 trial. Rheumatology (Oxford). 2019;58:2193–2202.
21. Song NK, Musa H, Soriano M, et al. Safety and efficacy comparisons of rituximab biosimilars to the reference product in patients with cancer: a systematic meta-analysis review. J Pharm Pract Res. 2022;52:331–355.
22. Gulacsi L, Brodszky V, Baji P, et al. The rituximab biosimilar CT-P10 in rheumatology and cancer: a budget impact analysis in 28 European countries. Adv Ther. 2017;34:1128–1144.
23. Almaaytah A. Budget impact analysis of switching to rituximab's biosimilar in rheumatology and cancer in 13 countries within the Middle East and North Africa. Clinicoecon Outcomes Res. 2020;12:527–534.
24. Holm JEJ, Ruppert JG, Ramsden SD. Impact of changing regulations and the dynamic nature of European risk management plans for human medicines on the lifecycle of safety concerns. Pharmaceut Med. 2022;36:33–46.
25. Ball G, Reblin T, Buchanan J, et al. A framework for safety evaluation throughout the product development life-cycle. Ther Innov Regul Sci. 2020;54:821–830.
26. Lin LA, Zhang Y, Straus W, et al. Integrative analysis of randomized clinical trial and observational study data to inform post-marketing safety decision-making. Ther Innov Regul Sci. 2022;56:423–432.
27. Zinzani PL, Dreyling M, Gradishar W, et al. Are biosimilars the future of oncology and haematology? Drugs. 2019;79:1609–1624.
28. Blandizzi C, Galeazzi M, Valesini G. Transitioning from first- to second-generation biosimilars: an appraisal of regulatory and post-marketing challenges. Pharmacol Res. 2018;128:306–314.
29. European Medicines Agency. Truxima (rituxumab): public assessment report. 2016. Available at: https://www.ema.europa.eu/en/documents/assessment-report/truxima-epar-public-assessment-report_en.pdf [cited 29 November 2022].

30. US Food and Drug Administration. Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for industry. 2015. Available at: https://www.fda.gov/media/82647/download [cited 29 November 2022].
31. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 2014. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf [cited 29 November 2022].
32. Ministry of Food and Drug Safety. 2015. Truxima (rituximab): prescribing information [Korean]. Available at: https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetail?itemSeq=201504895 [cited 29 November 2022].
33. Stone JH, Hoffman GS, Merkel PA, et al. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSYS). Arthritis Rheum. 2001;44:912–920.
34. Mendes D, Abrantes J, Rigueiro G, et al. Real-world intensive safety monitoring of biosimilars rituximab and trastuzumab in a Portuguese oncology hospital. J Oncol Pharm Pract. 2021;27:1432–1438.
35. Yun H, Xie F, Delzell E, et al. Risks of herpes zoster in patients with rheumatoid arthritis according to biologic disease-modifying therapy. Arthritis Care Res (Hoboken). 2015;67:731–736.
36. Curtis JR, Xie F, Yun H, et al. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. Ann Rheum Dis. 2016;75:1843–1847.
37. Liao TL, Chen YM, Liu HJ, et al. Risk and severity of herpes zoster in patients with rheumatoid arthritis receiving different immunosuppressive medications: a case-control study in Asia. BMJ Open. 2017;7:e014032.
38. Liao T-L, Lin C-H, Chen -H-H, et al. Significant associations of neurological complications of herpes zoster with stroke in rheumatoid arthritis patients. J Am Heart Assoc. 2017;6:e006304.
39. Rutherford AI, Patarata E, Subesinghe S, et al. Opportunistic infections in rheumatoid arthritis patients exposed to biologic therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Rheumatology (Oxford). 2018;57:997–1001.
40. Lunardon L, Tsai KJ, Propert KJ, et al. Adjuvant rituximab therapy of pemphigus: a single-center experience with 31 patients. Arch Dermatol. 2012;148:1031–1036.
41. Kwak LW, Sancho JM, Cho SG, et al. Efficacy and safety of CT-P10 versus rituximab in untreated low-tumor-burden follicular lymphoma: final results of a randomized phase III study. Clin Lymphoma Myeloma Leuk. 2022;22:89–97.
42. Lee K, Ha JY, Jung AR, et al. The clinical outcomes of rituximab biosimilar CT-P10 (Truxima®) with CHOP as first-line treatment for patients with diffuse large B-cell lymphoma: real-world experience. Leuk Lymphoma. 2020;61:1575–1583.
43. McBride A, Daniel S, Driessen MT, et al. Assessment of rituximab-abbs, a biosimilar, and rituximab outcomes in patients with CLL or NHL: a real-world UK study. Leuk Res. 2021;111:106671.
• **Real-world study highlighting the similar effectiveness and tolerability or CT-P10 and reference rituximab in patients with CLL and NHL.**
44. Coiffier B, Haioun C, Ketterer N, et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood. 1998;92:1927–1932.
45. Walewski J, Paszkiewicz-Kozik E, Michalski W, et al. First-line R-CVP versus R-CHOP induction immunochemotherapy for indolent lymphoma with rituximab maintenance. A multicentre, phase III randomized study by the Polish Lymphoma Research Group PLRG4. Br J Haematol. 2020;188:898–906.
46. Ghielmini M, Schmitz SF, Cogliatti S, et al. Effect of single-agent rituximab given at the standard schedule or as prolonged treatment in patients with mantle cell lymphoma: a study of the Swiss Group for Clinical Cancer Research (SAKK). J Clin Oncol. 2005;23:705–711.
47. Haematological Malignancy Research Network. QuickStats. 2022. Available at: https://hmrn.org/statistics/quickstats [cited 29 November 2022].
48. Chatzidionysiou K, Lie E, Lukina G, et al. Rituximab retreatment in rheumatoid arthritis in a real-life cohort: data from the CERERRA collaboration. J Rheumatol. 2017;44:162–169.
49. Vander Cruyssen B, Durez P, Westhovens R, et al. The Belgian MIRA (MabThera In Rheumatoid Arthritis) registry: clues for the optimization of rituximab treatment strategies. Arthritis Res Ther. 2010;12:R169.
50. Melville AR, Md Yusof MY, Fitton J, et al. Real-world experience of effectiveness of non-medical switch from originator to biosimilar rituximab in rheumatoid arthritis. Rheumatology (Oxford). 2021;60:3679–3688.