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Efficacy and safety of rituximab biosimilar in refractory lupus

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ABSTRACT

Aims To characterise patients with refractory SLE receiving rituximab biosimilar (CT-P10) and to explore short-term efficacy and safety associated with rituximab biosimilar use.

Methods We retrospectively analysed data from the medical records of patients with refractory SLE who received CT-P10 in Ramathibodi Hospital, Mahidol University, Thailand. Baseline characteristics, disease activity (modified Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)), response to treatment at 6 months after CT-P10 and infection over 6 months were recorded.

Results Thirty-two patients with SLE received CT-P10 from April 2018 to June 2019. Of these, 29 (90.6%) were female and the mean±SD age was 36.8±15.2 years. The median (IQR) disease duration was 9.5 (1.3–13.0) years. All patients received glucocorticoid treatment and used 1.7±0.1 immunosuppressive agents at baseline, excluding antimalarial drugs. Baseline Systemic Lupus International Collaborating Clinics Damage Index score was 0.5 (0.0–1.0). Overall response, which was defined as a reduction in the modified SLEDAI score of ≥4, was achieved in 25.0% of patients at 6 months. The modified SLEDAI score reduced from 4 (1.3–8.0) at baseline to 1 (0.0–5.8) at 6 months (p=0.005). Response by active organ involvement was 71.8%. Serious infection occurred in four patients (12.5%), resulting in one death. The median time of onset of infection after CT-P10 infusion was 35.5 (17.0–72.5) days.

Conclusion Rituximab biosimilar is associated with improvement in active organ involvement in patients with refractory SLE. Infection occurred early after rituximab biosimilar infusion.

INTRODUCTION

Polyclonal B cell hyper-reactivity has been well described in SLE, and B cells have been considered a potential therapeutic target.[1] Rituximab (RTX) is a chimeric monoclonal antibody that depletes CD20+ B cells. Two randomised, placebo-controlled trials of RTX failed to reach their primary endpoints.[2 3] However, other observational studies of RTX use in patients with SLE and refractory lupus are promising.[4–11]

Preclinical and clinical data have demonstrated the equivalence and similarity of RTX biosimilar, CT-P10, to RTX originator.[12] In this retrospective cohort, our primary objective was to characterise patients with refractory lupus receiving CT-P10 and to explore its short-term efficacy and safety.

PATIENTS AND METHODS

We retrospectively analysed data of patients with refractory SLE who commenced RTX biosimilar therapy in Ramathibodi Hospital, Mahidol University, Thailand, between April 2018 and June 2019.

Patients with SLE, classified according to the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria, aged above 16, refractory to treatment (failure of at least one immunosuppressant), commenced a new biologic therapy with CT-P10 and with follow-up up to 6 months were included. We also included patients who expired before 6 months. Patients who previously received any biologic agent within 1 year or were diagnosed overlapping with other rheumatic diseases were excluded from the study.

Demographic data, disease duration, comorbidities and SLICC Damage Index (SDI) score were collected at baseline. Disease activity (modified SLEDAI[13]), laboratory data and immunosuppressive agents use were recorded at baseline and 6 months after the first infusion of CT-P10.

Efficacy analysis

Overall response was defined as a reduction in the modified SLEDAI-2K score of ≥4. Disease flare was defined as an increase in the modified SLEDAI-2K score of ≥4. Response by specific organ was defined as ≥50% improvement of that organ according to SLEDAI-2K Responder Index-50 (SRI-50) definitions.[14] For a specific organ that was not mentioned in SRI-50, response was defined as a significant improvement (≥50%) of initial disease, based on clinical judgement. Complete renal response was defined as normal kidney function (within 10% of normal GFR) and proteinuria <0.5 g/day. Partial renal response was defined as near-normal GFR and ≥50% reduction of proteinuria to subnephrotic levels.

