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Research Article

Clinical Characteristics and Treatment Response to Rituximab in Refractory Chronic Inflammatory Demyelinating Polyradiculoneuropathy: A Retrospective Observational Study from a Single Tertiary Center in Thailand

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Abstract

Background: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a disabling condition requiring immunosuppressive or immunomodulatory drug treatment. However, approximately 20% of patients do not respond to classical immunosuppressive drugs. Rituximab (RTX) is beneficial for patients with refractory CIDP.

Objective: This study aimed to evaluate the efficacy of RTX in treating refractory CIDP.

Methods: This retrospective study evaluated 11 patients with refractory CIDP who were treated with RTX. The Medical Research Council (MRC) sum score, Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale, and Modified Rankin Scale (MRS) were analyzed at 12 and 24 weeks after RTX treatment compared to baseline.

Results: The main clinical characteristics of refractory CIDP were distal weakness predominance (54.5%), accompanied by tremors (54.5%), and sural nerve pathology without onion bulb formation (100%). At 12 and 24 weeks post-RTX treatment, the median MRC sum score improved from 46 (interquartile range [IQR] 36-56) to 50 (IQR 48-58, p-value = 0.005) and 58 (IQR 52-60, p-value = 0.008), respectively. The median INCAT disability scale score improved from 6 (IQR 6-7) to 5 (IQR 4-6, p-value = 0.006) and 3 (IQR 1-5, p-value = 0.004), respectively. The median MRS sum score improved from 6 (IQR 6-7) to 3 (IQR 2-4, p-value <0.016) and 3 (IQR 1-3, p-value < 0.003), respectively.

Conclusion: RTX was effective in treating patients with refractory CIDP. Clinical features like distal weakness, tremors, and nerve pathology without onion bulb formation may prompt clinicians to consider refractory CIDP as a diagnosis.

Keywords: Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP); Refractory CIDP; Rituximab; Nodal and Paranodal Polyneuropathies; Inflammatory Neuropathy Cause; Treatment (INCAT)

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an autoimmune peripheral nerve disease characterized by inflammation-induced demyelination, which destroys the myelin sheaths of the peripheral nerves, leading to chronic, progressive, or relapsing-remitting symptoms. The prevalence of CIDP is approximately 8.9 cases per 100,000 population [1]. Patients may experience generalized weakness and numbness, with gradual progression lasting more than 8 weeks [2]. Diagnosis

typically involves a thorough medical history, physical examination, laboratory tests, and electrodiagnostic study following the criteria of the European Academy of Neurology/Peripheral Nerve Society [3]. Standard treatments include corticosteroids, intravenous immunoglobulin (IVIg), and plasmapheresis [3-7]. Approximately 50-80% of patients respond to standard treatment, experiencing reduced disability. However, some patients do not respond adequately, leading to refractory CIDP. In such cases, nodal and paranodal antibodies, such as anti-neurofascin-155 (NF-155), anti-NF-140/186, and anti-contactin-1 (CNTN-1) antibodies, particularly of the immunoglobulin G4 (IgG4) subtype, may be detected. These antibodies attack protein structures around the node of Ranvier, causing nerve dysfunction. Due to the significant involvement of IgG4 antibodies in the pathogenesis, patients with refractory CIDP often exhibit poor responses to corticosteroids or IVIg treatment [8].

Rituximab (RTX), a cancer treatment drug, is currently used as an alternative for treating refractory CIDP [3]. RTX reduces the production of B lymphocytes [9], which are implicated in abnormal immune responses targeting myelin sheaths. Many studies, including case series, cohort studies, systematic reviews, and meta-analyses, suggest that RTX has shown better treatment responses than standard treatments in patients with refractory CIDP [10-14]. From the meta-analysis published in 2021, the pooled estimate of responsiveness was 75%, measured by the improvement of the Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale and Medical Research Council (MRC) sum score after treatment [12]. However, limited research exists in the Asian and Thai populations regarding the use of RTX in patients with CIDP. Therefore, this study aimed to investigate the efficacy of RTX in patients with refractory CIDP. Additionally, we explored the clinical characteristics of laboratory findings, including nerve pathology, in patients with refractory CIDP.

