Tacrolimus combined with corticosteroids effectively improved the outcome of a cohort of patients with immune-mediated necrotising myopathy

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Abstract

Objective

To assess the efficacy and safety of tacrolimus in combination with corticosteroids in patients with immune-mediated necrotising myopathy.

Methods

The medical records of 20 hospitalised patients with immune-mediated necrotising myopathy (IMNM) who had received tacrolimus combined with oral prednisone from January 2014 to August 2017 were retrospectively reviewed. The recruited patients were shifted to the combined therapy because they failed to respond well to monotherapy with oral prednisone. The clinical efficacy during an average follow-up of 21 months (range, 14–24 months) was assessed by evaluating the changes of serum creatine kinase (CK) levels, the Medical Research Council (MRC) grading of the weakest muscle groups and dosage of oral prednisone. Adverse effects were monitored to assess the safety of tacrolimus.

Results

After starting tacrolimus, most of the 20 patients showed significant improvement in muscle strength and remarkable decline in serum CK levels at the follow-up points ($p<0.0001$). In addition, the daily dosage of prednisone was statistically significantly reduced ($p<0.0001$) after the combination therapy. No serious adverse events attributable to tacrolimus occurred in the patients.

Conclusion

Early co-administration of tacrolimus with corticosteroid promoted the remission and recovery of patients with IMNM and seemed to be a relatively safe treatment programme for physician managing immune-mediated necrotising myopathy.

Key words

immune-mediated necrotising myopathy, tacrolimus, corticosteroids

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Introduction

Immune-mediated necrotising myopathy (IMNM), also known as necrotising autoimmune myopathy (NAM), is a relatively new subgroup of idiopathic inflammatory myopathies (IIMs) (1). Currently, by the 119th European Neuro Muscular Centre (ENMC) workgroup in 2004 (2), the IIMs are divided into polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM), immune-mediated necrotising myopathy (IMNM), and non-specific myositis. Histopathologically, IMNM harbors necrotic and regenerated myofibres but with scarce infiltration of inflammatory cells on muscle biopsy. The clinical presentation features symmetrical proximal muscular weakness with increased level of creatine kinase (CK), and dysphagia and dyspnea in severe cases, in a subacute, acute or chronic progression mode. IMNM is a heterogeneous subgroup, related to some risk factors such as autoantibodies (3-5), statin exposure (6), connective tissue diseases (CTD) (7), or paraneoplastic disease (8).

There have been no optimal therapeutic strategies from large prospective studies and treatments are mainly based on case series. IMNM is often refractory to monotherapy and is prone to relapse on tapering immunosuppressive agents (9). Aggressive and sustained immunosuppressive therapy is often required for long-term remission, and severe cases may be treated with combined corticosteroids and immunosupressants or intravenous immunoglobulin (IVIG) (10-12). Tacrolimus (FK506) is a relatively new immunosuppressant, widely used for various autoimmune diseases and the prevention of allograft rejection. The agent acts as a calcineurin inhibitor, and selectively suppresses T cell activation and immune signalling (13, 14). There have been several reports stating the positive effects of tacrolimus on dermatomyositis and polymyositis (15-20), while the treatment of tacrolimus on IMNM patients is scarce. In this cohort study, we retrospectively reviewed patients with IMNM who had received tacrolimus and corticosteroid in combination, in order to assess the efficacy and safety of the therapeutic regimen.

Methods

Patients

We reviewed medical records of IMNM patients who had been treated and followed up at Tongji Hospital from January 2014 to August 2017. Twenty participants who had received tacrolimus in addition to oral prednisone were recruited in the cohort study. The diagnosis of IMNM was made based on the criteria of idiopathic inflammatory myopathies from the ENMC International Workshop (Table I) (2). The muscle for biopsy was determined by clinical evaluation and MRI imaging and serum autoantibodies profile of the patients with IMNM were tested by Kindstar Global company. Other causes of myopathy, such as muscular dystrophy, metabolic, hypo-thyroidic and toxic myopathies, were excluded. Detailed clinical data of the patients were documented during their hospitalisation and the follow-up period in the out-patient clinic, including history of medication, especially the use of statins. During subsequent follow-up interviews, serum CK levels and manual muscle testing (MMT) were routinely tested to evaluate the therapeutic efficacy. Laboratory examinations including blood and urine routines, liver and renal functions, and blood glucose, which may indicate the possible side effects of the therapeutic agents, were performed regularly.

