Original Article

Clinical Characteristics and Factors Related to Outcome in Immune-Mediated Necrotizing Myopathy Associated with Anti-SRP and Anti-HMGCR Antibodies at Neurological Institute of Thailand

อาการทางคลินิก และปัจจัยที่มีผลต่อการฟื้นตัวของผู้ป่วยโรคกล้ามเนื้ออักเสบจากความผิดปกติจากภูมิคุ้มกันชนิดกล้ามเนื้อตายที่สัมพันธ์กับแอนติบอดี้ชนิดเอสอาพี และเอชเอ็มจีซีอาในสถาบันประสาทวิทยา ประเทศไทย

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บทคัดย่อ

ภูมิหลัง: โรค immune-mediated necrotizing myopathy (IMNM) เป็นโรคกล้ามเนื้ออักเสบจากความผิดปกติของภูมิคุ้มกันที่ค่อนข้างรุนแรง และโรคมีการกำเริบได้บ่อย

วัตถุประสงค์: เพื่อศึกษาอาการทางคลินิก ผลตรวจทางห้องปฏิบัติการ และการตอบสนองต่อการรักษาด้วยยากดภูมิคุ้มกัน รวมทั้งหาปัจจัยที่มีผลต่อการฟื้นตัวของผู้ป่วย IMNM ชนิด anti-SRP และ anti-HMGCR

วิธีการ: เป็นการศึกษาแบบย้อนหลังโดยเก็บข้อมูลทางคลินิกของผู้ป่วยโรคกล้ามเนื้ออักเสบจากความผิดปกติภูมิคุ้มกันชนิด anti-SRP 15 คน และ anti-HMGCR 2 คน ในสถาบันประสาทวิทยาระหว่างปี พ.ศ. 2558 ถึง พ.ศ. 2565 ผลลัพธ์หลักประเมินจากการตอบสนองต่อการรักษาหลังให้ยากดภูมิคุ้มกันที่ระยะเวลา 6 เดือน และ 12 เดือน โดยใช้ modified Rankin Scale (mRS) ซึ่งถ้ามีคะแนน 0-1 แปลว่า ฟื้นตัวดี แต่ถ้าคะแนนมากกว่าเท่ากับ 2 แปลว่าฟื้นตัวไม่ดี นอกจากนี้ยังเก็บข้อมูลการกำเริบของโรค และโรคสงบที่การนัดครั้งสุดท้าย สถิติที่ใช้คือ Fisher's exact test (two-tailed) หรือ Mann–Whitney U test สำหรับตัวแปรต้นที่เป็นแบบคู่ หรือต่อเนื่องตามลำดับ โดยจะมีความแตกต่างอย่างมีนัยสำคัญทางสถิติเมื่อ $p < 0.05$ วิเคราะห์ด้วยโปรแกรม SPSS รุ่นที่ 16

ผลการศึกษา : ผู้ป่วยเป็นเพศหญิง 11 คน (ร้อยละ 66.67) มีอายุเฉลี่ยประมาณ 49±11.9 ปี (มีช่วงอายุระหว่าง 26-66 ปี) ผู้ป่วย 9 คน (ร้อยละ 52.9) มีอาการอ่อนแรงแบบรุนแรง (MRC 1–2/5) ค่ากลาง (median) ของคะแนน MRC รวมแรกรับ (initial MRC sum score) เท่ากับ 44 โดยมีช่วงอยู่ระหว่าง 20-58 ค่าเฉลี่ย (mean) ของ mRS แรกรับเท่ากับ 3.12±0.93 และค่ากลาง (median) ของระดับเอ็นไซม์กล้ามเนื้อ (CK) เท่ากับ 3,925 ยูนิต/ลิตร โดยมีช่วงอยู่ระหว่าง 1,888 ถึง 16,640 ยูนิต/ลิตร พบผู้ป่วยในการศึกษานี้ 5 คน (ร้อยละ29.4) ต้องได้รับ IVIG หรือ Rituximab เนื่องจากอาการอ่อนแรงหรือระดับ CK แย่ลงหลังให้การรักษาด้วยยาคอร์ติโคสเตียรอยด์ร่วมกับยากดภูมิคุ้มกันอีก 1 ชนิด ระยะเวลาติดตามเฉลี่ยของผู้ป่วยในการศึกษานี้อยู่ที่ 4.72±2.73 ปี โดยมีช่วงระยะเวลาติดตามตั้งแต่ 17 เดือน ถึง 12.28 ปี หลังให้การรักษาด้วยยากดภูมิคุ้มกันที่ระยะเวลา 6 และ 12 เดือน พบว่าผู้ป่วยฟื้นตัวดีร้อยละ 29.1 และ 64.7 ตามลำดับ นอกจากนั้น พบผู้ป่วย 7 คน (ร้อยละ 41.18) มีภาวะโรคสงบ (remission) โดยที่ไม่มีการกำเริบของโรคที่การติดตามครั้งสุดท้าย และอีก 7 คน (ร้อยละ 41.18) พบมีการกำเริบของโรคระหว่างติดตามการรักษา สำหรับปัจจัยที่มีผลต่อการฟื้นตัวไม่ดีที่ระยะเวลา 6 เดือนหลังให้การรักษา คือคะแนน MRC sum score ในระยะแรกรับมีค่าน้อย โดย MRC sum score เฉลี่ยในระยะแรกของ