Materials and Methods

Patients and study design

This single-center retrospective study was conducted at the Neurological Institute of Thailand and focused on patients diagnosed with definite or probable CIDP, according to the EFNS-PNS 2019 criteria, between January 2017 and October 2023. Refractory CIDP was defined as patients who received adequate first-line treatments, such as corticosteroid 1 mg/kg/day or IVIG 2 gm/kg for at least 4 weeks, without achieving a satisfactory response. The response was defined according to a previous study, [3] where, for instance, the INCAT disability scale score did not improve by more than 1 point, or the MRC sum score did not improve by more than 2 points or worsened. Patients initially diagnosed with CIDP and later identified to have associated hematological diseases, such as lymphoma, leukemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome, Waldenstrom macroglobulinemia (WM), multiple myeloma (MM), were excluded from the study.

Clinical evaluation

All patients' demographic data: age, sex, underlying diseases, smoking, and alcohol drinking; their clinical characteristics: time from onset to diagnosis, the pattern of weakness and sensory loss at first presentation, cranial nerve involvement, neuropathic pain, tremor, course of disease (whether progressive or relapsing-remitting fashion); previous CIDP first-line treatments (either corticosteroids or IVIG); and the time from onset to treatment and duration of treatment were collected. The clinical presentations of each patient were classified into typical CIDP and CIDP variants (motor CIDP, distal CIDP, sensory CIDP, and multifocal CIDP) according to the 2021 European Academy of Neurology/Peripheral Nerve Society criteria. [3] All patients received RTX treatment at a dosage of 1000 mg IV 2 weeks apart for the induction dose and then 1000 mg IV every 6 months for the maintenance period. The time from the disease onset to RTX treatment was also recorded. The MRC sum score, INCAT disability scale, and Modified Rankin Scale (MRS) scores were evaluated at disease onset, before RTX treatment, and at 12 and 24 weeks after RTX treatment. The outcomes were the MRC sum score, INCAT disability scale, and Modified Rankin Scale (MRS) scores at 12 and 24 weeks compared to those before the first RTX infusion. Adverse events of RTX were also recorded from the first infusion until 6 months.

Electrophysiological and other laboratory evaluation

Nerve conduction studies (NCSs) were performed in all patients at diagnosis and interpreted for pattern, distribution, primary pathology (axonopathy or demyelination), and evidence of motor conduction blocks. Moreover, we collected the cerebrospinal fluid (CSF) profile, white blood cell (WBC) count, protein, and CSF/blood

glucose ratio of all patients at diagnosis. Sural nerve biopsy results were also obtained. Nodal and paranodal antibodies, including anti-NF-155, anti-CNTN-1, and anti-NF-140/186, were tested by cell-based assay technique (Euroimmun, Luebeck, Germany).

Statistical analysis

All statistical analyses were performed using STATA (version 13). Demographics, clinical characteristics, and electrophysiological and other laboratory results were reported in descriptive results as percentages and medians (interquartile range, IQR) for categorical and continuous data, respectively. The MRC sum score, INCAT disability scale, and MRS scores at 12 and 24 weeks after RTX treatment compared to the scores before the first RTX infusion were analyzed using the Wilcoxon rank sum test. Statistical significance was set at p-value <0.05.

The study design was approved by the Institutional Review Board of the Neurological Institute of Thailand (approval number: 66053).

Results

Demographics and clinical characteristics

Seventy-eight patients with CIDP were identified from the hospital database between January 2017 and October 2023. Among them, 17 were classified as patients with refractory CIDP. Six patients were diagnosed with hematological disorders and were excluded from the study. Finally, 11 patients with refractory CIDP were included (Figure 1). All patients were treated with RTX. The demographic data comprised seven men and four women (Table 1). The median age at disease onset was 41 years (IQR 35-65). Regarding clinical presentation, six (54.3%) patients had typical CIDP, three (27.3%) had distal CIDP, and two (18.2%) had motor CIDP. Five (45.5%) patients had progressive fashion in the disease course, whereas six (54.5%) had a relapsing-remitting course. Weakness was the presenting symptom in all patients, with nine (81.8%) experiencing quadriparesis. Five (45.4%) patients were presented with tremors, and one (9.1%) reported neuropathic pain. No patient exhibited cranial nerve involvement, autonomic failure, or concomitant CNS demyelination throughout the disease course (Table 1).

