Clinical phenotypes and long-term outcomes of anti-SRP *versus* anti-HMGCR immune-mediated necrotising myopathy: a 13-year single-centre study

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Abstract

Objective

To characterise and compare the clinical phenotypes, malignancy risk, and long-term outcomes of anti-SRP and anti-HMGCR immune-mediated necrotising myopathy (IMNM). Given the rarity of this condition, we aimed to validate established findings within our large, ethnically diverse cohort managed over a 13-year period.

Methods

We conducted a retrospective, observational single-centre study of all patients with anti-SRP or anti-HMGCR positive myopathy managed at our tertiary neuromuscular centre between 2010-2023.

Results

We included 57 patients (15 anti-SRP, 42 anti-HMGCR). The anti-SRP cohort was younger at disease onset (median 53 vs. 66.5 years, p<0.001) and had a higher frequency of extra-muscular features, including interstitial lung disease (26.7% vs. 2.4%) and arthritis (33.7% vs. 0%). The overall malignancy incidence was 12.3% and was low in both subgroups. In the anti-HMGCR cohort, antibody titres showed a significant positive correlation with creatine kinase (CK) (r=0.692, p<0.001) and troponin T levels (r=0.476, p=0.014). A greater proportion of anti-HMGCR patients achieved treatment-free remission compared to anti-SRP patients (21.4% vs. 13.0%).

Conclusions

Our findings are in line with previous reporting, demonstrating that the majority of patients respond to immunosuppressive therapy, and the association of anti-SRP myopathy with more prominent systemic involvement. Anti-HMGCR antibody titres are a potentially valuable biomarker for disease activity and may have utility in guiding immunosuppression withdrawal.

Key words

myositis, signal recognition particle, hydroxymethylglutaryl-CoA reductase inhibitors

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Introduction

Immune mediated necrotising myopathy (IMNM) is a rare form of myopathy, affecting about 2/100,000, and accounting for around 20-30% of idiopathic inflammatory myopathies (IIM) (1). It is histopathologically characterised by skeletal muscle necrosis in the absence of prominent inflammatory cells (2). Although IMNM can be associated with certain environmental factors such as alcohol, cancer, or viruses, there is a well-documented association with the presence of autoantibodies, specifically anti-signal recognition peptide (anti-SRP) or anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) antibodies. An association between statin-exposure and anti-HMGCR myopathy is well described (1) and is estimated to affect around 2/100,000 statin-exposed individuals, but not all patients with anti-HMGCR myopathy are exposed to statins (3). Statin-associated anti-HMGCR myopathy make up about 26% of the INMN, with anti-SRP accounting for up to 39% (4).

Clinically, individuals with anti-HMGCR and anti-SRP myopathy present with proximal muscle weakness, elevated creatinine kinase (CK), and in some extremes, rhabdomyolysis. Atypical presentations, such as that resembling limb girdle muscular dystrophy have also been described in anti-HMGCR cases (5). Rarely, muscle weakness is so profound that dysphagia and respiratory weakness also ensue. Biochemically, individuals can present with a CK of more than 1000 IU/L, but CK greater than 5000 IU/L is not unusual. Anti-SRP antibody levels have been shown to correlate directly to CK levels (6, 7), and anti-SRP antibodies have been shown to be pathogenic and target skeletal muscle fibres (8). Data also suggest a correlation between anti-HMGCR titres and CK levels (9).

The characteristic histological hallmarks of anti-HMGCR and anti-SRP myopathy are those of a necrotising myopathy, showing scattered necrotic and regenerating muscle fibres, myophagocytosis of necrotic muscle fibres by macrophages, paucicellular lymphocytic infiltrates invading non-necrotic fibres and MHC-I upregulation with regional focal differences in intensity, rather than widespread, diffuse sarcolemmal positivity (3). Additional features include deposition of complement (c5b–9) on the sarcolemma and fibres with fine-granular sarcoplasmic staining for p62 (10). However, these changes are known to be variable.

Although IMNM is rare, the relationship between these conditions and extra-muscular manifestations, malignancies and association with other connective tissue disease (11) is gradually becoming clearer. There is also an emerging histopathological spectrum of disease (3, 12, 13). The best long-term management practice including management of hypercholesterolaemia is not fully established. Data regarding the risk of relapse, possibility of sustained remission after treatment withdrawal, and whether antibody titres have potential use in predicting disease course (10), are lacking.

