Neurology Asia 2024; 29(1) : 193 – 199

Direct cost of rituximab treatment in multiple sclerosis: A real-world finding from Malaysia

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Abstract

Background & Objective: Multiple sclerosis (MS) imposes a significant economic burden on the healthcare system. In 2022, more than half of the Neurology budget of Hospital Seberang Jaya was spent on rituximab, an off-label drug for treating MS. Recently, the availability of rituximab biosimilar had provided an opportunity for cheaper treatment alternatives for subsidised patients or patients opting to self-purchase the medication. This study aimed to estimate the clinical outcome and cost of treatment of MS patients on Mabthera (originator) and Truxima (biosimilar). *Methods:* A retrospective analysis of MS patients treated with rituximab from April 2018 to April 2023 was performed. Clinical charts and documented adverse events were reviewed. Healthcare costs were estimated based on rituximab treatment, hospitalisation charges, personnel and other diagnostic costs. Results: Four patients treated with Mabthera and three with Truxima, with follow-up, ranging from 1 to 5 years (median: 3 years), were included. Two relapses occurred during follow-up, whereby one Mabthera and Truxima patient, respectively. Expanded Disability Status Scale (EDSS) score improved in four patients, three patients treated with Mabhtera and one patient treated with Truxima. MR imaging reported no new changes in all the patients and a new lesion in one Truxima-treated patient. The estimated treatment drug cost of Mabthera was USD 7294.62 per patient/year and Truxima USD 3612.90 per patient/year. The total estimated personnel cost for a typical 2-day admission without complication is USD 62.26, the diagnostic cost for a complete blood count and urinalysis is USD 2.37, and the bedding cost is USD 1.29 for a typical two days. The total cost difference in treatment is affected mainly by the rituximab drug cost unless patients with urinary tract infection on day 14 are treated, and the length of stay is prolonged with antibiotics administration.
Conclusion: Our findings showed that Mabthera and Truxima were well tolerated. There is a significant difference in the cost of rituximab (p=0.026), bedding cost (p=0.048), healthcare professional cost(p=0.048) and the total cost (p=0.032) among patients on Mabthera and Truxima. However, as the number of patients treated with Truxima is limited, a longitudinal cohort or multi-centre approach could be carried out.

Keywords: Multiple sclerosis, Mabthera, Truxima, Expanded Disability Status Scale (EDSS), cost

INTRODUCTION

Rituximab is a monoclonal antibody that kills B cells through cellular cytotoxicity, complement activation and apoptosis induction. By preventing B lymphocytes from acting as antigen-presenting cells and activating T lymphocytes, as well as by preventing B lymphocytes from differentiating into new plasma cells that could produce autoreactive antibodies and release cytokines, this depletion would modify the pathogenic process. Rituximab is licensed and approved mostly for treating non-Hodgkin lymphoma and rheumatoid arthritis. In recent years, rituximab has appeared to be an appealing substitute for traditional immunomodulatory drugs as a swiftly acting, targeted treatment with mounting evidence of effectiveness and tolerance in numerous neuroinflammatory conditions, including multiple

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Date of Submission: 3 November 2023; Date of Acceptance: 24 January 2024
https://doi.org/10.54029/2024epj

sclerosis (MS).[1] However, it is not licensed for use in MS and is still used as off-label for this indication.

In 2017, the European Medicines Agency (EMA) authorised Truxima (CT-P10) a biosimilar of Mabthera for use in the European Union (EU). It was created as a biological pharmaceutical product comparable to Mabthera's reference medicinal product and contains the active ingredient rituximab. The pharmacological form, concentration, formulation, and mode of administration of CT-P10 are all the same as those of the original rituximab. CT-P10 is a glycoprotein having one N-linked glycosylation site in the CH2 domain of each heavy chain, similar to other IgG subclasses. Each heavy chain has 11 cysteine residues and 450 amino acids, whereas each light chain has 5 cysteine residues and 213 amino acids. Both healthy and cancerous B cells have the CD20 antigen on their surfaces, which CT-P10 binds to. By binding to CD20 antigen, the main mechanisms of CT-P10 are complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and induction of apoptosis. The finished product is presented as a sterile solution for injection containing 500 mg of CT-P10 as an active substance.[2]