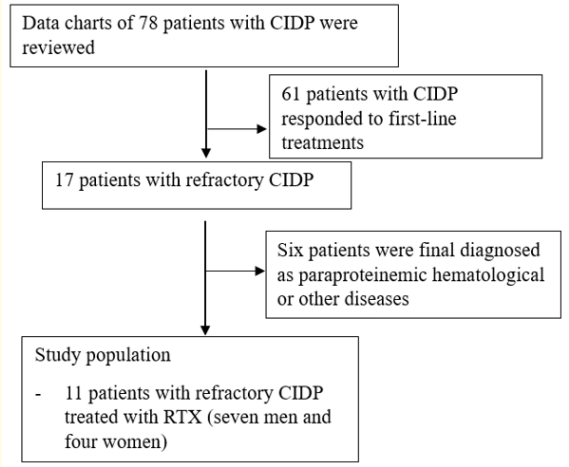

Figure 1: Study flow diagram.

RTX: Rituximab; CIDP: Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Table 1: Demographic data, clinical manifestations, and treatment and investigation results.

Parameters	Value
No. (n)	11
Age at onset (years) • Median (IQR) • Range	 41 (35-65) 25-75
Sex (male: female)	7:4
Underlying disease (n, %) • None (n, %) • Hypertension (n, %) • Hypothyroidism (n, %) • Normal pressure hydrocephalus (n, %)	 7 (63.6) 4 (36.3) 1 (9.1) 1 (9.1)
Smoking (n, %)	0
Alcohol drinking (n, %)	1 (9.1)
Clinical manifestations	
Time from onset to diagnosis (days) (median, IQR)	62 (46-71)
Weakness (n, %) Pattern • Bibrachial weakness (n, %) • Paraparesis (n, %) • Quadriparesis (n, %) Distribution* • Proximal predominant (n, %) • Distal predominant (n, %) • Proximal and distal (n, %)	11 (100) 1 (9.1) 1 (9.1) 9 (81.8) 3 (27.2) 6 (54.5) 2 (18.2)

Sensory loss (n, %) Sensory ataxia (n, %)	9 (81.8) 9/9 (100)
Neuropathic pain (n, %)	1 (9.1)
Cranial nerve involvement (n, %)	0
Tremor (n, %)	5 (45.4)
Respiratory failure (n, %)	0
Autonomic symptoms* (n, %)	0
Concomitant CNS demyelination (n, %)	0
Type of CIDP • Typical CIDP (n, %) • Distal CIDP (n, %) • Pure motor CIDP (n, %)	 6 (54.5) 3 (27.3) 2 (18.2)
Course of disease • Progressive (n, %) • Relapsing remitting (n, %)	 5 (45.5) 6 (54.5)
Investigations	
NCS • Part involvement • Pure motor (n, %) • Pure sensory (n, %) • Sensorimotor (n, %) Distribution • Polyneuropathy (n, %) Primary pattern • Demyelination (n, %) • Axonopathy (n, %) • Motor conduction block (n, %)	 2 (18.2) 0 9 (81.8) 11 (100) 11 (100) 0 6 (54.5)
CSF profile • WBC (cell/mm^3) (median, IQR) • Protein (mg/dL) (median, IQR) • Sugar/blood sugar (%) (median, IQR)	 0 (0, 0) 159 (88-448) 70.5 (62.3-81.5)
Sural nerve biopsy (%, n) Onion bulb formation (n, %) Inflammatory cell infiltration (n, %) Axonal degeneration (n, %)	7/11 (63.6) 0 5/7 (71.4) 7/7 (100%)
Nodal/paranodal antibody positive (n, %) NF-155 (n, %) CTCN-1 (n, %) NF-140/186 (n, %)	6/11 (54.5) 5/6 (83.3) 1/6 (16.7) 0
First-line treatments	
Previous treatment with steroid (n, %) • Time from onset to treatment (days) (median, IQR) • Duration of treatment (days) (median, IQR)	11 (100) 62 (57-77) 86 (41-448)
Previous treatment with IVIG (n, %) • Time from onset to treatment (days) (median, IQR) • Duration of treatment(days) (median, IQR)	9 (81.2) 150 (67-158) 65 (28-122)

*Distribution of weakness: proximal predominant; proximal muscles showed muscle power at least 1 MRC grade lower than distal muscles, distal predominant; distal muscles showed muscle power at least 1 MRC grade lower than proximal muscles, proximal and distal; proximal and distal muscles showed equal power by MRC grading.

IQR, interquartile range; CSF, cerebrospinal fluid; CNS, central nervous system; WBC, white blood cell; IVIG, intravenous immunoglobulin; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; NCS, nerve conduction study; NF, neurofascin; CTCN, contactin.