Table 1 Characteristics of 32 patients with SLE receiving rituximab biosimilar

Characteristics	n (%)
Female	29 (90.62)
Age (at first RTX biosimilar infusion), mean±SD, years	36.75±15.22
Disease duration, median (IQR), years	9.50 (1.25–13.00)
2012 SLICC classification criteria	
Clinical criteria	
Acute cutaneous lupus	10 (31.25)
Chronic cutaneous lupus	8 (25.00)
Oral ulcers	5 (15.62)
Non-scarring alopecia	8 (25.00)
Synovitis	16 (50.00)
Serositis	3 (9.38)
Renal	16 (50.00)
Neurological	9 (28.13)
Haemolytic anaemia	6 (18.75)
Leucopenia	14 (43.75)
Thrombocytopaenia	15 (46.88)
Immunological criteria	
ANA level above laboratory reference range	32 (100.00)
Anti-dsDNA antibody level above laboratory reference range	18 (56.25)
Anti-Sm	3 (9.38)
Antiphospholipid antibody positivity	8 (25.00)
Low complement	27 (84.38)
Direct Coombs test in the absence of haemolytic anaemia	0 (0.00)
Comorbidity and damage	
Chronic HBV infection	2 (6.25)
Hypertension	8 (25.00)
Dyslipidaemia	8 (25.00)
End-stage renal disease	3 (9.38)
SLICC Damage Index, median (IQR)	0.50 (0.00–1.00)
RTX biosimilar administration	
1 g × 2 infusions per 2 weeks	13 (40.63)
500 mg × 2 infusions per 2 weeks	10 (31.25)
1 g × 1 infusion	5 (15.63)
500 mg × 1 infusion	1 (3.13)
Other regimen	3 (9.38)
RTX biosimilar-associated treatment (prior/concurrent)	
Glucocorticoids	32 (100.00)
Oral	32 (100.00)
Intravenous	13 (40.63)
Immunosuppressive agents	
Intravenous cyclophosphamide	12 (37.50)
Oral cyclophosphamide	2 (6.25)
Mycophenolate mofetil	21 (65.63)
Azathioprine	14 (43.75)
Ciclosporin	9 (28.13)
Tacrolimus	3 (9.38)
Methotrexate	6 (18.75)
Hydroxychloroquine	23 (71.88)
Number of immunosuppressive agents (excluding antimalarial drugs) before RTX biosimilar infusion, mean±SD	1.72±0.13
Intravenous immunoglobulin	4 (12.50)
Plasma exchange	4 (12.50)

dsDNA, double-stranded DNA; HBV, viral hepatitis B; RTX, rituximab; SLICC, Systemic Lupus International Collaborating Clinics.

Safety analysis

Immediate infusion reaction (within 48 hours) was recorded. Serious infections were defined as any infection requiring hospitalisation and/or intravenous antibiotics or resulting in disability or death.

Statistical analysis

Paired t-test and Wilcoxon test were used to compare paired continuous variables with normal distribution and non-normal distribution, respectively. P values less than 0.05 were considered statistically significant. Data were analysed using SPSS V.22.0 software.

RESULTS

Patient characteristics

A total of 32 patients were enrolled in this study. Of these, 29 (90.6%) were female and the mean±SD age was 36.8±15.2 years. The median (IQR) disease duration was 9.5 (1.3–13.0) years. The median SDI and modified SLEDAI-2K scores were 0.5 (0.0–1.0) and 4.0 (1.3–8.0), respectively (table 1). The most common organ involvement during RTX biosimilar administration was lupus nephritis (n=13). Six patients had more than one organ involvement.

At baseline, all patients received glucocorticoid and 1.7±0.1 immunosuppressive agents, excluding antimalarial drugs. Mycophenolate mofetil (65.6%), cyclophosphamide (43.8%) and azathioprine (43.8%) are among the most common CT-P10-associated treatment. The most common RTX biosimilar regimen was two infusions of 1000 mg in a 2-week interval (13 patients, 40.6%).

Efficacy of RTX biosimilar

Overall response was achieved in 25.0% of patients. The median modified SLEDAI-2K score reduced from 4 (1.3–8.0) at baseline to 1 (0.0–5.8) at 6 months

Table 2 Response to rituximab biosimilar at 6 months after treatment of patients with SLE