รับต้นฉบับ 31 ธันวาคม 2566, ปรับปรุงต้นฉบับ 15 มกราคม 2567, ตอบรับต้นฉบับตีพิมพ์ 19 มกราคม 2567

กลุ่มที่ฟื้นตัวดีที่ 6 เดือน เท่ากับ 50.4±8.53 เมื่อเปรียบเทียบกับ MRC sum score ของกลุ่มที่ฟื้นตัวไม่ดี จะมีค่าเท่ากับ 39.75±9.76 ซึ่งมีความแตกต่างอย่างมีนัยสำคัญทางสถิติ (p=0.048) ในการศึกษานี้ ไม่พบปัจจัยใดที่มีผลต่อการฟื้นตัวดีที่ระยะเวลา 12 เดือน และ การกลับเป็นซ้ำ หรือโรคสงบที่การติดตามนัดครั้งสุดท้าย

สรุป: คะแนน MRC sum score ที่น้อยในระยะแรกก่อนการรักษา สัมพันธ์กับการฟื้นตัวที่ไม่ดีหลังการรักษาด้วยยากดภูมิคุ้มกันที่ระยะเวลา 6 เดือน ในผู้ป่วยกลุ่มโรค anti-SRP หรือ anti-HMGCR IMNM ดังนั้น การให้ยากดภูมิคุ้มกันที่แรงในระยะแรก ๆ โดยเฉพาะ IVIG หรือ Rituximab ร่วมในกลุ่มผู้ป่วยกลุ่มนี้ อาจจะมีประโยชน์

คำสำคัญ: โรคกล้ามเนื้ออักเสบจากความผิดปกติภูมิคุ้มกันชนิดกล้ามเนื้อตาย, การกำเริบใหม่, โรคสงบ, ผลลัพธ์การรักษา

Clinical Characteristics and Factors Related to Outcome in Immune-Mediated Necrotizing Myopathy Associated with Anti-SRP and Anti-HMGCR Antibodies at Neurological Institute of Thailand

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Abstract

Background: Immune mediated necrotizing myopathy (IMNM) was severe inflammatory myopathy caused severe morbidity to the patients.

Objective: This study aims to investigate factors related to treatment outcomes in patients with seropositive immune-mediated necrotizing myopathy (IMNM).

Method: We retrospectively collected data in patient diagnosed anti-SRP or anti-HMGCR IMNM at Neurological Institute of Thailand (NIT) between the year 2015 and 2022. We identified 17 patients with IMNM; 15 with anti-SRP antibodies; 2 with anti-HMGCR antibodies. Baseline demographic, recovery outcome measure by Modified Rankin Scale (mRS); classified as good recovery was mRS;0-1 and poor recovery was mRS≥2, relapse rate and complete remission (full Medical Research Council (MRC)-sum score, no relapse and CK less than 1.5 time of ULN) were collected to determine the factor related outcomes at 6, 12 months and last follow up. Fisher's exact test (two-tailed) or Mann–Whitney U test was used to analyze by SPSS version 16. For all statistical analyses, significance was accepted as $p < 0.05$.