Laboratory findings

NCS examination demonstrated sensorimotor polyneuropathy involvement in nine (81.8%) patients, whereas two (18.2%) showed a pure motor pattern. Demyelination was the primary pathology observed in all patients, with a motor conduction block pattern detected in six (54.5%). The CSF profile showed albumin cytologic dissociation without low sugar levels in all patients. The median WBC count was 0 cell/mm^3, the median CSF protein was 159 mg/dL (IQR 88-448), and the median CSF/blood glucose ratio was 70.5% (IQR 62.3-81.5). Sural nerve performed in seven patients (63.6%) did not show onion bulb formation typical of classical CIDP. However, inflammatory cell infiltration and axonal degeneration were observed in five (71.4%) of the cases. Nodal and paranodal antibodies, including anti-NF-155, anti-CNTN-1, and anti-NF-140/186, were examined in all patients, with positive results in six (54.5%) patients, five of which were anti-NF-155 positive and one was anti-CNTN-1 positive (Table 1).

First-line treatment and effectiveness of RTX in refractory CIDP

First-line treatment included corticosteroids and IVIG, with all patients receiving corticosteroids and nine (81%) also undergoing

concurrent IVIG therapy. The median durations of corticosteroid and IVIG treatments were 86 (IQR 41-448) and 65 days (IQR 28-122), respectively, indicating sufficient treatment duration. However, some patients exhibited inadequate responses to first-line agents. RTX was used as a second-line treatment, and the median time from onset to RTX treatment was 244 days (IQR 133-515). Interestingly, at 12 and 24 weeks after RTX treatment, the median MRC sum score improved from 46 (IQR 36-56) to 50 (IQR 48-58, p-value = 0.005) and 58 (IQR 52-60, p-value = 0.008), respectively. The median INCAT disability scale score improved from 6 (IQR 6-7) to 5 (IQR 4-6, p-value = 0.006) and 3 (IQR 1-5, p-value = 0.004), respectively. The median MRS sum score improved from 6 (IQR 6-7) to 3 (IQR 2-4, p-value <0.016) and 3 (IQR 1-3, p-value < 0.003), respectively (Figure 2).

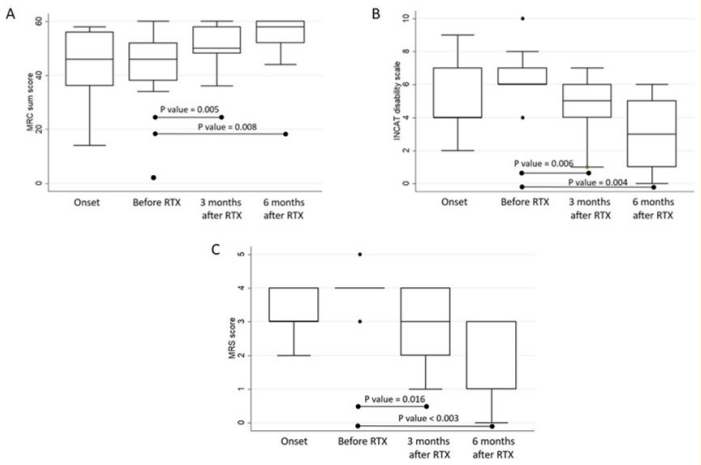

Figure 2: Outcomes of post-RTX treatment include MRC sum score (A), INCAT disability scale (B), and MRS score (C). MRC; Medical Research Council, INCAT; Inflammatory Neuropathy Cause and Treatment, MRS; Modified Rankin Scale, RTX; rituximab.

Adverse events

Adverse drug reactions were observed in three patients. Two patients experienced transient deterioration after the first infusion of RTX. The first patient's MRC sum and INCAT disability scale scores were reduced by 8 and 2 points, respectively. Moreover, the second patient's MRC sum and INCAT disability scale scores were reduced by 6 and 1 point, respectively. Both patients received no further treatment, and their disabilities spontaneously improved within 2 weeks. An infusion-related reaction was observed only in one (9.1%) patient.

Discussion

This study showed that RTX treatment significantly improved disability, MRC sum, INCAT disability scale, and MRS scores in patients with refractory CIDP. Our findings align with previous studies and meta-analyses, [11-13] indicating consistency in patients with nodal and paranodal antibodies positivity and negativity.