Currently, in Hospital Seberang Jaya, a secondary healthcare hospital in Penang of Northern peninsular Malaysia, there are an estimation of 20 patients who are on intravenous rituximab for various auto-immune neurological diseases besides MS including neuromyelitis optica (NMO), myasthenia gravis (MG) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Hospital Seberang Jaya neurology unit is the second largest user of rituximab for the treatment of MS in the country after Hospital Kuala Lumpur. As rituximab is not licensed for use in MS, and is not listed for MS treatment in the Malaysia Ministry of Health (MOH) drug formulary, it is given as off-label treatment with the approval of permission to use from the Director General of Health or in the Malay language is known as Kelulusan Pengarah Kesihatan (KPK) and patient written consent. The hospital purchasing of medication under the purview of the Pharmacy Department is separated into financial allocation as per discipline including the Neurology Department. The Neurology budget is used for procurement of medication for various diseases ranging from stroke, Parkinson disease, myasthenia gravis and MS. MS related medication have been the most expensive among all the neurology related medication. As only rituximab (Mabhtera) is listed in the government tender, not many patients are able to be treated as the high cost of Mabthera with limited healthcare budget in Hospital Seberang Jaya. Therefore, the availability of Truxima had provided an opportunity for cheaper treatment alternatives for subsidized patients or patients opting to self-purchase the medication. The present study aimed to evaluate both rituximab (Mabthera and Truxima) related efficacy and safety, also to determine direct treatment cost from the healthcare perspective for MS patients in the spectrum of relapsing-remitting MS and secondary progressive MS. There have yet to be published studies pertaining to the above in the Malaysian setting, and limited papers are available on biosimilar rituximab usage in MS patients.

METHODS

Study design and location

A retrospective analysis was conducted on the medical records of MS patients receiving rituximab treatment in Seberang Jaya Hospital for a minimum of 1 year. Data on the patients' age and rituximab related clinical outcomes, any emergency admission or hospitalization and documented adverse events were retrieved.

Outcome measures

The direct treatment cost consists of the drug cost of rituximab for both Mabthera and Truxima, hospitalization cost, healthcare personnel cost, laboratory cost for routine tests and specific diagnostic test for MS. The costs were obtained from hospital pricing list for drugs, personnel cost from Public Service Department pay schedule, laboratory cost from Fee Act 1951 Malaysia and specific lab test cost was sourced from private labs in Penang, Malaysia. The clinical outcomes were assessed based on disability status using Expanded Disability Status Scale (EDSS) pre and post rituximab dose, number of clinical relapses and side effect such as urinary tract infection (UTI).

Ethical approval

The research was registered with National Medical Research Registry with the registration identification NMRR ID-23-02346-NU4.

Statistical analysis

Patients' age, rituximab related clinical outcomes and direct treatment costs were compared between

the Mabthera and Truxima using Mann Whitney U-test. A p value of $p<0.005$ was determined to be significant.

RESULTS

Majority of the cost is from the drug cost, followed by healthcare service cost, laboratory service cost mainly diagnosis markers, aquaporin-4, MOG AB, ANA and oligoclonal bands IgG (CSF and serum). (Table 1)

Four patients treated with Mabthera and three patients with Truxima, with follow-up, ranging 1 to 5 years (median: 3 years), were included. Two relapses occurred during follow-up, whereby one Mabthera and Truxima patient, respectively. EDSS score improved in four patients (Mabthera n=2 & Truxima=2), two remained static (Mabthera n=1 & Truxima n=1) and worsened in one (Mabthera=1). MRI imaging reported no new changes in all patients and a new lesion in one Truxima patient. Urinary tract infection is the only side effect seen for both Mabthera and Truxima. (Figure 1)

Table 2 shows there were no significant differences in the baseline characteristics such as age, disease duration, number of Rituximab doses and EDSS (pre). There were also no significant differences in the EDSS (post), number of UTI, number of relapses. However, prolonged stay due to UTI among Mabthera and Truxima group of patients were significantly different (p=0.048).