Here, we present a comprehensive analysis of our single-centre cohort to validate established clinicopathological features of anti-SRP and anti-HMGCR myopathy and further define their long-term trajectories in an ethnically diverse patient cohort.

Methods

A retrospective, observational single-centre study was carried out at our tertiary neuromuscular clinic. This work formed part of a service evaluation registered and independently approved by the Clinical Audit and Quality Improvement Subcommittee, Barts Health NHS Trust. The catchment area of patients is in East London and Essex covering around 4 million people, known for its ethnically diverse populations. All patients with antibody positive myopathy from 2010-2023, seen in the neuromuscular clinic at the Royal London Hospital, were included. Data on demographics, investigations, and treatments were recorded from the patients' records, as well as long term outcomes. Clinical assessments of muscle strength were recorded using the MMT8 (Manual Muscle Testing) scoring.

Included patients were cross referenced with the laboratory, and over

90% of patients with positive anti-SRP and anti-HMGCR antibodies had been reviewed in the clinic, therefore we felt this was representative of the population within the region. Comparisons between groups was made with non-parametric tests (Mann-Witney U Test or Chi-squared tests for categorical comparisons), with significance levels being reported as $p<0.05$.

Assessments for extra-muscular involvement were as follows: Malignancy screening was done at initial assessment, and repeated if any clinical concern over the subsequent 5 years. This included serum tumour markers (CA199, CA125, CEA), CT-scan, PET scan, colonoscopy and endoscopy, and breast USS if indicated. ILD diagnosis was made on HRCT. Presence of myocarditis was assessed with Troponin T and BNP on blood tests, echocardiogram, and ECG, and a cardiac MRI if concern remained. Dysphagia was assessed by the treating clinician at the time of presentation, and if there was concern, a barium swallow was arranged. Disease remission was assessed by normalisation of the CK and troponin T, and subsequent MRI confirmation that there is no evidence of active myositis.

Since October 2018, exact titres of anti-HMGCR have been made available in the clinical setting. Where these were available, correlations between anti-HMGCR and CK and troponin T, as well as clinical response were recorded. Correlation coefficient was calculated using Pearson's correlation, and p values of <0.05 were considered significant. Anti-SRP titres were not available as these are not documented by our laboratory.

Results

In total there were 15 anti-SRP positive, and 42 anti-HMGCR positive individuals. Within our cohort, anti-SRP and anti-HMGCR were mutually exclusive. 26.7% of individuals with anti-SRP, and 16.7% of anti-HMGCR were also positive for another autoantibody (Table I).

Demographic details of each cohort are provided in Table I. There were significantly more individuals with anti-SRP positivity who were Black-British or Black-African (73.3%) compared to 11.9% of anti-HMGCR individuals. 61% of individuals in the anti-HMGCR group were of white British or European ethnicity.

Table I. Demographics. Results are given as number and percentage (in brackets). Median and interquartile range (in brackets) are documented where appropriate.

	SRP (n=15)	HMGCR (n=42)	*p*-value
Age at disease onset (years)	53 (33-55)	66.5 (60-70.5)	**<0.001**
Female (%)	9 (60)	27 (64.2)	0.77
Ethnicity			
Black (%)	11 (73.3)	5 (11.9)	**<0.001**
White (%)	3 (20)	27 (59.5)	**0.003**
Asian (%)	1 (6.7)	8 (19.1)	0.25
Chinese (%)	0	2 (4.8)	0.39
Other autoantibodies positive			
ANA	1 (6.7)	2 (4.8)	0.78
Ro	2 (13.3)	0	**0.016**
ANCA	1 (6.7)	4 (9.5)	0.74
RNA pol	0	1 (2.4)	0.547
Median peak troponin T	750 (328-2364)	347.5 (265-1025.5)	0.81
Median peak creatine kinase	8542 (5446-12106)	8122 (5338-13296)	0.204

ANA: anti nuclear antibody; ANCA: antineutrophilic cytoplasmic antibody; anti-RNA pol: anti-RNA polymerase III antibody.

Table II. Frequency of comorbidities, extra-muscular features and alternative cholesterol lowering therapy used within the anti-SRP and anti-HMGCR necrotising myopathy cohort of patients.