Result: The female was 11 patients (66.67%). The mean onset age was 49±11.9 years (range; 26-66). Nine patients (52.9%) were severe muscle weakness at presentation. The median initial MRC-sum score was 44 (range; 20-58). The mean initial mRS was 3.12±0.93 and 12 patients (70.59%) had mRS more than 2. Median creatine kinase level was 3,925 U/L (range 1,888-16,640 U/L). Five patients required IVIg or Rituximab due to severe weakness or refractory to corticosteroid plus others oral immunosuppressive therapy. The mean follow-up duration was 4.72±2.73 years (17 months to 12.28 years). At 6 and 12 months after treatment, the patients had good recovery were 29.1% and 64.7%, respectively and complete remission without relapse at last follow up was 41.18%. The mean initial MRC-sum score in the good recovery group and poor recovery group at 6 months were 50.4±8.53 and 39.75±9.76, respectively with statistically significant (p=0.048). But no factors related recovery outcome at 12 months. 7 patients (41.18%) had

complete remission and 7 cases (41.18%) had relapse, but no factors were associated with relapse and complete remission at last follow up. **Conclusion:** Initial low MRC-sum score has been associated with poor recovery outcome at 6 months in Thai patient who develop anti-SRP and HMGCR associated IMNM. Early aggressive combine multiple immunotherapy such as IVIg or rituximab may be required in this group of patients.

Keywords: Immune-mediated necrotizing myopathy (IMNM), Anti-signal recognition particle (SRP) antibody, Relapse, Outcomes, Complete remission

Introduction

Immune-Mediated Necrotizing Myopathy (IMNM) is characterized by subacute proximal limb muscle weakness and elevated serum creatine kinase (CK) levels.[1] The presumed autoimmune origin of IMNM is supported by its subacute onset, favorable response to immunotherapy, and distinctive serum autoantibody profile. The ENMC International Workshop in 2016 established three subgroups for IMNM classification (2016 ENMC – IMNM), categorized based on positive autoantibodies: anti-3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) IMNM, anti-signal recognition particle (SRP) IMNM, and seronegative IMNM.[2] Currently, there's a lack of prospective evaluation for treatment strategies, mostly relying on case series and expert opinions. Prior research has highlighted IMNM's tendency to resist corticosteroid monotherapy, requiring a minimum of three immunosuppressive agents to enhance motor function. However, it's significant to mention that around 10% of cases don't experience clinical improvement, and the relapse rate stays notably high (55% of cases) during medication tapering or treatment discontinuation.[1,3]

This study aimed to document clinical, serologic, and pathologic aspects, along with treatment strategies. Additionally, it sought to identify differences among patients with anti-SRP and anti-HMGCR IMNM, considering associated factors and potential determinants affecting recovery, relapse, and complete remission outcomes.

Methods

1.1 Patient selection

We conducted a retrospective review of medical records for patients at the Neurological Institute of Thailand (NIT) from January 1, 2015, to January 31, 2022, utilizing the myositis-specific autoantibodies (MSA) database. We focused on those testing positive for anti-SRP or anti-HMGCR. This study excluded seronegative IMNM cases and followed inclusion criteria were adapted from the European Neuromuscular Center (ENMC) International Workshop on Idiopathic Inflammatory Myopathies: (1) acute or subacute onset of proximally predominant muscle weakness without rash, (2) elevated CK level, (3) abnormal spontaneous activity by electromyography (EMG) revealing fibrillation potentials and short-duration motor unit potentials, and (4) biopsy evidence of necrotic and regenerating myofibers with minimal or no inflammatory infiltrates.[2] We also consistently excluded other causes of necrotizing myopathy like hypothyroidism, muscular dystrophy, and toxic myopathies. Participants received consistent motor power evaluations and CK level measurements, meticulously recorded with the Medical Research Council (MRC) sum

score and modified Rankin scale (mRS). These assessments occurred during clinic visits, initially monthly and later transitioning to three months for most patients. Follow-up spanned a minimum of 12 months, and individuals with less than 12-month follow-up were excluded.