Table 3 shows there is a significant difference in the cost of rituximab (p=0.026), bedding cost (p=0.048), healthcare professional cost (p=0.048) and the total cost (p=0.032) among patients on Mabthera and Truxima.

DISCUSSION

As per literature search conducted in November 2023 using the key MeSH (Medical Subject Headings) terms "rituximab" AND "multiple sclerosis" AND "biosimilar" showed only five results in PubMed. A review paper on the current evidence of rituximab in the treatment of MS highlighted that observational data have shown that rituximab has high efficacy in different MS population.[3] The review also concluded that optimal dosing regimen and duration of rituximab for MS is not conclusive and rituximab biosimilar is a cost-effective option for resource limited setting.[3]

Truxima, a biosimilar ritixumab is relatively cheaper compared to Mabthera.[3] The biosimilar rituximab available worldwide are Truxima, Rixathon and Reditux. In Malaysia, disease modifying therapy such as fingolimod and interferon beta are the main therapy used in MS is as evidence-based medicine supports the use of these DMTs in lowering hospitalisation and relapses. However, the high cost of DMTs makes it unaffordable for Malaysians for self-purchase if it not funded by the government similar to the situation faced by other lower and middle income countries (LMIC). In the public hospital scenario, a hospital's neurology budget is significantly used for the procurement of DMTs causing budget constraint for other purchases if DMT procurement is prioritised. In Malaysia, rituximab is used as the second-line and off-label use for MS. Rituximab is prescribed as an off-label medication for MS similar to many other countries. Mabthera, the innovator rituximab is twice more expensive compared to the biosimilar brand Truxima. However, the awarding of a tender for the purchase of Mabthera has made Ministry of Health facilities unable to purchase the biosimilar brand during tender contract period. Patients on self-purchase and Civil Service Department claims can purchase the biosimilar brands. The following study was conducted to compare the clinical outcome, cost incurred and side effect of Mabthera and Truxima. A recent Thai study concluded that biosimilar rituximab reduced overall cost of MS treatment with higher effectiveness. The probability of relapse was the most sensitive parameter.[4] There has been a change in prescribing rituximab since a retrospective study showed the superiority of rituximab to Rebif (interferon beta) in relapsing-remitting MS.[5] A recent study comparing the cost of monoclonal antibodies in managing relapsing-remitting MS also showed that rituximab is more effective and less costly than natalizumab, another monoclonal antibody used in MS.[6] In our study, there was a significant difference in the cost of rituximab (p=0.026), bedding cost (p=0.048), healthcare professional cost (p=0.048) and the total cost (p=0.032) among patients on Mabthera and Truxima. To the best of our knowledge, this is the first study in Malaysia comparing rituximab to biosimilar brand for MS indication. A recent prospective, nonrandomized study comparing the efficacy, safety, and tolerability of CT-P10 to the originator MabThera® in MS patients showed that ARR, EDSS scores, MRI activity, and adverse events at 1 year were similar between the two drugs.[7] These findings supported the use of biosimilar rituximab as an alternative therapeutic option for MS patients, particularly those in low-/middle-income countries or with limited access to standard DMTs.[7]

Table 1: Description on cost of inpatient and outpatient multiple sclerosis patient