Clinical parameter	Patients evaluable for outcome	Baseline	6 months	P value	Overall response* (%)
Modified SLEDAI-2K, median (IQR)	32	4 (1.25–8.00)	1 (0.00–5.75)	0.005	8/32 (25.00)
Anti-dsDNA level, median (IQR), IU/mL	20	10.70 (0.00–109.28)	0.00 (0.00–89.68)	0.041	–
C3 mean±SD (range), g/L	32	0.90±0.33 (0.23–1.60)	1.05±0.28 (0.55–1.55)	0.015	–
Prednisolone dose, median (IQR), mg	32	20 (12.50–40.00)	10 (7.50–15.00)	<0.001	–
Response according to specific organ†					**Response (%)**
NPSLE	7	–	–	–	7/7 (100.00)
Seizure	1	–	–	–	1
Myelitis‡	1	–	–	–	1
Peripheral neuropathy‡	2	–	–	–	2
Organic brain syndrome	2	–	–	–	2
Lupus headache	1	–	–	–	1
Vasculitis	2	–	–	–	2/2 (100.00)
Gastrointestinal‡	1	–	–	–	1
Cutaneous	1	–	–	–	1
Arthritis	3	–	–	–	3/3 (100.00)
Proteinuria, median (IQR), g/day	13	4.10 (1.20–6.65)	0.85 (0.36–2.45)	0.012	8/13 (61.54)
Rash	1	–	–	–	1/1 (100.00)
Thrombocytopaenia (<140 x 10^9/L), median (IQR)	9	74 x 10^9 (42 x 10^9–108.5 x 10^9)	186.5 x 10^9 (132 x 10^9–241.75 x 10^9)	0.092	5/9 (55.56)
Leucopenia (<4 x 10^9/L), median (IQR)	3	3.16 x 10^9 (1.20 x 10^9–3.97 x 10^9)	3.68 x 10^9 (1.88 x 10^9–3.84 x 10^9)	0.285	0/3 (0.00)
Others	1	–	–	–	1/1 (100.00)
Total response	39	–	–	–	28/39 (71.79)

*Reduction in SLEDAI-2K or modified SLEDAI-2K score of ≥4.
†≥50% improvement according to SLEDAI-2K Responder Index-50 definitions; six patients had more than one specific organ involvement.
‡Significant improvement (≥50%) of initial disease, based on clinical judgement.
dsDNA, double-stranded DNA; NPSLE, neuropsychiatric SLE; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000.

(p=0.005). Total response according to specific organ was 71.8% (table 2). Complete and partial renal response were achieved in three (23.1%) and five (15.6%) patients, respectively. Serological improvement was also observed, with an increase in C3 levels and a decrease in anti-double-stranded DNA level (table 2). RTX biosimilar treatment facilitated steroid reduction from 20 (12.5–40.0) mg to 10 (7.5–15.0) mg (p<0.001). Disease flare was observed in two patients (6.3%) at 6 months, who had new onset of microscopic haematuria and pyuria, without a decline in renal function. Details of the 32 enrolled patients are summarised in table 3.

Safety of RTX biosimilar

Immediate infusion reaction was observed in three patients (9.4%) (flushing and skin pruritus). No severe infusion reactions were observed.

Infections were noted in six patients (18.8%) and were severe in four patients (12.5%). Acute pyelonephritis (3 patients, 9.4%) and cytomegalovirus (CMV) infection (3 patients, 9.4%) were the most common infections. Two patients had multiple infections, resulting in one death. The median time of occurrence of infections in all infected patients was 35.5 (17.0–72.5) days after CT-P10 infusion.

DISCUSSION

Our study is based on retrospective data of patients with refractory SLE using CT-P10 in actual clinical practice. Overall response was achieved in only 25.0% of patients. This number is much lower than the previous meta-analysis of RTX originator in refractory SLE that reported

Table 3 Characteristics, main indication for rituximab biosimilar, regimen and response to treatment of 32 enrolled patients