This study was approved by the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (IRB ID: TJ-C20121221) and written informed consent was obtained from all patients.

Treatment with corticosteroids and tacrolimus

Once the diagnosis was definite, all the 20 patients were treated with intravenous methylprednisolone at 500 mg per day for consecutive 3–5 days. In severe cases who presented with prominent dysphagia and/or dyspnea, IVIG at 0.4 g/d was administered for consecutive 5 days. Later on, oral prednisone at 0.8–1 mg/kg/day was substituted in all the cases. At the same time, tarcrolimus at 3 mg per day was added. The initial oral dose of prednisone was kept for 6–8

weeks and gradually decreased according to our dosage reduction regimen, *i.e.* prednisone reduced by 5mg/tablet every month, unless the patients showed any signs of weakened muscle strength or elevated CK levels. After the CK levels decreased to the nearly normal range and the muscle power returned to the nearly baseline, the oral prednisone was maintained at 10–15 mg per day. The pharmaceutical therapy would be discontinued after the muscle power had recovered for at least 6 months under the condition of normal CK levels. After the discontinuation of the therapy, all the patients had been asked to visit the clinic every 6 months in order to monitor CK levels and muscle strength.

Prior to the initiation of tacrolimus, routine laboratory examinations mentioned above in all the patients were completed, including electrocardiogram (EEG) and chest CT. Tacrolimus was generally administrated at a dosage of 3 mg/day, and the trough concentration was monitored at least every other month to ensure the targeting concentration at range of 5–10 ng/ml. When the trough concentration was below 5 ng/ml, Wuzhi capsules, a Chinese medicine preparation which may interfere the activity of cytochrome P450 3A (CYP3A4/5) (21), were used to increase the concentration of tacrolimus. Likewise, when the trough concentration exceeded 15 ng/ml, the daily dose of tacrolimus was reduced to maintain the trough concentration at the range of 5 to 10 ng/ml.

Clinical assessments

After commencing tacrolimus treatment, all the patients have been clinically assessed at least once every two months, including muscle strength testing, serum CK levels, lactate dehydrogenase (LDH) and myoglobulin, as well as the regular laboratory tests such as blood and urine routine, renal and hepatic functions, and blood glucose for monitoring the possible side effects of tacrolimus. The most widely used scoring method of manual muscle testing, the Medical Research Council (MRC) muscle strength grading system, was employed to evaluate the patients' muscle power graded 0 to 5 (22, 23). According to the MRC scoring and ability of daily living of individuals, the therapeutic response was graded as no improvement, mild improvement, moderate improvement, marked improvement, and return to baseline (24) (Table II). If clinical deterioration was determined, additional treatment with another immunomodulator such as IVIG would be considered in the case of worsening of symptoms, or presenting a new symptom, or persistent increase of serum CK level. A relapse was determined when the symptoms reappeared or CK levels dramatically increased from a very close level to normal range after a patient achieved remission.

Table I. Diagnosis of necrotising autoimmune myopathy.

Clinical features:
Onset after 18 years
Subacute or insidious onset
Muscle weakness: Symmetric proximal > distal; Neck flexor> neck extensor
Elevated serum creatine kinase
Muscle biopsy:
Predominant feature is necrotic and regenerating muscle fibres
sparse or only slightly inflammatory infiltrate
One of the following additional supportive features :
Abnormal electromyography
Pathologic MRI
Presence of myositis specific antibodies

Table II. Grades of patients' response to treatment.

Grade	State of patients
Mild improvement	1 MRC grade in 1-2muscle groups, persistently requiring assistance for ambulation and activities of daily living
Moderate improvement	>1 MRC grade in multiple muscle groups, requiring minimal assistance with ambulation and with activities of daily living
Marked improvement	symptoms and signs of mild weakness, but no functional limitation
Return to baseline	no symptoms or signs of weakness

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics v. 20.0 (Chicago, IL). The Kolmogorov-Smirnov test was used to evaluate the distribution of quantitative variables. Data were expressed as mean ± standard deviation (SD) or median (interquartilic range [IQR]) and were compared using Dunnett's T3 test. Categorical variables were expressed as percentages (%). A p-value less than 0.05 was regarded as statistically significant.