	Anti SRP (n=15) (%)	Anti HMGCR (n=42) (%)	*p*-value
Extra-muscular features			
Malignancy	2 (13.7)	5 (11.9)	0.88
ILD	4 (26.7)	1 (2.4)	**0.004**
Arthritis	5 (33.7)	0 (0.0)	**<0.001**
Dermatological	4 (26.7)	3 (7.1)	**0.047**
Cardiac myocarditis	1 (6.7)	0 (0.0)	0.091
Dysphagia	4 (26.7)	6 (14.3)	0.28
Exposure Statin	0	39 (92.9)	
Comorbidities			
DM type 2	0	29 (69)	**<0.001**
HTN	1 (6.7)	25 (59.5)	**<0.001**
Alternative cholesterol lowering therapy			
Ezetimibe		18 (42.9)	
Bezafibrate		1 (2.4)	
Inclisiran		1 (2.4)	
Alirocumab		1 (2.4)	
Evolucumab		1 (2.4)	
Ezetimibe/bempedoic acid		2 (4.8)	
Fenofibrate		1 (2.4)	

ILD: interstitial lung disease; HTN: hypertension; DM: diabetes mellitus.

Table III. Histopathological findings in IINM: number and percentage of histopathological findings in muscle biopsies by autoantibody.

Histopathology	Anti-SRP (n=15) (%)	Anti-HMGCR (n=42) (%)	*p*-value
Necrotising myopathy	10 (66.7)	31 (75.6)	0.86
Inflammatory myopathy	3 (20)	3 (7.3)	0.163
Inflammatory and necrotising myopathy	1 (6.7)	2 (4.9)	0.776
Regeneration alone	1 (6.7)	2 (4.9)	0.776
Additional features	0	2 (4.9)	
Not done	0	1 (2.4)	
Not available	0	1 (2.4)	