Number	Previous therapy (other than steroids and antimalarial)	Specific organ involvement	Baseline prednisolone (mg/day)	RTX biosimilar regimen (mg) × infusion(s)	Concomitant therapy (other than steroids and antimalarial)	Prednisolone at 6 months (mg/day)	Response by organ involvement
1	IVCY	Seizure*	60	1000×2	IVCY	15	Y
2	IVCY	Transverse myelitis*	60	1000×2	AZA	7.5	Y
3	MTX, TAC, MMF, IVIG	Chronic inflammatory demyelinating polyneuropathy*	30	1000×2	LEF, TAC, MMF	30	Y
4	MMF, CY	Small fibre neuropathy*	15	500×2	CY	10	Y
5	IVCY, IVIG, PLEX	Acute confusional state, lupus nephritis*	60	1000×1	AZA	17.5	Y, Y
6	IVCY	Acute confusional state, lupus nephritis, thrombocytopaenia*	75	1000×1	AZA	10	Y, Y, Y
7	AZA, IVCY	Lupus headache*	20	1000×2	AZA, CYA	10	Y
8	IVCY, PLEX	Gastrointestinal vasculitis*, lupus nephritis (class III)	50	1000×1	MMF, IVCY	30	Y, Y
9	MMF, CY	Cutaneous vasculitis*	15	1000×2	MMF, AZA	15	Y
10	CYA, IVCY	Arthritis*	30	1000×2	CYA, MTX	10	Y
11	MTX	Arthritis*	17.5	500×2	MTX, MMF	10	Y
12	MTX	Arthritis*	5	500×2	MTX, MMF	10	Y
13	MMF, IVCY	Lupus nephritis*	25	500×2	MMF, TAC	10	Y
14	IVCY, PLEX	Lupus nephritis*	40	500×2	MMF	10	Y
15	CYA, MMF, IVCY	Lupus nephritis (class IV)*	20	1000×2	CYA, MMF	10	Y
16	MTX, MMF	Lupus nephritis*	1.5	1000×2	MTX, MMF	0.5	N
17	CYA, MMF	Lupus nephritis (class IV+V)*	10	1000×2	CYA, MMF	7.5	N
18	MTX, MMF	Lupus nephritis*	5	1000×2	MTX, CYA, MMF	5	N
19	MMF, IVCY	Lupus nephritis (class III)*	75	500×2	MMF, IVCY	20	Y
20	AZA, MMF	Lupus nephritis*, thrombocytopaenia	40	1000×1	AZA, MMF	7.5	Y, Y
21	IVCY	Lupus nephritis*, thrombocytopaenia	60	500×3	None (expired from infection)	–	N, N
22	MMF, IVIG	Lupus nephritis (class III+V)*, thrombocytopaenia	30	1000×1	MMF	20	N, Y
23	MMF	Photosensitive lupus rash*	15	500×2	MMF	10	Y
24	AZA, CYA, MMF	Thrombocytopaenia*	12.5	500×2	AZA, CYA, MMF	7.5	N
25	MMF	Thrombocytopaenia*	20	500×2, 1000×1	MMF, IVIG	10	N
26	AZA, CYA	Thrombocytopaenia*	15	1000×2	AZA, CYA	5	Y
27	AZA, CYA	Thrombocytopaenia*	15	1000×2	AZA, CYA	2.5	Y
28	AZA, CYA, MMF	Thrombocytopaenia*	12.5	500×2	AZA, CYA, MMF	10	N
29	AZA, TAC	Leucopenia*	12.5	500×2	AZA, TAC	7.5	N
30	AZA	Leucopenia*	40	1000×2	AZA	25	N
31	AZA, MMF	Leucopenia*	5	500×1	AZA, MMF	5	N

Continued

Table 3 Continued

Number	Previous therapy (other than steroids and antimalarial)	Specific organ involvement	Baseline prednisolone (mg/day)	RTX biosimilar regimen (mg) × infusion(s)	Concomitant therapy (other than steroids and antimalarial)	Prednisolone at 6 months (mg/day)	Response by organ involvement
32	AZA	Coagulation factor inhibitor*	75	500×4	MMF	30	Y

*Main indication for rituximab biosimilar infusion.
AZA, azathioprine; CY, oral cyclophosphamide; CYA, ciclosporin A; IVCY, intravenous cyclophosphamide; IVIG, intravenous immunoglobulin; LEF, leflunomide; MMF, mycophenolate mofetil; MTX, methotrexate; N, no; PLEX, plasma exchange; RTX, rituximab; TAC, tacrolimus; Y, yes.

the overall response to be 72.0%.[9] First, this discrepancy might be explained by a different definition of overall response. Second, the modified SLEDAI-2K cannot distinguish features of clinical activities that are only partly improved. Third, this index also misses out some clinical features of patients in this study. The reason for relatively low disease activity in our study may be explained by the main indication for RTX biosimilar use in 16 patients (50.0%) being non-severe manifestations or organ that is not included in the modified SLEDAI-2K score. Response according to specific organ using more sensitive criteria able to capture partial improvement was 71.8%, much higher than the overall response number.

RTX biosimilar displayed promising effects in neuropsychiatric SLE with 100% clinical response. Renal response (complete and partial) was 61.5%, comparable with previous studies (56.9%–67.0%).[3 6] Patients with immune thrombocytopaenia demonstrated 55.6% response. Moreover, RTX biosimilar might be used as a steroid-sparing drug, demonstrated by reducing the median dose of prednisolone from 20 (12.5–40) to 10 (7.5–15) mg/day.