Results

The clinical profiles of all the patients enrolled were shown in Table III. Twenty patients (5 men and 15 women; aged from 18 to 66 years; mean 44.3±12.1 years) met the diagnostic criteria for IMNM and had been treated with oral tacrolimus in combination with oral prednisone. The rationale for adding tacrolimus was difficulty in tapering oral prednisone in 15 patients and recurrence of muscle symptoms and CK elevation in 5. All patients showed the typical presentation including weakness of limbs with more serious affection of the proximal portions. Dysphagia occurred in 14 (70%) patients and myalgia occurred in 11 (55%) patients. Seven patients who presented with prominent dysphagia and/or dyspnea had received IVIG. Myositis specific autoantibodies (MSA) and myositis-associated autoantibodies (MAA) were summarised in Table III and anti-signal recognition particle (anti-SRP) antibodies were detected positive in 16 patients. However, unfortunately, the anti-hydroxy-methyl-glutaryl-coenzyme A reductase (anti-HMGCR) antibody was not determined because of the technical limitation.

Table III. Clinical profiles of the patients enrolled in this study.

Patient	Age at onset (y)	Onset to treatment (months)	Reason for adding TAC	CK at onset (IU/L)	Positive MSA/MAA	Weakness on Examination				Dysphagia	Myalgia	Prior treatment
						PU	DU	PL	DL			
1/F	36	6	DRP	4697	SRP, Ro52	+	+	+	+	–	–	IVMP
2/F	44	6	Relapse	4111	SRP, Ro52	+	+	+	+	–	+	IVMP
3/M	46	2	DRP	4963	SRP, Ro52	+	+	+	+	+	+	IVMP, IVIG
4/F	45	2	DRP	1966	SRP	+	+	+	+	+	–	IVMP, IVIG
5/F	35	12	Relapse	4169	SRP, Ro52	+	+	+	+	+	+	IVMP, IVIG
6/F	44	25	DRP	1885	SRP, Ro52	+	+	+	+	+	–	IVMP, IVIG
7/F	66	5	DRP	2334	SRP, Ro52	+	+	+	+	+	+	IVMP, IVIG
8/F	40	3	DRP	3569	SRP	+	+	+	+	–	–	IVMP
9/M	31	12	DRP	1457	SRP	+	+	+	+	–	+	IVMP
10/F	28	4	Relapse	4989	ND	+	+	+	+	+	–	IVMP, CYC, AZA
11/M	52	12	DRP	3652	ND	+	+	+	+	+	–	IVMP, IVIG
12/F	59	1	DRP	5283	SRP, Ro52	+	+	+	+	+	+	IVMP
13/M	50	2	Relapse	4330	Ro52	+	+	+	+	–	–	IVMP
14/F	35	2	DRP	1966	NXP2, Ro52	+	+	+	+	+	–	IVMP
15/F	57	15	DRP	4839	SRP	+	+	+	+	+	–	IVMP
16/F	40	6	Relapse	4130	SRP, Ro52	+	+	+	+	+	+	IVMP
17/F	51	6	DRP	4395	SRP, Ro52	+	+	+	+	–	+	IVMP
18/F	64	9	DRP	4069	SRP	+	+	+	+	+	+	IVMP
19/F	45	2	DRP	4202	SRP	+	+	+	+	+	+	IVMP, IVIG
20/M	18	2	DRP	4326	SRP, Ro52	+	+	+	+	+	+	IVMP, MTX

M: male; F: female; TAC: tacrolimus; DRP: difficulty in reducing prednisone; ND: No data; PU: proximal upper extremity; DU: distal upper extremity; PL: proximal lower extremity; DL: distal lower extremity; IVMP: intravenous methylprednisolone; CYC: cyclophosphamide; AZA: azathioprine; MTX: methotrexate.

Although 5 patients were found to have dyslipidaemia after admission, none of them had been treated with statins in the past. ECG abnormalities were observed in 6 out of 20 patients, including atrial premature beats in 2 patients, ventricular premature beats in 1, left anterior hemiblock in 1 and left ventricular high voltage in 2 patients. In addition, chest CT findings showed pulmonary interstitial changes in 6 patients, patchy shadows in 5, fibrous stripe in 4, nodus in 3, pleura thickening and adhesion in 3, pleura effusion in 3, and mediastinal or hilar lymphadenectasis in 7.