1.2 Serum myositis antibody test

We determined the presence of autoantibodies using the Euroimmun (EUROLINE Autoimmune Inflammatory Myopathies 18 Ag IgG) kit, which originates from Lubeck, Germany. This kit was specifically used to identify autoantibodies associated with myositis. The Euroimmun Autoimmune Inflammatory Myopathies 18 Ag platform includes a comprehensive array of antibody tests, covering Mi2∂, Mi2ß, PM/Scl75, PM/Scl100, Ku, Jo-1, SRP, PL-7, PL-12, EJ, OJ, TIF1y, MDA-5, NXP-2, SAE, Ro52, CN-1A, and HMGCR. A result indicating ++ or a higher value was regarded as a positive outcome. Notably, it's important to highlight that all participants in the study displayed a positive result (++), either for SRP or HMGCR.

1.3 Muscle pathology

Muscle samples were obtained from patients' biceps brachii or quadriceps femoris. Each biopsy adhered to a standardized muscle biopsy protocol, involving a sequence of staining procedures. These included hematoxylin and eosin (H&E), modified Gomori trichrome, periodic acid-Schiff, oil red O, adenosinetriphosphate (ATP) enzyme assays at both pH 4.6 and 10.8, NADH-tetrazolium reductase, succinate dehydrogenase (SDH), and cytochrome C oxidase (COX) stains. Following the staining procedure, a thorough examination of these samples was carried out by a neuropathologist.

1.4 Clinical follow-up and treatment outcome evaluation

We assessed patients' muscle strength using the Medical Research Council (MRC) classification, with categories including severe weakness (MRC 1–2/5), moderate weakness (MRC 3/5), and mild weakness (MRC 4–5/5). This classification was determined based on muscle strength in 1-2 muscles during initial, 3-month, 6-month, 12-month, and final follow-up assessments.

Our focus on outcomes involves recovery, relapse, and achieving comprehensive clinical and biochemical remission post immunosuppressive therapy. MRC-sum score assess ments occurred at intervals: initial, 3-month, 6- month, 12-month, and final follow-up. To measure functional results, we used the mRS at initial, 6-month, and 12-month points. Within the mRS classification, a score below 2 meant favorable recovery, while exceeding 1 indicated unfavorable recovery. The relapse criteria were that the serum creatine kinase(CK) returned to above the patient's baseline level, rose to more than three times the reference upper limit and over 1 point MRC-sum score drop from previous assessment.[4] The criteria for complete clinical and biochemical remission were an MRC-sum score of 60 (normal strength), CK below 1.5 times the upper limit normal[2], and no relapses during the follow-up period.

1.5 Statistical analysis

We used statistical analysis software (IBM/SPSS V.16, Armonk, New York, USA) for all analyses, covering recovery, relapse, and complete remission. We used the two-tailed Fisher's exact test for dichotomous variables and the Mann–Whitney U test for continuous

variables. For all statistical analyses, significance was accepted as $p < 0.05$.

The study received approval from the Ethics Committee of the Neurological Institute of land (NIT), which determined that informed consent was not required (approval number 66062).

Results:

Seventeen patients (88%) with anti-SRP positive and 2 patients (11.8%) with anti-HMGCR positive, who had previous statin exposure, were included in this study. Among the enrolled patients, 11 patients (66.67%) were of the female. The average age of symptom onset was 49 ± 11.9 years (range: 26-66 years), and the disease duration ranged from 20 days to 12 months, with a median presentation duration was 3 months. According to the MRC classification, we found that 9 patients (52.94%) had severe weakness (MRC 1–2/5). The median initial MRC-sum score was documented at 44 (with a range of 20-58). The mean initial mRS was calculated to be 3.12±0.93. Additionally, the median initial CK level was measured at 3,925 U/L (range: 1,888-16,640 IU/L). For demographic data, refer to Table 1. Muscle biopsies were conducted on 16 patients (94.11%). All biopsies exhibited regenerating fibers, and necrotic fibers were present without significant endomysial inflammation.

As part of the treatment regimen, 5 patients received intravenous methylprednisolone, followed by high-dose prednisolone plus a single other immunosuppressive agent (four on azathioprine (AZA), one on mycophenolate mofetil (MMF)). Seven patients received a prednisolone and azathioprine combination. Three patients received intravenous immunoglobulin (IVIg) due to severe muscle weakness, and 2 patients had Rituximab induction due to unresponsiveness to prior treatment. Case examples showing MRC sum score and creatine kinase over time with associated immunotherapy are present in Figure 1.