Severe infections were noted in 12.5% of patients, slightly higher than a previous study of RTX originator (4.7%–11.0%).[5 7 8 11] The high incidence of CMV infection in the current study (9.4%) might be explained by the use of high-dose corticosteroids and strong immunosuppressive drug, such as intravenous cyclophosphamide.[15]

The majority of infections occurred in the first 2 months post RTX biosimilar infusion, when most of the patients were still in high disease activity, on high-dose steroid and a maximum period of B cell depletion. Immediate infusion reaction was 9.4%, comparable with previous studies of RTX originator (3.7%–21.2%).[5 7 8]

Our study possesses some limitations. First of all, the study design is retrospective. The sample size in this study is relatively small. Moreover, this study only reported short-term outcomes up to 6 months.

The unmet need in the therapeutics of SLE is to develop affordable treatment regimens that are more efficacious but associated with fewer side effects. Our findings demonstrate that RTX biosimilar achieved significant efficacy and an acceptable safety profile in refractory SLE. The results are comparable with RTX originator studies.

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Competing interests None declared.

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REFERENCES

1 Liossis S-NC, Staveri C. B cell-based treatments in SLE: past experience and current directions. *Curr Rheumatol Rep* 2017;19:78.
2 Merrill JT, Neuwelt CM, Wallace DJ, *et al*. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum* 2010;62:222–33.
3 Rovin BH, Furie R, Latinis K, *et al*. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the lupus nephritis assessment with rituximab study. *Arthritis Rheum* 2012;64:1215–26.
4 Ramos-Casals M, Soto MJ, Cuadrado MJ, *et al*. Rituximab in systemic lupus erythematosusA systematic review of off-label use in 188 cases. *Lupus* 2009;18:767–76.
5 Terrier B, Amoura Z, Ravaud P, *et al*. Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French autoimmunity and rituximab registry. *Arthritis Rheum* 2010;62:2458–66.
6 Díaz-Lagares C, Croca S, Sangle S, *et al*. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. *Autoimmun Rev* 2012;11:357–64.
7 Witt M, Grunke M, Proft F, *et al*. Clinical outcomes and safety of rituximab treatment for patients with systemic lupus erythematosus (SLE) - results from a nationwide cohort in Germany (GRAID). *Lupus* 2013;22:1142–9.
8 Iaccarino L, Bartoloni E, Carli L, *et al*. Efficacy and safety of off-label use of rituximab in refractory lupus: data from the Italian multicentre registry. *Clin Exp Rheumatol* 2015;33:449–56.
9 Alshaiki F, Obaid E, Almuallim A, *et al*. Outcomes of rituximab therapy in refractory lupus: a meta-analysis. *Eur J Rheumatol* 2018;5:118–26.
10 Iwata S, Saito K, Hirata S, *et al*. Efficacy and safety of anti-CD20 antibody rituximab for patients with refractory systemic lupus erythematosus. *Lupus* 2018;27:802–11.
11 McCarthy EM, Sutton E, Nesbit S, *et al*. Short-Term efficacy and safety of rituximab therapy in refractory systemic lupus erythematosus: results from the British Isles lupus assessment group biologics register. *Rheumatology* 2018;57:470–9.

12 Coiffier B. Pharmacokinetics, efficacy and safety of the rituximab biosimilar CT-P10. *Expert Rev Clin Pharmacol* 2017;10:923–33.
13 Uribe AG, Vilá LM, McGwin G, *et al*. The systemic lupus activity Measure-revised, the Mexican systemic lupus erythematosus disease activity index (SLEDAI), and a modified SLEDAI-2K are adequate instruments to measure disease activity in systemic lupus erythematosus. *J Rheumatol* 2004;31:1934–40.
14 Touma Z, Gladman DD, Ibañez D, *et al*. Development and initial validation of the systemic lupus erythematosus disease activity index 2000 Responder index 50. *J Rheumatol* 2011;38:275–84.
15 Choo HMC, Cher WQ, Kwan YH, *et al*. Risk factors for cytomegalovirus disease in systemic lupus erythematosus (SLE): a systematic review. *Adv Rheumatol* 2019;59:12.