THE EFFICACY OF RITUXIMAB IN THE TREATMENT OF REFRACTORY CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY IN CHILDREN: A REPORT OF THREE CASES FROM NORTHERN VIETNAM

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Rituximab has been reported to be effective in patients with refractory CIDP, especially those with IgG4 autoantibodies against nodal and paranodal proteins. This study reports the clinical characteristics of three cases diagnosed with refractory CIDP successfully treated with rituximab, although testing for IgG4 antibodies is currently not available in Vietnam. Patients were evaluated using the MRC (Medical Research Council Scale for Muscle Strength) and INCAT (Inflammatory Neuropathy Cause and Treatment) scores before and after rituximab treatment. The duration of the disease before rituximab treatment ranged from 6 to 10 months, with total MRC scores of 16 - 26 points, INCAT scores of 8 - 9 points, and the first response noted after 1 - 4 months. Patients recovered well after a follow-up period of 8 to 12 months without adverse effects, with MRC and INCAT scores improving to 48 - 58 points and 1 - 2 points, respectively. Rituximab may be effective in treating refractory CIDP patients.

Keywords: CIDP, treatment resistance, children, rituximab.

I. INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune disease characterized by progressive weakness and impaired sensory function lasting more than 2 months, with a prevalence of 0.8 - 8.9 per 100,000.[1] The disease is diagnosed according to the guidelines of the European Neurological Institute/Peripheral Nervous Society (EAN/PNS) in 2021.[2] Symptoms include symmetrical muscle weakness, sensory disorders, and decreased or absent tendon reflexes that progress over at least 8 weeks.

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Treatment aims to improve symptoms of muscle weakness, loss of sensation, and loss of balance while minimizing disability. Effective first-line therapies include high-dose immunoglobulin (IVIg), corticosteroids, and plasma exchange (PLEX); however, approximately 25 - 30% of patients are resistant to treatment.[3] Refractory CIDP is defined as unchanged or worsened functional status following a combination of steroids, IVIg, or PE, and second-line immunosuppression with azathioprine or mycophenolate mofetil for at least 6 months. In refractory cases, alternative therapies include rituximab, cyclophosphamide, or autologous stem cell transplantation after careful consideration of the diagnosis.

Rituximab (RTX) is a monoclonal antibody

against the CD20 antigen on B lymphocytes, which prevents antibody production by inhibiting differentiation into plasma cells. RTX has been used to treat polyneuropathy associated with anti-glycoprotein antibodies (MAG) and is currently in phase 2 clinical trials for CIDP.[4] RTX has been reported to effectively treat some cases of refractory CIDP with or without antibodies to Ranvier nodal and paranodal proteins.[5] However, data on the treatment of rituximab in children are quite limited.

In Vietnam, refractory CIDP in children is very rare, and no specific treatment protocol has been established. We report three cases of patients diagnosed with refractory CIDP according to the EAN/PNS 2021 criteria at the Neurology Center of the National Children's Hospital, the largest medical center for children in Northern Vietnam. Muscle strength was assessed based on MRC (Medical Research Council Scale for Muscle Strength) scores; the level of upper and lower limb dysfunction on both sides was evaluated according to the INCAT (Inflammatory Neuropathy Cause and Treatment) scale before and after treatment.[2,6] The MRC sum score was defined as the sum of MRC scores from six muscles in the upper and lower limbs on both sides, each muscle group scoring from 0 - 5, resulting in a range from 60 (normal) to 0 (quadriplegic). The INCAT score ranged from 0 - 5 for upper and lower limb scores, totaling 10, inversely related to limb function, with no functional impairment (0) and the inability to perform any purposeful movement of the limbs (10). These children were successfully treated with rituximab 375 mg/m^2 weekly for 4 weeks at the time of diagnosis of refractory CIDP. Neurological assessments were performed by medical doctors at the center, with MRC and INCAT scores increasing by at least 2 points or reducing/stopping previous therapies.