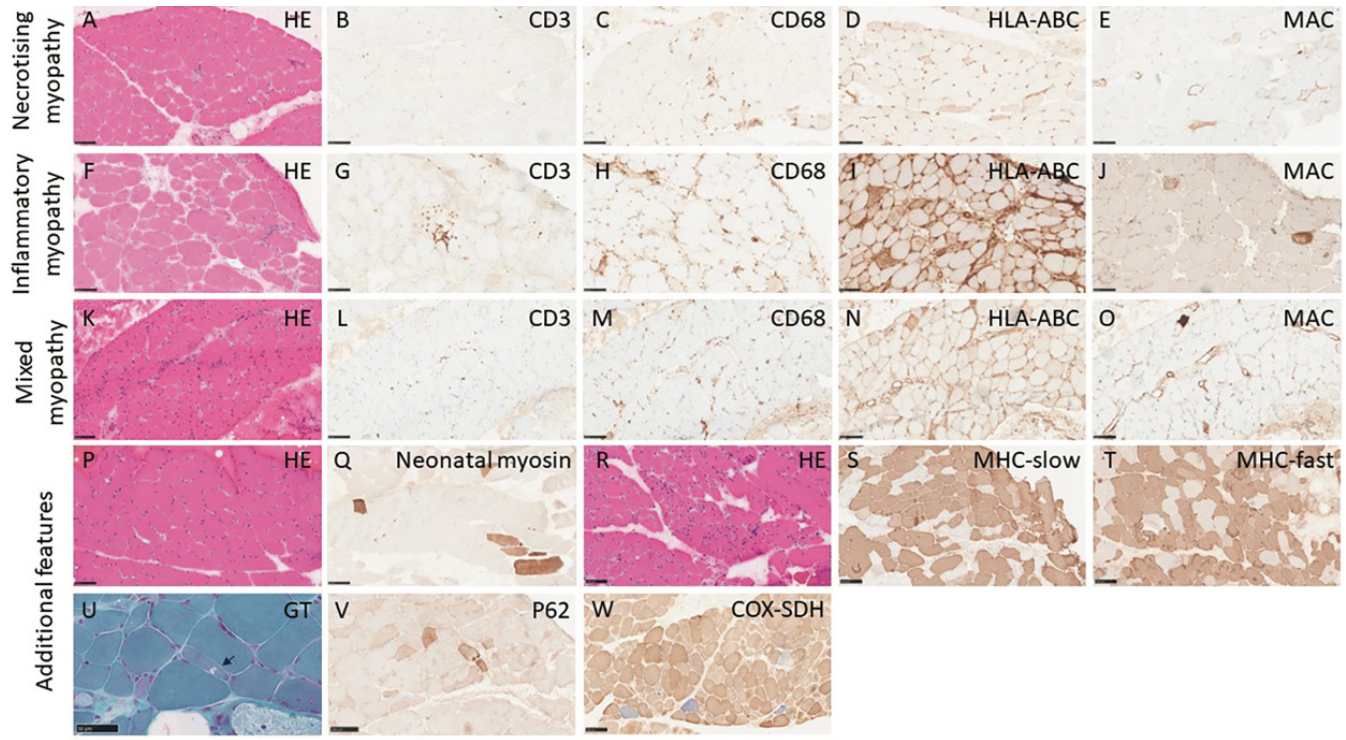

Fig. 1. Case examples showing the spectrum of muscle pathology observed in the study cohort. An example of a case with necrotising myopathy can be seen in panels A-E. An example of an inflammatory myopathy can be seen in panels F-J. A case with a mixed necrotising/inflammatory myopathy is seen in panels K-O. Fibre regeneration is seen in P-Q. Neurogenic changes, including grouped atrophy and fibre-type grouping are seen in R-T. A rimmed vacuole with Gomori trichrome stain is seen in U. A possible P62 positive inclusion is seen in V (as well as fine-granular sarcoplasmic deposits). COX-negative fibres appear blue in W.
Scale bars are 100 μm in A-T, V-W. Scale bar is 50 μm in U.
GT: Gomori trichrome; HE: haemotoxylin and eosin; HLA: human leukocyte antigen; MAC: membrane attack complex; MHC: myosin heavy chain.

Anti-SRP positive individuals were significantly younger (median 53 years) at disease onset compared to the anti-HMGCR patients (median 66.5 years) ($p<0.001$). 92.9% of those with anti-HMGCR myopathy had been exposed to a statin. Three cases of anti-HMGCR myopathy were never exposed to statins prior to disease onset.
Of the anti-HMGCR positive cases, two individuals had atypical courses of disease. One patient presented with a limb-girdle muscular dystrophy pattern of weakness, and more indolent disease progression. Another was negative for anti-HMGCR at presentation, but on subsequent repeat testing, was positive (14).

Muscular features
With the exception of one patient who presented with a limb-girdle muscular dystrophy pattern of weakness, all other patients presented with a typical pattern of proximal weakness as is typical for IMNM. There were no significant differences between peak CK titres in both antibody cohorts (median CK 8542 units/L in anti-SRP and 8122 units/L in anti-HMGCR, $p=0.81$). There was a trend towards greater peak troponin T levels in anti-SRP, but this was not statistically significant (750 ng/L and 347.5 ng/L in anti-SRP and anti-HMGCR, respectively $p=0.204$) (Table I). 1/8 patient with anti-SRP myopathy had evidence of myocarditis on cardiac MRI, and 0/15 patients had cardiac involvement with anti-HMGCR antibody.

Extra-muscular features
The incidence of malignancy across both cohorts combined was 12.3%. In the two individuals with anti-SRP, malignancies were confirmed years after diagnosis (four years post symptom onset for a breast cancer, and 14 years for prostate cancer), making the anti-SRP myopathy less likely to be paraneoplastic. For those with anti-HMGCR, two malignancies were diagnosed at the time of symptom onset (breast and thyroid), while three were diagnosed after symptom onset (prostate 1 year later, tubo-ovarian high grade 7 years later, and non-Hodgkin's lymphoma within 1 year of disease onset). Extra-muscular features were frequently reported in anti-SRP patients (Table II). Most notably, arthritis, interstitial lung disease, skin manifestations were significantly higher in anti-SRP patients than anti-HMGCR patients ($p<0.05$) (Table II).