The patients were followed up and assessed 3, 6, 12 and 24 months after starting the combination therapy. Because of difference in the enrolment time, 7 patients had been followed-up for less than 24 months, so we evaluated their clinical data of the last follow-up visit. The mean last follow-up time was 21 months (range, 14–24 months). The temporal profiles of serum CK levels were shown in Figure 1. Median CK at onset, 3 months, 6 months, 12 months and the last follow-up were 4149.5 IU/L (IQR: 3260.25–4470.5), 704.5 IU/L (IQR: 53–2052.5), 453.5 IU/L (IQR: 259.25–689.75), 198.5 IU/L (IQR: 148.25–326.75) and 107 IU/L (IQR: 86.5–178.75), respectively. Overall, the serum CK levels began to statistically significantly decrease ($p<0.0001$) since 3 months after adding tacrolimus, and approximate normalisation of serum CK was seen in 2 (10%), 9 (45%), 13 (65%) and 17 (85%) patients at 3, 6, 12 months and the last follow-up, respectively. During the whole follow-up period, there was no obvious re-elevation in serum CK in all patients except for 2 patients, whose serum CK levels at the 12 months (Patient 5) and the last follow-up (Patient 20) were higher than that at 6 months and 12 months.

MRC scoring and ability of daily living were used to evaluate the efficacy of the combined treatment in the patients (Table III) (24). As shown in Figure 2, after 3 months of initiating the therapy, 6 (30%) patients had achieved moderate improvement, 12 (60%) cases mild improvement, but 2 (10%) patients no improvement. Six months after the therapy, 1(5%) patient returned to the baseline, 3 (15%) patients achieved marked improvement, 10 (50%) patients obtained moderate improvement and 6 (30%) patients mild improvement. At 12 months after the combined treatment, 4 (20%) patients returned to the baseline, 9 (45%) patients achieved marked improvement, 4 (20%) patients moderate improvement and 2 (10%) patients mild improvement, but 1 (5%) patient (Patient 5) underwent a deteriorating process. A mild decrease of muscle strength on her extremities was evident, and serum CK level was elevated at the same time. The patient got improvement after increasing the dosage of prednisone and united use of IVIG. At the last follow up visit, 11 (55%) patients returned to baseline, 7 (35%) patients were markedly improved and 1 (5%) patient was moderately improved. However, 1 (5%) patient (Patient 20) suffered a relapse, presenting sudden increase in serum CK level and a lower MRC score when dosage of tacrolimus tapered to 2 mg/d because of a mild increase in serum creatinine (192 umol/L). Later on, the case was shifted to a different combined therapy with oral methotrexate (MTX, 15 mg per week), cyclosporine A (CSA, 150 mg/day) and prednisone. The relapse finally reversed after the combined regimen in corporation with IVIG.

The daily dosage of prednisone needed for the individuals was an important index for the assessment of status. The details were shown in Figure 3, the daily dosage of oral prednisone at onset, 3 months, 6 months, 12 months and the last follow-up were 44.75±5.25 mg, 32.25±4.72 mg, 17±4.41 mg, 11.25±4.83 mg and 6.13±4.9 mg, re-