II. CASE REPORTS

Case 1

A 12-year-old healthy boy presented with ascending weakness and numbness in both arms, progressing to weakness in both legs and the inability to walk for 2 months before admission. Upon admission, the patient was conscious with flaccid paralysis of all limbs. His MRC score was 30 points, INCAT upper limbs was 4 points, and INCAT lower limbs was 3 points. Tendon reflexes were reduced, the Babinski sign was negative, and there were no cranial nerve palsies or autonomic nerve dysfunctions. Blood tests were normal. Cerebrospinal fluid (CSF) analysis showed normal cell counts (4 cells/mm^3), increased protein level (1.19 g/l), normal glucose level (3.82 mmol/l), and negative PCR results for Epstein Barr virus (EBV), enterovirus (EV), and herpes simplex virus (HSV). Electromyography of all limbs showed demyelinating sensorimotor polyneuropathy. CIDP was diagnosed, and the patient was treated with intravenous methylprednisolone (MP) at 20 mg/kg/day for 5 days, followed by maintenance with prednisolone 1 mg/kg/day, but muscle strength improved slowly. Patient then received IVIg combination therapy but relapsed and received monthly boluses of MP and PLEX (5 procedure courses) and mycophenolate mofetil without improvement, experiencing 4 relapses during 5 months. Eight months after disease onset, his symptoms relapsed, with an MRC score of 16 points, INCAT upper limbs of 5 points, and INCAT lower limbs of 4 points. He was diagnosed with treatment-resistant CIDP and incomplete response to conventional medications, leading to the indication for sole rituximab treatment. Muscle strength improved after 3 months of rituximab infusion, with an MRC score of 28 points, INCAT upper limbs

of 4 points, and INCAT lower limbs of 3 points. Ten months later, he fully recovered with an MRC score of 48 points and INCAT upper and lower limbs of 1 (Chart 1). Tendon reflexes were slightly reduced, and no side effect was observed during and after the rituximab infusion.

Case 2

A 12-year-old girl with a history of COVID-19 infection 1 month before the onset of numbness and weakness in her legs, which spread to her arms. Ten days after onset, the girl was admitted to the hospital with flaccid quadriplegia. Her MRC score was 28 points, INCAT upper limbs were 3 points, INCAT lower limbs was 4 points, reduced tendon reflexes, negative Babinski sign, and other neurological alterations. CSF analysis showed normal cell counts (2 white blood cells/mm^3), and slightly increased protein level (0.46 g/l). Electromyography showed demyelinating sensorimotor polyneuropathy. Initially, she was diagnosed with Guillain-Barré syndrome (GBS) and was treated with MP 20 mg/kg/day for 5 days, resulting in improved muscle strength. However, two weeks later, symptoms recurred, and MP was repeated with a gradually decreasing dose, but adverse effects of prednisolone appeared after 3 months of treatment, and the MRC score reached 50 points, leading to the cancellation of the treatment. The symptoms relapsed again, and the child received PLEX (5 procedure courses) monthly maintenance for 4 months, and oral mycophenolate mofetil, resulting in improved muscle strength, with an MRC score of 58 points. Ten months after disease onset, her symptoms relapsed again, with an MRC score of 24 points, INCAT upper limbs of 4 points, and INCAT lower limbs of 4 points. Refractory CIDP was diagnosed, and tests for anti-nuclear antibodies, anti-double chain antibodies, anti-phospholipid antibodies, cardiolipin antibodies, beta2 glycoprotein, anti-Sm antibodies, and Jo-1 antibodies were all negative. C3 and C4 levels were normal, and brain and spinal cord MRI showed no abnormality. Electromyography showed mixed nerve injury with demyelination and axonal injury. All other therapies were discontinued while she received rituximab infusion at 375 mg/m^2 weekly for 4 weeks. Muscle strength gradually improved after 1 month, with an MRC score of 32 points, INCAT upper limbs of 3 points, and INCAT lower limbs of 3 points. Follow-up at 7 months after rituximab showed an MRC score of 52 points and INCAT upper limbs of 1 point and INCAT lower limbs of 1 point (Chart 1).

Case 3

An 8-year-old healthy boy experienced weakness on the left side, gradually increasing and spreading to the right side about 1 month before admission, accompanied by numbness in the limbs. Initially diagnosed with GBS on the 14th day of illness at the provincial hospital, he did not receive proper treatment. On the 30th day of the disease, with an MRC score of 34 points, INCAT upper limbs of 3 points, and INCAT lower limbs of 3 points, reduced tendon reflexes, and no circular muscle dysfunction, the patient was admitted and diagnosed with GBS. He was treated with IVIG at a total dose of 2 g/kg, and the MRC score increased to 58 points within 1 week. During the next two months, his symptoms relapsed 4 times, leading to a CIDP diagnosis and respective treatments with MP and IVIG infusion and oral mycophenolate mofetil without full recovery. Six months into the disease, symptoms relapsed again with an MRC score of 26 points, and INCAT upper and lower limbs of 4 points. Refractory CIDP was diagnosed with secondary axonal degeneration on electromyography, and tests for antinuclear antibodies, anti-double chain antibodies,

anti-phospholipid antibodies, cardiolipin antibodies, beta2 glycoprotein, anti-Sm, and Jo-1 antibodies were all negative. C3 and C4 levels and MRI images of the brain and spinal cord were normal. All other therapies were dscontinued while the patient was treated with rituximab; muscle strength began to improve after 4 months, with an MRC score of 36 points and INCAT upper and lower limbs of 3 points. Follow-up at 12 months after rituximab showed the patient had clinically recovered well, with an MRC score of 58 points and INCAT upper limbs of 1 point, and INCAT lower limbs of 0 points (Chart 1).