Type of Cost	Cost data resource	Details
Rituximab 500mg	Hospital pricing list (contract item)	(Mabthera) - RM5,500 per vial (Truxima) - RM2,200 per vial
Healthcare service	Pay schedule of Public Service Department (Calculation based on	
Neurologist UD56	minimum basic pay for the service	RM 6504/month
Medical officer UD48	grade which will be divided by	RM 5211/month
Pharmacist UF48	the number of hours of service)	RM 5211/month
Nurse UF29 x 2 ppl		RM 1312/month
Biochemist cost C41		RM2317/month
Biochemist cost C44		RM3605/month
Laboratory cost per sample run	Depending on type of sample	
Prothrombin time		RM 3.00
Activated partial thromboplastin time		RM 3.00
White blood cell		RM 2.35
Differential count		RM 20
Coagulation factor IX		RM 20
inhibitors		RM 7.30
Coagulation factor IX		RM 6.40
activity		RM 5.10
HIV serology		RM 12.80
Hepatitis B surface Ab (Hbs Ab)		RM 0.30
Hepatitis B surface Ag (Hbs Ag)		RM 0.30
Hepatitis C virus (HCV Ab)		RM 0.30
Liver function test		
Total bilirubin		RM 0.25
Total protein		RM 0.25
Alkaline phosphate		RM 0.25
Alanine transaminase		RM 0.25
Renal profile		
Urea		RM 0.30
Sodium		RM 0.30
Potassium		RM 0.30
Chloride		RM 0.30
Creatinine		RM 0.30
Pricing of specific lab test in multiple sclerosis	**Obtained price from private sector (Source Lab Link**	
Aquaporin-4 and MOG AB		RM 750
ANA		RM 54
Oligoclonal bands IgG, CSF and serum		RM 406