Histopathology
Muscle biopsy was performed in all patients except one, and one patient's biopsy was not available to be reviewed. The findings are summarised in Table III. Histopathological features of necrotising myopathy (Fig. 1A-E) were seen in 10/15 of anti-SRP patients and 31/39 anti-HMGCR individuals. In these cases, there was prominent fibre necrosis (Fig. 1A), the inflammation was predominantly macrophagic (Fig. 1B-C), there was limited subsarcolemmal upregulation of HLA-ABC (Fig. 1D), and there was membrane attack com-

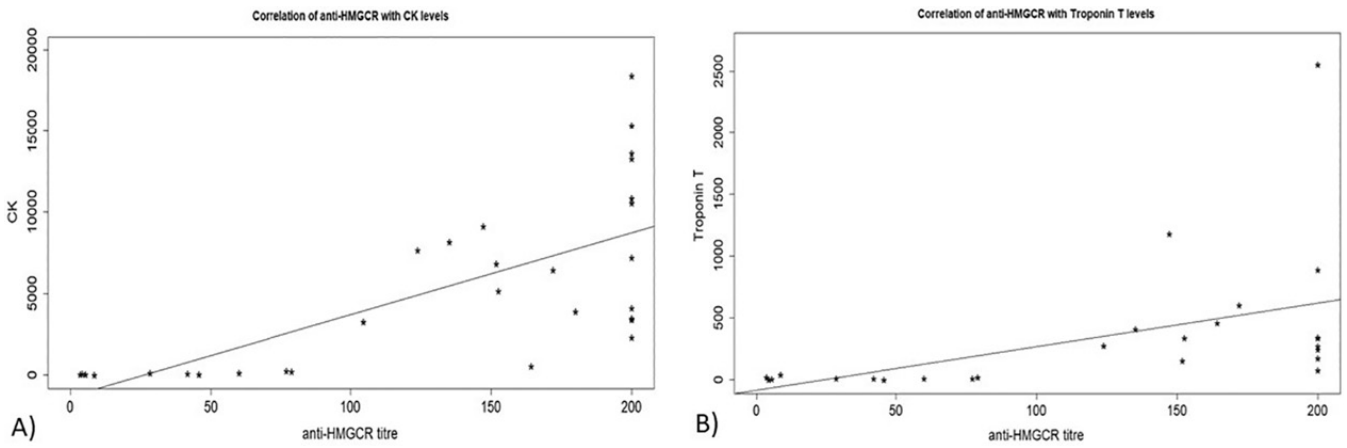

Fig. 2. Graphs of anti-HMGCR and troponin concentrations against creatinine kinase in the study cohort. **A**) scatter plot of HMCGR titres with CK levels. Line represents linear regression line. Correlation coefficient was significant $p<0.001$). **B**) Scatter plot of anti-HMGCR titres with troponin T concentration. Line represents linear regression line. Correlation coefficient was significant ($p=0.013$).

plex (MAC) (Fig. 1E) positive deposits. Features of inflammatory myopathy without prominent fibre necrosis (Fig. 1F-J) were seen in 3/15 of anti-SRP and 3/39 anti-HMGCR cases. In these cases, the inflammation was predominantly lymphocytic (Fig. 1F-H), there was diffuse subsarcolemmal upregulation of HLA-ABC (Fig. 1I) and limited MAC positive deposits (Fig. 1J). The features above were seen in combination in 1/15 of anti-SRP and 2/39 of anti HMGCR cases (Fig. 1K-O). Regeneration alone was noted in 1/15 of anti-SRP and 2/39 of anti HMGCR cases (Fig. 1P-Q). One of the HMGCR cases showed a mixed necrotising/inflammatory picture and additionally showed neurogenic changes (Fig. 1R-T) as well as very rare rimmed vacuoles (Fig. 1U) and one possible p62 positive inclusion (Fig. 1V). Another HMGCR case showed inflammatory myopathic changes with vacuoles, denervation and COX-negative fibres (Fig. 1W).

Co-morbidities

Co-morbidities were common in the anti-HMGCR cohort of individuals, with 69% having diabetes, and nearly 60% being treated for hypertension (Table II). Given this is a cohort of individuals with a high prevalence of hypercholesterolaemia, diabetes and hypertension, it is important that these risk factors are still adequately treated. We therefore assessed the alternative cholesterol lowering therapy used. Ezetimibe was the most frequently prescribed cholesterol lowering therapy, with 42.9% being initiated as monotherapy, and 2 individuals receiving it in combination with bempedoic acid. Three individuals were initiated on PCSK9 blockers, and two individuals were treated with fibrates (bezafibrate or fenofibrate).

Table IV. Frequency and percentage of therapeutic strategies in IMNM used for anti-SRP and anti-HMGCR myopathy.

