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ORIGINAL RESEARCH

Therapeutic Effect Comparisons of Cyclophosphamide and Methotrexate in Immune-Mediated Necrotizing Myopathy

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Background: Immune-mediated necrotizing myopathy (IMNM) is a rapidly progressing autoimmune muscle disease that severely affects the proximal, respiratory, and cardiac muscles. There is no globally unified consensus on treatment. Here, we compare the effects of cyclophosphamide (CTX) and methotrexate (MTX) in IMNM to provide evidence for treatment strategies.

Methods: This is a retrospective single-center study. Patients were assigned into a CTX group or an MTX group based on the type of immunosuppressant. Statistical analyses were compared using SPSS 23.0.

Results: A total of 35 patients were included—19 in the CTX group, and 16 in the MTX group. Before treatment, the aspartic transaminase (AST) levels were significantly higher in the CTX group than in the MTX group ($P < 0.05$). All patients received high-dose glucocorticoids as basic therapy. After inductive treatments, the proportion of patients whose creatine kinase (CK) decreased by more than 50% was higher in the CTX group (18 cases, 94.7%) than in the MTX group (10 cases, 62.5%; $P < 0.05$). The descent degree of laboratory indicators were analyzed further. Reductions in CK (6919.1 U/L vs. 3245.3 U/L), lactate dehydrogenase (LDH, 964.0 U/L vs. 318.5 U/L), and AST (225 U/L vs. 52.5 U/L) were also greater in the CTX group than in the MTX group ($P < 0.05$).

Conclusion: In this cohort of IMNM patients, CTX achieved greater improvements in CK, LDH, and AST levels compared to MTX. CTX may be more beneficial than MTX for disease inductive treatment in IMNM patients. This finding provides evidence for selecting clinical treatment schemes.

Keywords: immune-mediated necrotizing myopathy, cyclophosphamide, methotrexate

Introduction

Immune-mediated necrotizing myopathy (IMNM) is a rare subtype of idiopathic inflammatory myopathy characterized by acute or subacute onset, rapid progression, and severe weakness of the proximal, respiratory, and cardiac muscles. IMNM is commonly divided into three types according different autoimmune-antibodies: anti-signal recognition particle (anti-SRP) antibody-positive, anti-3-hydroxy-3-methylglutaryl coenzyme A reductase (anti-HMGCR) antibody-positive, and seronegative IMNM.[1]

The pathogenesis of IMNM is not fully understood, but some studies consider it a T cell-mediated disease,[2,3] with B cells playing an auxiliary role.[4,5] Pathologically, it is marked by prominent muscle fiber necrosis and regeneration, with little or no obvious lymphocytic infiltration.[6] Compared to other idiopathic inflammatory myopathies, IMNM manifests with more severe proximal, respiratory, and cardiac muscle weakness and higher creatine kinase (CK) levels.[7,8] IMNM is usually severe and develops rapidly. If the disease is not treated promptly, it may lead to severe muscle damage or death.[9]

Currently, there is no globally unified consensus on treatment for IMNM. Because there have been no randomized trials and there are no large enough case series available to make definite conclusions or formal recommendations.[1] Typically, the condition is treated with corticosteroids, immunosuppressants, and intravenous immunoglobulin (IVIG). At

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present, methotrexate (MTX) is recommended as an initial immunosuppressant for IMNM.[1] However, we found the curative effect of MTX combined glucocorticoids or/and IVIG were dissatisfactory in remission induction. So, we tried to use CTX in clinical practice and found better efficacy. However, due to the lack of randomized controlled studies on CTX in the treatment of IMNM, the therapeutic effect has not been fully recognized, and it has not been widely used in the clinic. To provide new ideas for selecting clinical treatment schemes, this paper describes a retrospective study to compare the effect between CTX and MTX in IMNM.

Materials and Methods

Patients and Sera

This is a retrospective single-center study. We reviewed clinical data on IMNM patients admitted and treated at the Department of Rheumatology and Immunology, the Second Affiliated Hospital of Chongqing Medical University from October 2016 to September 2025. The patients included met the diagnostic criteria for IMNM set by the European Center for Neuromuscular Diseases in 2016[1] and were admitted to our department for regular follow-up visits and IMNM treatment. Patients who did not conduct follow-up visits and treatment were excluded. All patients were treated with high-dose glucocorticoids (≥ Methylprednisolone 40 mg/d) as basic therapy and they were divided into a CTX group (0.8–1.2g every month) or MTX (10–12.5mg once every week) group based on the type of immunosuppressant. This study was conducted in accordance with the Declaration of Helsinki, and it was approved by the ethics committee in the Second Affiliated Hospital of Chongqing Medical University under the 2026EC078 project number. As this study was retrospective in nature, the requirement for informed consent was waived and general confidentiality principles were abided by.