Exchange rate RM 1 = USD 0.22

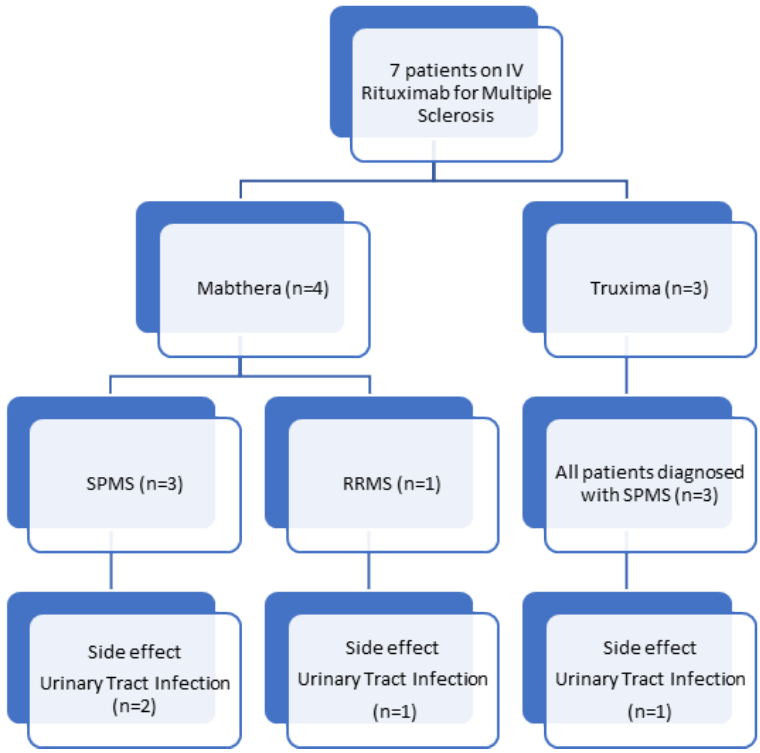

Figure 1. Characteristics of Multiple Sclerosis Patient in the study

In a recent review paper conducted among patients with relapsing-remitting MS treated with rituximab showed reduction in inflammatory activity, incidence of relapses, and new brain lesions on MR imaging.[8] Similarly, no new lesions were observed in the MR imaging imaging for Mabthera patients and one new lesion in Truxima patient in our study. So far, rituximab has shown benefits in the treatment of MS in two randomized placebo-controlled clinical trials. The "Helping to Evaluate Rituxan in Relapsing–Remitting Multiple Sclerosis (HERMES)" and "A Study to Evaluate the Safety and Efficacy of Rituximab in Adults With Primary Progressive Multiple Sclerosis (OLYMPUS)" are two randomized placebo-controlled phase 2 trials which demonstrated the efficacy of rituximab for treatment of relapsing–remitting MS (RRMS) and primary progressive MS (PPMS).[9,10] Meanwhile, a study by Nagelin *et al*. showed that rituximab significantly reduced risk of disability progression in patients with secondary progressive MS.[11] In the phase II HERMES study, 104 patients with relapsing-remitting MS were selected, 69 assigned to receive rituximab intravenously in two single doses of 1000 mg, with an interval of 14 days between them and with a follow-up time of 48 weeks. In relation to the primary endpoint, evaluation of the total number of gadolinium-enhancing lesions at weeks 12, 16, 20, and 24, a relative reduction of 91% was observed in the treated group.[9,10]

In our study only adverse effect observed was urinary tract infection. In the landmark HERMES and OLYMPUS clinical trials, although the incidence of adverse events in patients treated with rituximab was high, the majority were infusion-associated reactions and were mild to moderate in intensity, i.e., grade 1-2 according to the Common Terminology Criteria for Adverse Events v. 3.0. In these respective studies, 78.3% and 67.1% of patients receiving rituximab versus 40% and 23.1% in the placebo group experienced reactions within 24 hours of the first infusion. A notable decrease in these reactions was observed with the successive infusions, reaching a value comparable to or lower than the placebo group. The most commonly reported effects were malaise, headache, nausea, pruritus, flushing, fever, chills, rigor, pharyngolaryngeal pain, dizziness, fatigue, and hypotension.[9,10] Regarding open prospective studies without a control group, the number of patients with infusion-associated reactions reached 42%. In retrospective observational studies, the reported

Table 2: Baseline characteristics and outcomes

	Brand	N	Mean	Std. Deviation	p value
Age (years)	Mabthera	4	34.25	6.397	0.724
	Truxima	3	37.00	13.528	
Disease duration (years)	Mabthera	4	10.00	3.367	0.558
	Truxima	3	9.00	0.000	
Number of rituximab doses	Mabthera	4	6.00	1.633	0.076
	Truxima	3	4.00	0.000	
EDSS Pre	Mabthera	4	6.50	1.225	0.589
	Truxima	3	6.83	1.041	
EDSS Post	Mabthera	4	5.88	2.175	0.844
	Truxima	3	5.33	2.309	
Number of UTI	Mabthera	4	1.00	0.816	0.711
	Truxima	3	1.00	1.732	
Number of relapse	Mabthera	4	0.75	1.500	0.386
	Truxima	3	0.00	0.000	
Prolonged stay due to UTI	Mabthera	4	13.00	3.742	0.048
	Truxima	3	8.33	0.577	

cases of infusion-associated reactions in general, regardless of the number of infusions received, were variable: 33% in the Spanish group , 14.7 % in an English observational study and 7.8% in the Swedish study.[10] An Italian study looking into eleven patients with MS, four with NMOSD and two with NMO showed six patient has relapses (two had a single relapse and four had multiple relapses). One patient with primary progressive MS and one with relapsing remitting MS stopped rituximab, the last one for severe lymphopenia.[12]

In conclusion, our findings showed that Mabthera and Truxima were well tolerated. The study also shows there is a significant difference in the cost of rituximab, healthcare professionals and bedding among Mabthera and Truxima, which contributes to the difference in the total cost. However, as the number of patients treated with Truxima and Mabthera is limited to a single medical centre, a prospective cohort or multi-