After three months of treatment, only 2 patients (11.76%) attained a full MRC-sum score, despite ongoing elevated CK levels. Immunosuppressive therapy for 6 and 12 months resulted in 4 patients (29.41%) and 7 patients (47.06%) achieving full MRC-sum scores, respectively. Moreover, during the respective 6-month and 12-month periods, 5 patients (29.41%) and 11 patients (64.7%) experienced favorable recovery as present in Table 1.

Table 1: Baseline demographic, clinical, laboratory and electromyographic features of IMNM patients.

Features	IMNM (n=17)
Age of onset (years), mean ± SD (range)	49±11.9 (26-66)
Female gender, n (%)	12 (66.67%)
Duration of symptoms (days), mean ± SD (range)	119.36±139.52 (20 days to 1 year)
Prior statins use, n (%)	5 (27.78%)
Clinical manifestation	
Myalgia, n (%)	
Generalized myalgia	3 (16.67%)
Lower limb myalgia	6 (33.33%)
Initial weakness (Motor power)	n (%)
Mild weakness (≥4/5)	4 (23.53%)
Moderate weakness (3/5)	4 (23.53%)
Severe weakness (<3/5)	9 (52.94%)
Weakness distribution: n (%)	
Dropped head syndrome (DHS)	2 (8%)
Dysphagia and/or dysarthria	6 (35.30%)
Dyspnea	3 (12%)
Lower limb predominate (LEs greater than UEs)	8 (32%)
Upper limb predominate (UEs greater than LEs)	1 (4%)
Initial MRC-sum scores: mean ± SD (range)	42.88 ±10.43 (20-58)
Myocarditis: n (%)	3 (17.64%)
Laboratory results	
Initial CK levels, Mean CK (SD) Range	6,754.29±4,895.86 (1,888-16,640)
Electromyography: n, muscles	12 (vastus lateralis 11, only deltoid 1)
Abnormal muscle membrane irritability: n	10
Early recruitment: n	10
Relapse: n (%)	7 (41.17%)
Favorable recovery (mRS 0-1) at 6/12 months: %	29.41%/64.7%
Full MRC-sum score at 3 / 6 / 12 months / last follow up*: %	11.76% / 29.41% / 47.06% / 52.94%
Complete remission: n (%)	7 (41.17%)

LEs; lower extremities; UEs; upper extremities. * Last follow up in 17-147.3 months

1.6 Factors influencing recovery, relapse and complete remission

1.6.1 Recovery outcome

The mean initial MRC-sum score at 6 months was 50.4±8.53 for the favorable recovery group, while the group with unfavorable recovery had a mean of 39.75±9.76. Notably, the initial MRC-sum score of the group with favorable recovery (mean rank = 12.8) was significantly higher than that of the group with unfavorable recovery (mean rank = 7.42), as indicated by U = 11, z = -2.02, and p = .048. Our analysis revealed no

significant associations in various parameters, including gender, age of diagnosis, disease duration, body mass index (BMI), weight loss, bulbar symptom at presentation, dyspnea, dropped head, myocarditis, initial CK level, duration of prednisolone tapering below 30 mg/day, or use of 3 immunosuppressive agents within 3 months from onset, between the two recovery groups, as analyzed via Fisher's exact test or the Mann-Whitney U test (Table 2).

Furthermore, at the 12-month interval, our investigation did not identify any statistically significant association between the group with favorable recovery and the group with unfavorable recovery concerning the initial MRC-sum score (p= 0.062) or the other aforementioned factors.

Table 2: Favorable recovery (mRS:0-1) and unfavorable recovery (mRS:2-6) at 6 months.