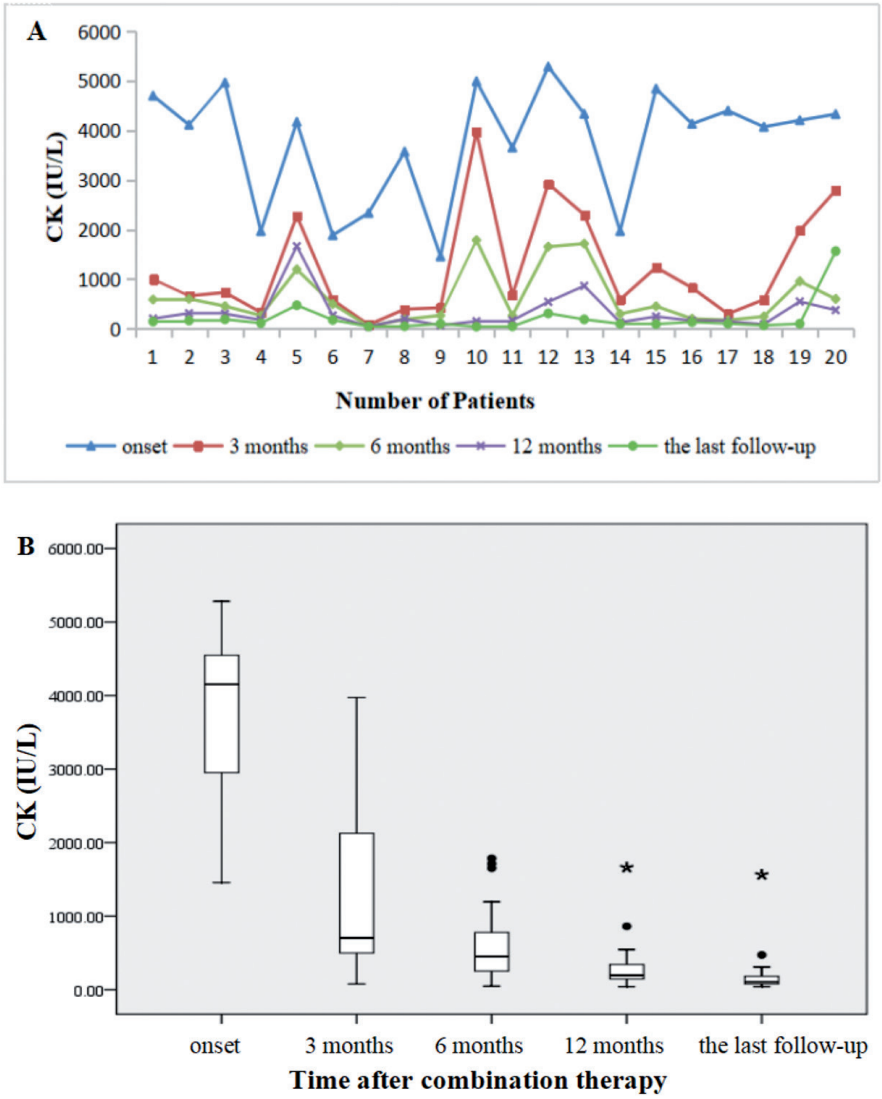

Fig. 1. Trend of serum CK levels over time.
A: Serum CK levels of the patients trend downward over follow-up time except Patient 5 and 20.
B: Serum CK levels are shown in box plots. A bar in the box represents median, a box represents an interquartile range, a vertical bar represents a range, and black dots and five-pointed stars represent outliers.

spectively. At the pointed follow-up interviews, the daily dosage was statistically significantly lower than the initial high dosage (all $p<0.0001$).

In terms of adverse events, hyperglycaemia were observed in 2 (10%) patients (Patients 12 and 14) after co-administration of tacrolimus with oral prednisone; 1 (5%) patient (Patient 2) experienced mild hair loss and 1 (5%) patient (Patient 20) experienced a transit slight elevation of serum creatinine. No serious side effects attributable to adding tacrolimus were found in the other patients.

Discussion

IMNM is often refractory to corticosteroids monotherapy and the optimal therapeutic schemes remain a concern for the treating physicians (9). It is generally recognised that most patients required at least two immunotherapeutic agents and supervised exercise training could be a beneficial coajuvant therapy (25, 26). Tacrolimus has been proved to be effective in several autoimmune diseases such as myasthenia gravis, systemic lupus erythematosus, rheumatoid disease, and neuromyelitis optica (27-31). The efficacy and safety of tacrolimus in the management of patients with PM/DM have been reported in several studies and case reports (15-17, 19, 20, 32, 33) since Oddis *et al*. (18) first reported its effectiveness in the treatment of refractory PM with interstitial lung disease. Favourable outcomes indicated that tacrolimus seemed to be a well-tolerated drug to improve muscle strength in patients with PM/DM, whereas few reports or studies have paid attention to efficacy and safety of tacrolimus in the management of IMNM.

As far as we know, our retrospective study first demonstrated that tacrolimus combined with a reduced dose of prednisone improved clinical outcomes in patients with IMNM, not only in relapsing cases, but also in the first-line therapy. During the follow-up period, almost all of the 20 patients showed favourable responses, with only 2 patients experiencing an evident rebound of CK level with the reduction of prednisone.

The other distinct advantage of combination treatment is the fact that it can reduce the dose of prednisone early and quickly to shorten the period of high dose corticosteroid therapy. Long-term glucocorticoid therapy usually induces multiple side effects such as peptic ulcer, osteoporosis, glaucoma, metabolic and endocrinal disturbance and so on. Furthermore, the severity of the side effects often depends on the dosage and duration of medication, and there is no safety threshold for adverse effects on bone. In our studies, the daily oral dosage of prednisone of all the patients significantly decreased since 3 months after starting tacrolimus compared with before. The results showed that the addition of tacrolimus is able to reduce daily dosage of prednisone which can be maintained at a relatively low dose with small probability of worsening the patients' condition.