Table 3: Total direct cost of patient on Mabthera or Truxima

	Brand	N	Mean (USD)	Std. Deviation (USD)	p value
FBC & urinalysis cost (USD)	Mabthera	4	14.22	3.870	0.076
	Truxima	3	9.48	0.000	
Bedding cost (USD)	Mabthera	4	8.39	2.413	0.048
	Truxima	3	5.38	0.372	
Rituximab cost (USD)	Mabthera	4	10,941.93	2978.016	0.026
	Truxima	3	3,612.90	0.000	
Healthcare professional cost (USD)	Mabthera	4	404.69	116.478	0.048
	Truxima	3	259.42	17.973	
Antibiotic cost (USD)	Mabthera	4	4.90	4.000	0.711
	Truxima	3	4.90	8.487	
Diagnostic laboratory cost (Aquaporin-4 and MOG AB, ANA and Oligonal bands IgG) (USD)	Mabthera	4	268.88	0.000	1.000
	Truxima	3	268.88	0.000	
Total cost (USD)	Mabthera	4	11,643.00	3100.744	0.032
	Truxima	3	4,160.95	26.832	

centre approach could be carried out in future study.

REFERENCES

1. Daniel HW, Emma CT, Stephen J, *et al*. Rituximab in neurological disease: principles, evidence and practice. *Pract Neurol* 2019;19(1):5. doi: 10.1136/practneurol-2018-001899.
2. Committee for Medicinal Products for Human Use. Assessment report: Truxima. 2017.
3. Techa-angkoon P, Siritho S, Tisavipat N, Suansanae T. Current evidence of rituximab in the treatment of multiple sclerosis. *Mult Scler Relat Disord* 2023;75:104729. doi: 10.1016/j.msard.2023.104729.
4. Aungsumart S, Turongkaravee S, Youngkong S, Apiwattanakul M, Thakkinstian A, Chaikledkaew U. Rituximab for the treatment of relapsing-remitting multiple sclerosis in Thailand: an economic evaluation and budget impact analysis. *BMC Health Serv Res* 2023;23(1):1096. doi: 10.1186/s12913-023-10099-1.
5. Spelman T, Frisell T, Piehl F, Hillert J. Comparative effectiveness of rituximab relative to IFN-β or glatiramer acetate in relapsing-remitting MS from the Swedish MS registry. *Mult Scler* 2018;24(8):1087-95. doi: 10.1177/1352458517713668.
6. Alharbi MA, Aldosari F, Althobaiti AH, *et al*. Clinical and economic evaluations of natalizumab, rituximab, and ocrelizumab for the management of relapsing-remitting multiple sclerosis in Saudi Arabia. *BMC Health Serv Res* 2023;23(1):552. doi: 10.1186/s12913-023-09462-z.
7. Perez T, Rico A, Boutière C, *et al*. Comparison of rituximab originator (MabThera®) to biosimilar (Truxima®) in patients with multiple sclerosis. *Mult Scler J* 2021;27(4):585-92. doi: 10.1177/1352458520912170.
8. Chisari CG, Sgarlata E, Arena S, Toscano S, Luca M, Patti F. Rituximab for the treatment of multiple sclerosis: a review. *J Neurol* 2022;269(1):159-83. doi: 10.1007/s00415-020-10362-z.
9. Hawker K, O'Connor P, Freedman MS, *et al*. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Ann Neurol* 2009;66(4):460-71. doi: 10.1002/ana.21867.
10. Hauser SL, Waubant E, Arnold DL, *et al*. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med* 2008;358(7):676-88. doi: 10.1056/NEJMoa0706383.
11. Naegelin Y, Naegelin P, von Felten S, *et al*. Association of rituximab treatment with disability progression among patients with secondary progressive multiple sclerosis. *JAMA Neurol* 2019;76(3):274-81. doi: 10.1001/jamaneurol.2018.4239.
12. D'Amico E, Zanghì A, Chisari C, *et al*. Effectiveness and safety of rituximab in demyelinating diseases spectrum: An Italian experience. *Mult Scler Relat Disord* 2018;27. doi: 10.1016/j.msard.2018.09.041.