Laboratory and Image Examinations

Routine blood examination included white blood cell (WBC) counts and lymphocytes. Biochemical tests included creatine kinase (CK), lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and troponin I (TnI). Immune indices included anti-SRP and anti-HMGCR. The myositis-specific autoantibodies were analyzed by immunoblot assay using an OMRMUN assay kit (EUROIMMUN, Beijing, China).

Statistical Analysis

Frequencies were evaluated with a chi-squared test or Fisher's exact test, as appropriate. The Mann–Whitney *U*-test was used for continuous data with non-normal distributions, and the results were expressed as medians with interquartile range (25%–75% percentiles). For comparisons of the descent degree of laboratory indicators, we used the multiple-independent nonparametric Kruskal–Wallis H-test. P-values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS 23.0 software (IBM SPSS Statistics version 23; IBM Corp., Armonk, NY, USA).

Results

A total of 35 patients were included. Thirty-two cases (91.4%) were initially diagnosed and treated. Our study comprised 25 patients with anti-SRP positivity and 10 patients with anti-HMGCR positivity, with no significant differences in antibody distribution. The dosage of MTX was used from 10mg to 12.5mg every week, while CTX was used from 0.8g to 1.2g every month.There were 19 cases in the CTX group (13 females and 6 males) and 16 cases in the MTX group (10 females and 6 males). The AST of patients in the CTX group was higher than that of the MTX group at admission before treatment ($P = 0.043$). There were no significant differences between the two groups in terms of sex, age of onset, absolute number of white blood cells and lymphocytes, CK, LDH, ALT, TnI, types of autoantibodies, and use of IVIG (all $P > 0.05$). Details are listed in Table 1.

The patients whose CK levels decreased by more than 50% after treatment were counted. The proportion of patients whose CK levels decreased by more than 50% was higher in the CTX group (18 cases, 94.7%) than in the MTX group (10 cases, 62.5%). This difference was statistically significant ($P = 0.024$). Details are presented in Table 2.

Table 1 Comparison of the Main Clinical Features Between CTX and MTX Groups

	CTX group (n = 19)	MTX (n = 16)	P
Gender (female/male)	13/6	10/6	0.574
Onset Age, median [IQR]	54 (44, 62)	58 (48, 67)	0.289
WBC, n*10^9, median [IQR]	8.46 (7.63, 10.3)	7.90 (6.31, 9.42)	0.305
L, n*10^9, median [IQR]	1.38 (1.15, 1.94)	1.43 (1.13, 2.79)	0.643
CK (U/L), median [IQR]	7518.5 (3336.0, 14,190.8)	4779.5 (2222.3, 7565.9)	0.085
LDH (U/L), median [IQR]	1319.0 (832.0, 1653.0)	897.0 (629.8, 1172.5)	0.051
ALT (U/L), median [IQR]	239 (118, 482)	168 (111, 286.8)	0.108
AST (U/L), median [IQR]	269 (154, 554)	163.0 (87.7, 261.8)	0.043*
TnI (ng/mL), median [IQR]	0.26 (0.03, 0.88)	0.07 (0.01, 073)	0.432
Anti-SRP, n (%)	14 (73.7%)	11 (68.8%)	0.605
Anti-HMGCR, n (%)	5 (26.3%)	5 (31.2%)	
IVIG, n (%)	11 (57.9)	9 (56.3%)	0.491
Follow-up time (weeks), median [IQR]	12 (8, 14)	12 (7.5, 18.75)	0.852

Note: *p-value was less than 0.05.
Abbreviations: IQR, interquartile range; CTX, cyclophosphamide; MTX, methotrexate; WBC, white blood cell count; L, absolute number of lymphocytes; CK, creatine kinase; LDH, actate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TnI, troponin I; SRP, signal recognition particle; HMGCR, 3-hydroxy-3-methylglutarylcoenzyme A reductase; IVIG, intravenous immunoglobulin.

Table 2 Comparison of Patients in the CTX and MTX Groups Whose CK Decreased by More Than 50%

	CK Decrease Over 50%	CK Decrease Less Than 50%	P
CTX, n (%)	18 (94.7%)	1 (5.3%)	0.024*
MTX, n (%)	10 (62.5%)	6 (37.5%)	

Note: *p-value was less than 0.05.
Abbreviations: CTX, cyclophosphamide; MTX, methotrexate.