Some clinical signs and laboratory findings from our study suggest that refractory CIDP requires RTX treatment, such as distal-more-than-proximal sensorimotor demyelinating polyneuropathy in both the upper and lower limbs. Tremors are also considered essential clinical markers in challenging patients with CIDP. Additionally, our results are similar to those of previous studies of nodal and paranodal demyelinating polyneuropathy, either anti-NF-155 or CNTN-1 autoantibody, usually characterized by subacute onset, predominantly distal phenotype, sensory ataxia, and disabling tremor, which are different from typical CIDP [15-22]. In this study, half of the patients tested positive for nodal and paranodal antibodies. Most patients presented with sensorimotor polyneuropathy. Nevertheless, all patients classified as having pure motor CIDP were antibody-negative.

NCS and CSF profiles, which presented generalized sensorimotor demyelination and CSF albumin cytologic dissociation without low sugar levels, respectively, did not differentiate refractory CIDP from CIDP. Notably, sural nerve pathology in seven patients showed no evidence of onion bulb formation, which typically indicates demyelination along with remyelination-a supportive criterion for CIDP diagnosis. All of these patients showed axonal degeneration with inflammatory cell infiltration, a characteristic feature observed in nodal and paranodal demyelinating polyneuropathy. These findings are similar to those reported by Koike., *et al*., [23] who found that nerve pathology in patients with anti-NF-155 and anti-CNTN-1 antibodies showed a slight reduction in myelinated fiber density, scattered myelin ovoids, and no macrophage-mediated demyelination or onion bulbs. Therefore, the clinical presentation of distal weakness surpassing proximal weakness along with tremors, coupled with nerve pathology lacking onion bulb formation, should raise suspicion of CIDP, especially when standard treatment fails to yield satisfactory results.

As nodal and paranodal antibodies belong to the IgG4 subclass, they typically do not respond well to IVIg and only show partial response

to corticosteroids [8]. Therefore, RTX emerges as a reasonable treatment of choice. Additionally, considering the nerve pathology discussed earlier, some patients with refractory CIDP may exhibit nodal and paranodal demyelinating polyneuropathy despite lacking identifiable antibodies. Our results provide additional data supporting the efficacy of RTX in refractory CIDP beyond cases with nodal or paranodal demyelination. Furthermore, two patients diagnosed with pure motor CIDP in our study, despite testing negative for antibodies, exhibited poor responses to IVIg. However, they showed significant improvement following RTX treatment. To the best of our knowledge, patients with pure motor CIDP are responsive to IVIg treatment, and their condition may deteriorate after corticosteroid treatment. Our study suggests RTX as a potential treatment for IVIg-resistant pure motor CIDP.

Regarding the adverse effects of RTX, we observed transient worsening and transfusion-related reactions, which were well tolerated and showed spontaneous recovery. In our opinion, RTX is an effective treatment with minimal adverse complications within 6 months of our study period. However, long-term monitoring is crucial to assess potential RTX infusion-related side effects in extended studies.

Our study's strength lies in being, to the best of our knowledge, the first in Thailand to explore the efficacy of RTX treatment for refractory CIDP. Our patient cohort was more homogenous with CIDP diagnosis compared to previous studies. We included patients diagnosed with CIDP without any coexisting diseases, ensuring that refractory symptoms were solely attributable to CIDP itself rather than other accompanying conditions, as observed in prior research [10,12,14].

This study had some limitations. Firstly, a small number of patients were recruited due to the rarity of refractory CIDP. Secondly, nerve biopsy was not performed in all patients, which could have provided valuable insights into refractory CIDP's pathogenesis.

Conclusion

This study contributes additional evidence supporting RTX's efficacy and acceptable side effects in treating patients with refractory CIDP, whether positive or negative for nodal and paranodal antibodies. Moreover, specific clinical presentations, like distal weakness and tremors, and nerve pathology findings, such as the absence of onion bulb formation, can alert clinicians to potential poor responses to first-line CIDP treatments.

Credit Authorship Contribution Statement

Chaichana Sinthuwong: Conceptualization; investigation; writing-original draft; methodology; validation; visualization; formal analysis; project administration; data curation; resources; writing-review and editing. Metha Apiwattanakul: methodology; writing-review and editing; project administration. Narupat Suanprasert: writing-review and editing; supervision. Saharat Aungsumart: methodology; validation; visualization; writing-review and editing; formal analysis; project administration; supervision.

Declaration of Competing Interest

Declarations of interest: none. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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