	Anti-SRP (n=15) (%)	Anti-HMGCR (n=42) (%)	*p*-value
DMARD (MTX, AZA, MMF)	15 (100)	33 (78.6)	0.051
IVIg	11 (73)	20 (47.6)	0.086
DMARD alone	3 (20)	12 (28.6)	0.517
Induction triple therapy (steroid, IVIg, DMARD)	5 (33)	14 (33.3)	1
Rituximab	10 (67)	8 (19)	**<0.001**
Abatacept	0	2 (4.8)	0.74
Flares of disease	4 (27)	4 (9.5)	0.1
In remission off immunosuppression	2 (13)	9 (21.4)	0.495

DMARD: disease modifying anti-rheumatic drugs; MTX: methotrexate; AZA: azathioprine; MMF: mycophenolate mofetil; IVIg: intravenous immunoglobulin.

HMGCR titres

31 individuals had at least one anti-HMGCR titre available. Anti-HMGCR titres correlated significantly with corresponding CK levels (r=0.692, $p<0.001$) sampled simultaneously (Fig. 2a). Troponin T also correlated significantly with anti-HMGCR levels (r=0.476, $p=0.014$) (Fig. 2b). Of the patients with more than one anti-HMGCR titre recorded, 8/14 reduced over time, and of those, 5/8 corresponded to a >50% reduction in CK, and 4/6 with a meaningful improvement in troponin (two patients did not have troponin available). Two patients had an improving CK, with a stable anti-HMGCR titre. 4/14 patients are in remission off all immunosuppression, of which two individuals had anti-HMGCR titres below the threshold of positivity, and two had falling titres.

Long-term management

In terms of immunosuppressive therapy, 33.3% of individuals were treated with induction triple therapy of high dose steroids, intravenous immunoglobulin (IVIg) and a disease modifying anti-rheumatic drug (DMARD) (Table IV). Although DMARDs were used for nearly every case, they were rarely prescribed on their own, without either IVIg, or a biologic treatment. Within anti-SRP, the commonest treatment was IVIg, followed by rituximab (67%). Biologic therapy was used less frequently in anti-HMGCR cases, with 47.6% receiving IVIg, 19% receiv-

ing rituximab, and 4.8% being treated with abatacept. Individuals with anti-HMGCR myopathy had fewer flares of CK and clinical parameters compared to anti-SRP (10% and 27% of individuals respectively). In terms of long-term remission, 21.4% of individuals with anti-HMGCR myopathy were able to stop immunosuppression completely and remain in remission, whereas only 13% of patients with anti-SRP myopathy were off treatment and in remission at the time of data collection.

Discussion

IMNM remains a rare form of autoimmune myopathy. Our patient cohort had greater numbers of individuals with anti-HMGCR compared to anti-SRP. This is in contrast to literature from Japan where anti-SRP myopathy is more common than anti-HMGCR myopathy (15), suggesting there may be some geographical variation.

All extra-muscular features were more frequently seen in patients with anti-SRP myopathy than those with anti-HMGCR myopathy. Arthritis/arthralgia was the most frequently reported symptom. Unlike in other studies, the incidence of dysphagia was lower in our cohort overall (11, 15); however, consistent with current literature, dysphagia was less frequently seen in anti-HMGCR myopathy compared to anti-SRP myopathy. The reason for this is unclear. It may reflect an earlier recognition of the IMNM presentations and thus earlier initiation of therapy. Alternatively, the increased use of rituximab and other DMARDs, may also be having benefit before some of these symptoms manifest (12).

ILD was more frequently identified in the anti-SRP antibody cohort (27%) compared to the anti-HMGCR antibody cohort (2.4%). This is in keeping with other studies with a higher incidence of ILD in anti-SRP myopathy, however the overall frequency can be up to 20% (15). Cardiac involvement remained rare in both cohorts (16).

The association with malignancy remains unclear (17) although recent data suggest low risk of malignancy (16). Within our cohort, we found an incidence of 12%. Although this is not a strong association compared to the numbers seen in patients with *e.g.,* anti-TIF1γ (OR 2.26) (18), it is worth keeping an open mind, and ensuring malignancy is investigated for thoroughly.