Factors	Unfavorable recovery (n=12)	Favorable recovery (n=5)	*P*-value
Female: n (%)	9 (75%)	2 (40%)	0.28*
Age of diagnosis: mean ± SD	50±13.24	45.3±8.05	0.44**
Mean rank	9.67	7.4	
The duration of disease at diagnosis (days):	75	90	0.88**
median (IQ1, IQ3)	(52.5,150)	(60,120)	
BMI: mean ± SD	22.66±3.94	21.96±5.25	0.88**
Mean rank	9.17	8.6	
Initial MRC sum score: mean ± SD	39.75±9.76	50.4±8.53	0.048**
Mean rank	7.42	12.8	
Bulbar symptom: n (%)	4 (33.3%)	2 (40%)	1*
Dyspnea : n (%)	2 (16.7%)	1 (20%)	1*
DHS: n (%)	1 (8.3%)	1 (20%)	0.51*
Significant weight loss >5% BW: n (%)	3 (25%)	3 (60%)	0.28*
CK level before treatment: median (IQ1, IQ3)	4925 (3,388.8, 12130.5)	4055 (3,850, 6210)	0.8**
Myocarditis: n (%)	3 (25%)	0	0.5*
Duration of taper pred<30 mg/day (month):	7.43±3.49	5.37±3.43	0.23*
mean ± SD, mean rank	10	6.6	
3 immunosuppressive within 3 months: n (%)	2 (16.7%)	1(20%)	1*
Initial immune therapy within 3 months			
PSL alone	-	1	
IVMP, PSL+AZA	4	1	
IVMP, PSL+MMF	1	-	
IVMP weekly+IVIg	1	-	
PSL+AZA	4	1	N/A
PSL+MMF	-	1	
IVIg+IVMP+PSL+AZA	1	-	
IVIg+RTX+IVMP	1	-	
IVIg+PSL+MMF	-	1	
Relapse: n (%)	5 (41.7%)	2 (40%)	1*

* By Fisher's exact(f<5), ** the Wilcoxon-Mann-Whitney test (Exact Sig. (2-tailed test)
F=female, M=male, UL: upper limb, LL: lower limb, DHS: drop head syndrome, IVMP: iv pulse methylprednisolone, PSL: prednisolone, AZA: azathioprine, MMF: mycophenolate mofetil, MTX: Methotrexate, RTX: rituximab, IVIg: intravenous immunoglobulin, FU: follow up, mRS: modified Rankin scale

1.6.2 Complete remission and relapse

In the latest follow-up, 10 patients (58.82%) achieved full MRC-sum scores, and 7 patients (41.18%) attained complete clinical and biochemical remission. The average follow-up time was 61±19 months (ranging from 2.85 to 12.28 years). During the final follow-up of the complete remission subgroup, three patients continued with AZA at doses of 25-50 mg per day, one patient used MMF at a dose of 1500 mg per day, and another maintained a regimen that combined prednisolone (15 mg per day) with AZA (100 mg per day). The reason for continuing immunosuppression was elevated creatine kinase levels during the tapering of immunosuppressive agents. Four patients with anti-SRP IMNM displayed persistent hyperCKemia without clinical relapse, while maintaining a consistent dosage of immunosuppressive agents. Among the remaining 13 cases, the median time taken for CK levels to return to normal was approximately 6.5 months (with a range of 3.07 to 12.2 months).

The relapse occurred in 4 patients (41.17%). The immunosuppressive regimen administered prior to relapse included prednisolone doses ranging from 5 to 15 mg/day, in combination with AZA at 100 mg/day, MMF at 1000 mg/day, or methotrexate at 7.5 mg/week. It was observed that none of the factors exhibited a statistically significant correlation with either complete remission or relapse status.

Discussion

We present a retrospective cohort of 17 IMNM cases (15 anti-SRP and 2 anti-HMGCR antibody positive). The majority of patients (52.9%) exhibited severe muscle weakness. These findings align with previous studies, which reported severe muscle weakness rates ranging from 51% to 67%.[1, 3, 5, 6] Previous research indicated that anti-SRP cases tend to show pronounced neck muscle weakness (70-78%), particularly in the neck flexor.[3, 6] In our study, 2 patients (11.76%) had drop head syndrome due to severe both neck flexor and neck extensor weakness. Additionally, 6 patients (35.29%) showed bulbar involvement, aligning with recent studies suggesting that between 33% and 46% of IMNM cases present with dysphagia.[3, 4, 6] Myocarditis was detected in three patients (17.65%) with anti-SRP antibodies, indicating a notably higher prevalence compared to previous reports (1.5-2%).[3, 6] We observed 2 patients who displayed anti-HMGCR antibody positivity and had a history of exposure to statin medication. One of them was a 57-year-old female who responded well to corticosteroids and azathioprine, achieving remission. The other patient was a 66-year-old male who required rituximab and IVIg for motor improvement. Prior studies suggested statin-exposed, anti-HMGCR-positive individuals are older and less severely affected. Statin-naïve patients with positive anti-HMGCR antibodies appear more resistant to therapy.[7] Our two anti-HMGCR-associated IMNM cases, exposed to statins, had older onset ages and varying severity levels. All patients underwent clinical screening for malignancy based on risk factors and age