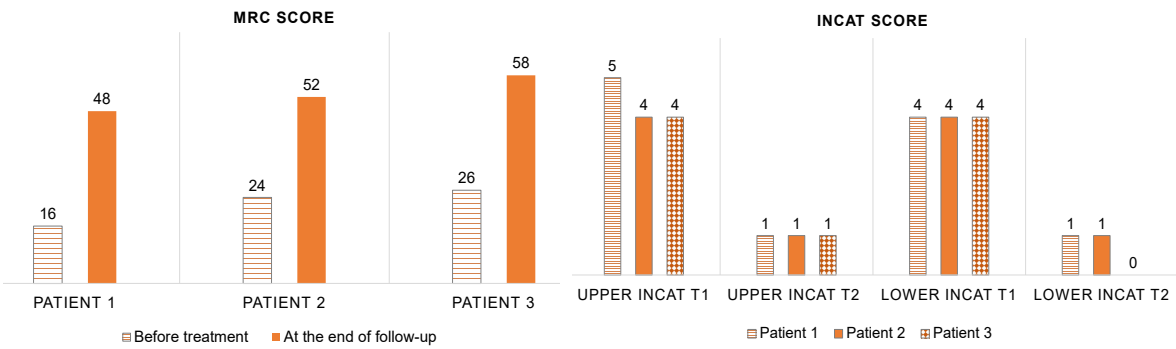

Chart 1. MRC and INCAT scores before rituximab treatment and at the end of follow-up

(T1: Time before rituximab treatment, T2: End of follow-up)

III. DISCUSSION

Refractory CIDP is a challenging subset of CIDP and a comprehensive understanding of its clinical profile remains to be further elucidated. Our study describes the clinical features and effectiveness of treatment of patients with refractory CIDP. Among acute phase diseases, CIDP needs to be distinguished from GBS, as both clinical and paraclinical symptoms. GBS often develops within 4 weeks with severe, monophasic symptoms, while CIDP develops chronically and tends to recur. If acute neurological symptoms occur and improve after first-line immunotherapy but then relapse or worsen after 8 weeks, or if clinical worsening occurs in more than three episodes, the possibility of CIDP should be considered.[7] In our report, two patients in the early stages of the disease (on the fourteenth and thirteenth day) were initially diagnosed with GBS, but symptom relapse soon followed. However, all three patients experienced relapses and worsening after undergoing first-line immunotherapy (methylprednisolone, IVIG, PLEX) and second-line immunotherapy (mycophenolate mofetil, azathioprine). We diagnosed them with refractory CIDP at 6 - 10 months of disease.

The clinical response to rituximab and adverse side effects were evaluated in a subset of patients with refractory CIDP for whom the anti-nodal/paranodal antibody status was unknown. Based on the MRC and INCAT scores assessed before treatment with rituximab and at the end of follow-up, significant improvement was observed in all three patients, indicating the efficacy of rituximab in the treatment of refractory CIDP. Querol et al. also confirmed rituximab as a good choice in the treatment of refractory CIDP.[8] A case series of 13 Italian patients reported by Benedetti et al. showed a responder rate to rituximab of 69%, with improvement occurring a median of 2 months after treatment and lasting up to a year.[9]

However, no randomized clinical trial has been reported yet. Fatehi F also found that rituximab may be effective in refractory CIDP, even though worsening may occur in some patients.[10]

Rituximab is reported to be effective in refractory CIDP patients with IgG4 autoantibodies against Ranvier nodal and paranodal proteins, although the frequency of this antibody is lower than 5% in CIDP patients.[8,11] Autoimmune antibodies such as antinuclear antibodies, anti-double stranded DNA, anti-phospholipid antibodies, anti-cardiolipin antibodies, beta2 glycoprotein, anti-Sm, and Jo-1 antibodies were negative in our patients. Tests for neurofascin-140/155 and contactin-1 antibodies are still not available in Vietnam, so the existence of IgG4 antibodies was not determined. However, the remarkable response to rituximab treatment supports its use as an option for children with refractory CIDP, regardless of antibody identification. Larger sample size studies are needed to confirm this.

IV. CONCLUSION

Our report of children with CIDP refractory to first-line therapies and unknown anti-nodal/paranodal antibody status suggests a substantial response to rituximab. However, the number of patients is small, so the report only provides preliminary evidence about this treatment method. A larger sample study and follow-up are needed for a more comprehensive evaluation, potentially opening a new treatment avenue for CIDP, especially treatment-resistant CIDP.

Disclosure

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Conflict of interest: None

Ethics statement: The patient's family consented to the study.

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