Occasionally, tacrolimus may cause various adverse events, such as liver and renal dysfunction, hyperglycaemia and infections, which usually depend on the blood concentration of the agent. The proper therapeutic window concentration of tacrolimus is narrow and pharmacokinetic parameters vary among different patients. Serious adverse effects of tarcrolimus can be adequately avoided by keeping the trough concentration below 10 ug/ml (19, 34). Therefore, it is relatively safe when tacrolimus is administered at a moderate dose. Regular blood concentration monitoring and reasonable dose adjust-

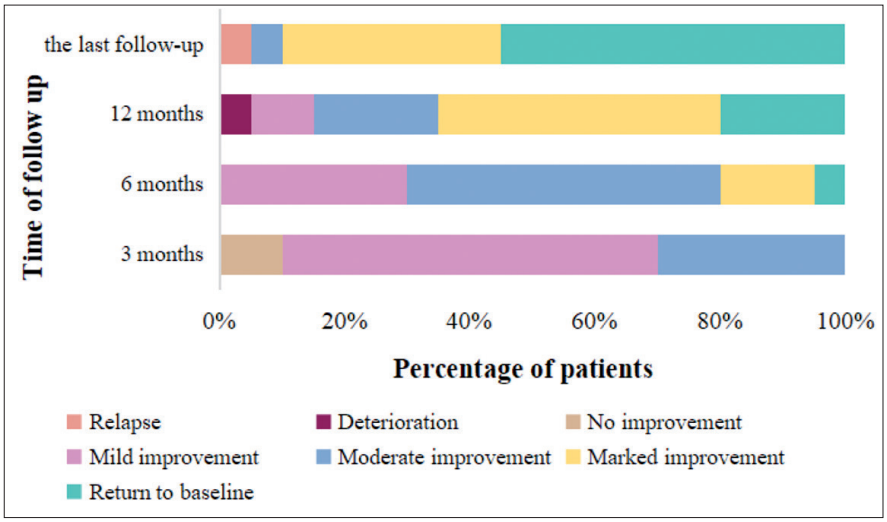

Fig. 2. Therapeutic effect at appointed time points after combination therapy.
Treatment response at 3 months, 6 months, 12 months and the last follow-up are displayed as percentage of patients at each level of treatment response.