groups; however, none of them showed signs of malignancy. The results of patient muscle biopsies displayed significant variation, revealing that the number of necrotic and regenerating fibers did not necessarily correlate with the severity of weakness or creatine kinase levels, as reported earlier.[4, 5]

Managing IMNM presents a formidable challenge, given that most cases demonstrate resistance to conventional immunotherapy and a high likelihood of relapse when attempting to taper steroids.[1, 7-9] Moreover, most patients require two or more steroid-sparing agents in conjunction with prednisolone.[5] In our study, most patients utilized two immunosuppressive agents (prednisolone plus AZA or MMF or methotrexate). However, refractory cases necessitated a combination of IVIg or Rituximab to address motor function or disease complications. Recent research has emphasized the crucial role of IVIG and Rituximab in treating refractory IMNM patients.[10, 11] Out of the five patients who required IVIg and/or rituximab therapy, one patient (anti-SRP) treated with rituximab achieved complete symptom resolution and normalized CK levels within 6 months (Figure 1; case C), albeit additional immunotherapy was still needed. In another case, a patient received weekly intravenous methyl prednisolone for 2 months without experiencing improvements in motor function or CK levels. However, after administering a single 2 g dose of IVIg, motor function and CK levels improved within 5 months post-treatment. While complete remission was achieved by the last follow-up, maintenance therapy with prednisolone plus azathioprine remained necessary. The remaining patients exhibited partial motor recovery and fluctuating CK levels during follow-up, necessitating the use of multiple immunosuppressive treatments to sustain motor function (Figure 1; A, B , D). Previous research found in patients with statin-induced IMNM with muscle weakness, early induction with corticosteroid, IVIg and a corticosteroid-sparing agents is efficacious and may allow accelerated corticosteroid taper and switch to single or double steroid sparing agents.[12] Achieving sustained remission with normal CK levels, normal strength, and no corticosteroids is indeed a goal of treatment. Two of our patients achieved complete remission after discontinuing immunotherapy—one with anti-SRP-associated IMNM and the other with anti-HMGCR-associated IMNM. Both patients have been followed for 3 years and 1 month. Additionally, 29.4% of patients achieved remission but continued to require ongoing immunotherapy for disease control.

This study aimed to investigate the factors that influence poor recovery, clinical and biochemical remission, and relapse following treatment for anti-SRP and anti-HMGCR associated IMNM. Our findings highlighted that only a low MRC-sum score correlated with unfavorable recovery outcomes at 6 months. Within our cohort, one case had persistent moderate proximal limb weakness at 4 years and 11 months follow-up, with muscle pathology showing marked endomysial fibrosis diagnosed before treatment initiation, over 4 months after symptom onset. Previous studies.[4, 6, 13-15] indicates early-onset disease, male gender, weight loss, severe weakness, dysphagia, muscular atrophy, concurrent interstitial lung disease (ILD), more than 3 months of 3 immunotherapies, rapid

muscle fatty infiltration seen in MRI, increased BAFF-R and B lymphocyte infiltration signal resistance to immunosuppressive therapy and poor prognosis in anti-SRP myositis. A previous report linked a 55% relapse rate with immunotherapy tapering or discontinuation, requiring resumption.[1] In our study, 7 patients (41.2%) relapsed, but no factors correlated with clinical relapse.