Table 3 Comparison of Descent Degree in Laboratory Indicators Between CTX and MTX

Decrease Value, Median [IQR]	CTX Group	MTX Group	P
Δ CK (U/L)	6919.1 (2973.0, 13,943.8)	3245.3(503.2,5263.3)	0.034*
Δ LDH (U/L)	964.0 (269.0, 1170.0)	318.5 (41.5, 608.3)	0.034*
Δ ALT (U/L)	162 (55, 350)	82.5 (21, 134.8)	0.074
Δ AST (U/L)	225 (75, 530)	52.5 (12.0, 147.5)	0.011*

Note: *p-value was less than 0.05.
Abbreviations: IQR, interquartile range; CTX, cyclophosphamide; MTX, methotrexate; CK, creatine kinase; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

The descent degree of laboratory indicators was analyzed further in two sets to evaluate the efficacy of medicine. In the CTX group, the decrease of CK, LDH, ALT, and AST median levels after treatment was respectively as follows: Δ CK: 6919.1 U/L; Δ LDH: 964.0 U/L; Δ ALT: 162 U/L; Δ AST: 225 U/L. The decrease of values in the MTX group was as follows: Δ CK: 3245.3 U/L; Δ LDH: 318.5 U/L; Δ ALT): 82.5 U/L; Δ AST: 52.5 U/L. The descent degree of the median values of CK, LDH, and AST levels was higher in the CTX group than in the MTX group (all $P < 0.05$). The ALT descent degree was not statistically significant between the two groups. Details are presented in Table 3.

Discussion

As we all know, IMNM has severe muscle damage and a significant impact on the patient's quality of life. However, as the first line recommended immunosuppressant, MTX might give slow onset of action. We consider the remission induction rapidly is important. We tried to use CTX and found outstanding efficacy. In this article, we divided patients

into the CTX and MTX groups. There were no statistical differences in the specific autoantibodies, age, sex, TnI, or baseline CK levels between the CTX and MTX groups.

IMNM is a potentially disabling condition that requires early and aggressive treatment to prevent irreversible muscle damage. High-dose glucocorticoids are the first-line therapy, but the long-term use of additional immunosuppressants is typically needed—the most common of which is MTX. IVIG may also improve muscle strength[10] if used early in IMNM treatment.[11] Our study involved a comparative analysis of the therapeutic effects of two different immunosuppressive treatments in the CTX and MTX groups. Patients were treated with high-dose glucocorticoids as basic therapy, and there was no statistically significant difference in IVIG use between the two groups. The baseline CK levels before treatment between two groups had no statistical significance. After inductive treatments, the proportion of patients whose CK levels decreased by more than 50% was higher in the CTX group (94.7%) than that in the MTX group (62.5%). The median reduction in CK levels was also substantially greater in the CTX group (6919.1 U/L) than in the MTX group (3245.3 U/L). These results indicated that CTX provides a more pronounced decrease in muscle enzyme activity and potentially more effective disease control. As a folate analogue, MTX binds to dihydrofolate reductase to prevent dihydrofolate from being reduced to tetrahydrofolate. This inhibit the synthesis of purine nucleotides and thymidylate and exerts cytotoxic effects by depleting the raw materials for ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) synthesis,[12,13] thus exerting immunosuppressive and anti-inflammatory effects. However, MTX might give slow onset of action. For refractory cases, CTX could be used.[14] CTX exerts therapeutic effects by non-specifically suppressing T cells, B cells, and plasma cells. CTX cross-links with DNA at all phases of the cell cycle, and can directly damage DNA structure. MTX mainly affecting the DNA synthesis phase by inhibiting RNA and DNA synthesis. Therefore, the immunosuppressive action of CTX is faster and more effective than that of MTX.

Lactate dehydrogenase is a marker of tissue injury in both cardiac and skeletal muscles, and commonly found in infections, hemolysis, liver disease, kidney disease, lung injury, myocardial injury, muscle injury and malignant tumor.[15,16] In our study, LDH levels were elevated in all patients at baseline, yet decreased significantly after treatment in both groups—although the reduction was more pronounced in the CTX group (964.0 U/L) than in the MTX group (318.5 U/L). Thus, CTX may be more effective than MTX at treating the muscle injury caused by IMNM.

IMNM also increases the transaminase. ALT is commonly expressed in the liver and skeletal muscle, while AST is abundant in the myocardium, skeletal muscle, and liver.[17] IMNM causes muscle damage and myocardial injury, thus leading to an increase in AST. Previous research has shown that anti-HMGCR-positive patients tend to exhibit increased ALT, whereas anti-SRP-positive patients have increased AST levels.[18] In the patients in our study, both enzymes were elevated before treatment and improved following immunosuppression. We found that CTX had a better therapeutic effect on AST than MTX, but the reduction in ALT did not significantly differ between the groups.

As a retrospective single-center study, our analysis has limitations. The sample size was small, particularly for patients with anti-HMGCR positivity. Moreover, no seronegative patients were included. Thus, information bias and selection bias cannot be excluded. Future studies with larger cohorts are warranted to validate these findings.

Conclusion

IMNM is a rare but serious autoimmune disease that requires timely and effective immunosupressive therapy. In this cohort of IMNM patients, CTX achieved greater improvements in CK, LDH, and AST levels compared to MTX. CTX may be more beneficial than MTX for disease inductive treatment in IMNM patients. This finding provides evidence for selecting clinical treatment schemes.

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Disclosure

The authors report no conflicts of interest in this work.

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