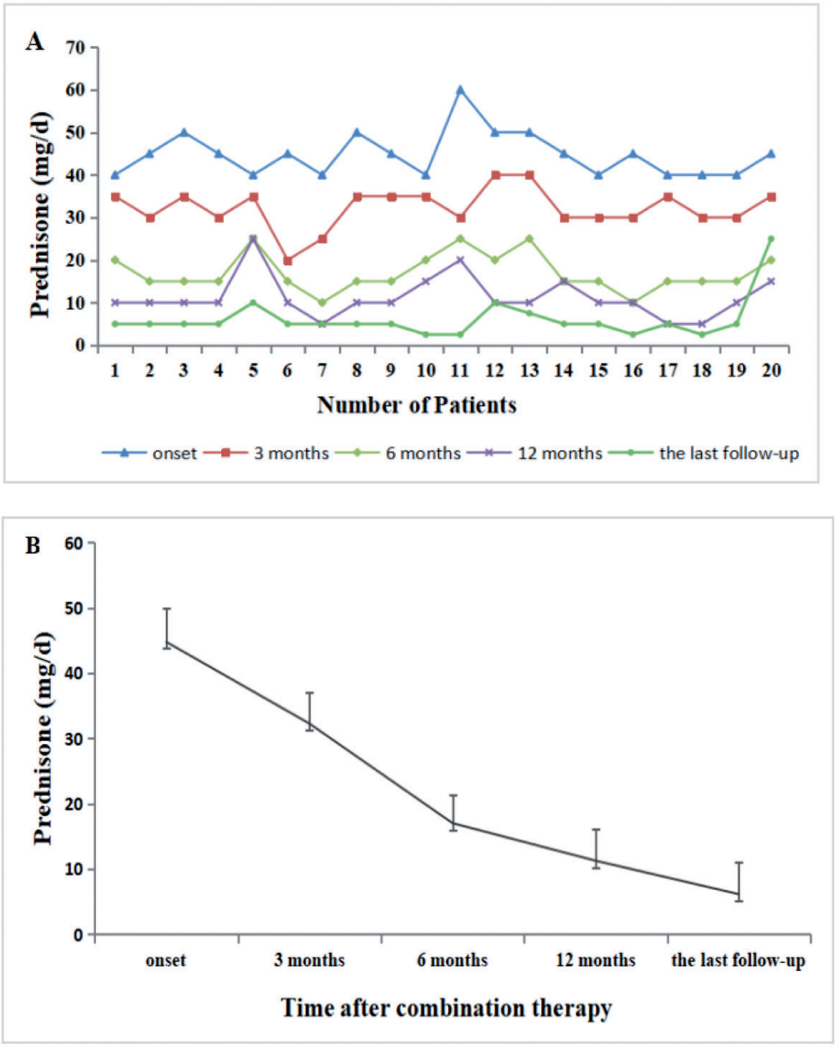

Fig. 3. Doses of prednisone at appointed time points after combination therapy.
A: Oral dosage of prednisone of the patients' trend downward over follow-up time.
B: Mean doses of prednisone at the follow up points are shown in line chart. Bars indicate standard error.

ment can increase the effectiveness and safety. The targeting trough concentration in our patients was set at 5–10 ug/ml and the daily dosage of tacrolimus was 2.0–3.0 mg. Once the concentration of blood was not within the appropriate range or adverse reactions occurred, the dose or therapeutic schedule was adjusted in time. In order to obtain the best therapeutic effects, our patients were advised to take the whole dose of tacrolimus at a draught in the morning. The one-time taking more definitively increased the trough concentration of tacrolimus than divided doses (35). Among all the 20 patients, mild hair loss and renal dysfunction were observed in 1 patient, respectively. Slight elevation of blood glucose level was observed in 2 patients, which returned to a normal range after proper intervention. No serious adverse effects occurred.

The typical pathological features of IMNM include marked muscle necrosis with regeneration and lack of inflammatory infiltrates. However, the pathogenetic mechanism that underlies IMNM is not yet well clarified (36). Although inflammatory cells are relatively few in muscle biopsy tissue, it is generally deemed that humoral immunity mediated by B cells plays a major role, so does the cellular immunity (37, 38). Some studies have shown that $CD68^+$ macrophages and T cells diffusely distribute throughout the endomysium (37, 39). Furthermore, whether humoral immunity or cell immunity requires the interactions between T cells and B cells. Considering the complex immune mediated process, T cells do also play an important role in the pathogenesis of IMNM. Tacrolimus exerts potent inhibitory effects on T lymphocyte activation. The agent suppresses transcription of early T cell activation genes for interleukin (IL) -2, tumour necrosis factor alpha (TNF-α) and other cytokines and inhibits the expression of IL-2 and IL-7 receptors. What is more, tacrolimus also inhibits the mixed lymphocyte reaction, generation of cytotoxic T cells and T cell-dependent B cell activation (40). Therefore, tacrolimus exerts its effects on T cells to suppress production of various cytokines and reduces production of antibodies by inhibiting B lymphocytes.

Several limitations exist in this study. First and foremost, this is a retrospective study with a relatively small sample from a single centre, which made it difficult to exclude the bias in selecting patients. Second, treatments before adding tacrolimus were not homogeneous. Whether previous therapies such as IVIG and other immunosuppressants played a role in the long-term efficacy in the patients remained unknown. Actually, early treatment with IVIG was reported to increase the likelihood of muscle strength improvement (25, 41). In our study, IVIG was used in 7 of the 20 patients during the early admission when they presented severe symptoms or showed insufficient response to the initial pulsed intravenous methylprednisolone. It is possible that IVIG or immunosuppressants prior to tacrolimus may influence the observation to some extent. However, the important role of tacrolimus in the clinical outcome was evident because the patients who did not achieve satisfactory response to monotherapy with prednisone have obtained favourable long-term outcome after adding tacrolimus.

In summary, despite the limitations of the study, our data indicate that co-administration of tarcrolimus with prednisone can be considered an effective, relatively safe therapy for patients with IMNM, not only in relapsing cases, but also as first-line treatment. Adding tarcrolimus also reduced the total dosage of prednisone, thus, the side effects of long-term prednisone therapy could be dramatically minimised. To more clearly demonstrate the therapeutic effects of tacrolimus in IMNM, a larger, multicentre, prospective study is necessary.

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