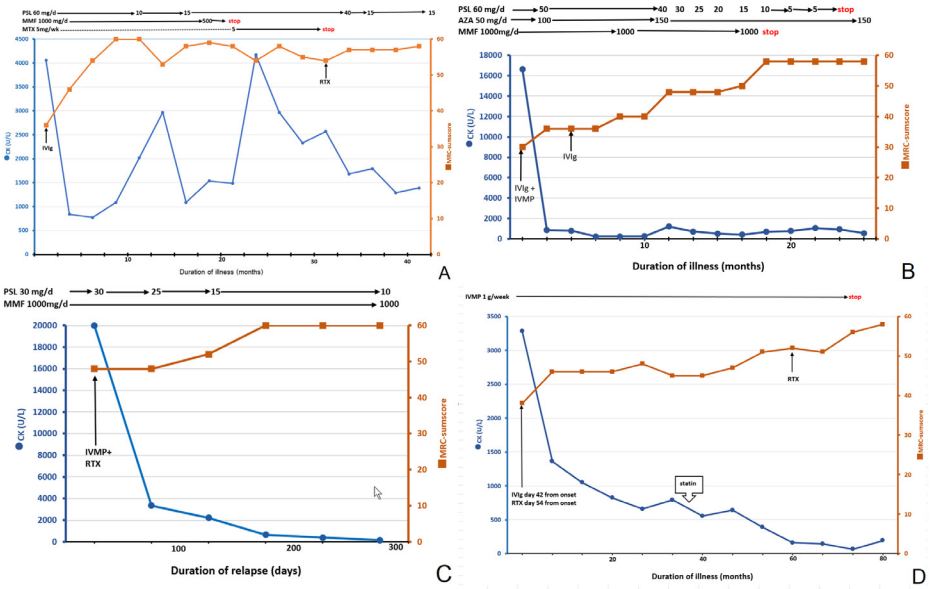

Figure 1: Case examples showing the induction with rituximab or IVIg demonstrate the MRC sum score (right bar ●) and creatine kinase (left bar ■) over time, along with the associated immunotherapy. Case A-C; anti-SRP IMNM and Case D; anti-HMGCR IMNM

A: Initial therapy with IVIg on day 60 and maintenance with PSL and MMF. The patient had recovery from severe weakness to full recovery within 6 months. But thereafter he had frequent relapse after 5 months and treat with RTX on 34 months after onset. The patient had mild bilateral hip flexor weakness at the end of follow up (MRC-sumscore = 58 and mRS=1). **B:** Initial therapy with IVMP with 2 courses of IVIg within 1 month of onset and maintenance with PSL plus AZA and MMF. She had slow improved MRC sumscore and fluctuate CK (242-1219 U/L). At end of follow up, she had mild hip flexor weakness. **C:** initial treatment with IVMP and rituximab within 17 days of relapse. The patient had full recovery with normalized CK within 167 days. **D:** Initial treatment with IVIg infusions within 42 days at onset and eventually rituximab infusions within 54 day and maintenance with IVMP 1 gram weekly. The patient had partial recovery at 12 months (MRC-sumscore 58, mRS=2).

AZA: azathioprine, MMF: mycophenolate mofetil, IVMP: intravenous -methyl prednisolone, IVIg: intravenous immunoglobulin, RTX: rituximab, PSL: prednisolone

Our study has limitations. First, it was a single-center, hospital-based investigation focused on urban patients, potentially limiting its representation of anti-SRP and anti-HMG-CR-associated IMNM situations in rural or remote areas. Patients who did not seek treatment or who died before reaching the hospital were excluded. Second, the study had a retrospective design and a small sample size, with a lack of a standardized therapeutic approach. To enhance reliability, larger prospective studies are needed.

Conclusions

Anti-SRP and anti-HMGCR associated IMNM are severe inflammatory myopathies with heightened immunotherapy resistance. About 60% of patients achieved favorable recovery (mRS:0-1) at 12 months, while 41% experienced mild weakness. We found that low initial MRC sum score with anti-SRP or anti-HMGCR IMNM have an unfavorable recovery, but this conclusion may still need to be confirmed in a larger patient. In our experience, Rituximab and IVIG are useful in symptom control and reducing steroid use.

Abbreviations

AZA: azathioprine, MMF: mycophenolate mofetil, IVMP: intravenous -methyl prednisolone, IVIg: intravenous immunoglobulin, RTX: rituximab, PSL: prednisolone

F=female, M=male, UL: upper limb, LL: lower limb, DHS: drop head syndrome, IVMP: iv pulse methylprednisolone, PSL: prednisolone, AZA: azathioprine, MMF: mycophenolate mofetil, MTX: Methotrexate, RTX: rituximab, IVIg: intravenous immunoglobulin, FU: follow up, mRS: modified Rankin scale

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