Our muscle biopsies confirm that not all cases have characteristic necrotising myopathy, and in some exhibited a mixed pathology of inflammatory and necrotising features. It might therefore be more accurate to define the cases as pauci-immune mediated myopathy, rather than IMNM, however the histopathological findings in IMNM are known to be variable (10, 12), and this reflects the broader challenges in classification. Notably, the widely used 2017 EULAR/ACR classification criteria did not include IMNM as a distinct subtype, frequently resulting in its misclassification as polymyositis or even non-myositis(19). Our observation that inflammation was predominantly macrophagic is also consistent with recent research focusing on the specific role of these cells; for instance, the density of perimysial CD163+ macrophages has recently been identified as a potential prognostic biomarker in IMNM (20). This underscores the importance of detailed histopathological analysis alongside autoantibody testing to correctly identify and prognosticate in IMNM.

Our cohort of individuals with anti-SRP myopathy is similar to that already published, with a mean age of onset is around 40-50 years old, with a female preponderance (ratio 1.6-3.6) (6, 21).

Published observational cohorts suggest that younger individuals with anti-SRP myopathy tend to have more severe disease (22), with more pronounced weakness at presentation than adults. This is especially true in individuals of European ancestry. However, our younger adult patients tended to be ethnically Black African, and more frequently with anti-SRP. We did not include any individuals presenting at <16 years of age.

Extra-articular features were not frequent in our cohort. Consistent with other studies, arthritis and arthralgia affects around 20-40% of individuals (23). Only one patient had evidence of cardiac involvement, whereas it has been reported in up to 60% of individuals, mostly in the form of diastolic dysfunction rather than myocarditis, which has been reported as low incidence in other studies (4).

Induction therapy of steroids, IVIg and a DMARD such as methotrexate or azathioprine was commonly used in our cohort. European Neuromuscular Centre guidelines recommend initiating glucocorticoids with methotrexate in the first instance, followed by or concurrently prescribing IVIg and or rituximab. The use of IVIg is heavily regulated in the UK, and thus its use is reserved for those with severe disease, and those where other treatments have failed (24). This is likely the reason for our use being lower than in other reported cohorts (25), where in line with our patients, they report steroid free remission is possible, but takes longer (13 months), compared to 3 months with steroid, IVIG and a steroid sparing agent.

Alternative therapy for IMNM includes plasma exchange, cyclophosphamide, cyclosporine, belimumab and rituximab, with some evidence suggestive of benefit from tocilizumab (2, 26). In our anti-SRP cohort, the majority of patients were treated with IVIg, and a third had a combination of IVIg, steroid and DMARDs. In 67% of cases, this did not amount to adequate disease control, and so treatment was escalated to rituximab.

A higher proportion of anti-HMGCR myopathy individuals went into complete remission off immunosuppression compared to the anti-SRP cohort, and fewer patients experienced flares in the anti-HMGCR myopathy cohort (27). Thus, treatment withdrawal is achievable in IMNM, but in carefully selected patients (22, 27).

Long term management of patients with anti-HMGCR myopathy must also include lipid-lowering therapy, especially given the association with statin exposure and onset of disease. Avoidance of further statin exposure is advisable. Given a large proportion of patients have a lipid profile that requires intervention, using medication that avoids the mevalonate pathway is

advisable. Treatment options include fenofibrate, ezetimibe, or the newer agents such as PCSK9 inhibitors (proprotein convertase subtilisin/kexin type 9). These have been shown to be safe in patients with HMGCR antibody and even allowed for reduction in immunosuppression, postulated to be due to the downregulation of HMGCR associated with it (28). In our cohort, the majority of patients were initiated on ezetimibe, however three patients were initiated on PCSK9 inhibitors, with no complications so far.

There have been a few case reports on the benefit of abatacept in refractory IMNM (29). These have mainly been patients with anti-SRP antibody. We have utilised it in two of our patient cohort with anti-HMGCR antibodies, with unclear response. In one small clinical trial, nearly half the patients with IMNM with refractory disease responded to abatacept (30). However, within the study population, only two individuals were positive for anti-SRP, and no individuals with anti-HMGCR antibodies were included, and neither of these patients were deemed to be responders to abatacept. Larger studies are needed to evaluate the effectiveness in IMNM.

The significance of reduction of anti-HMGCR titres is not fully understood, however we demonstrated here that the majority of our patients with a stable or improving antibody titre corresponded to a meaningful improvement in CK and troponin T, and clinical improvement as well. In the patients off immunosuppression who had available anti-HMGCR antibody titres, these were either undetectable or falling. There is potential that the autoantibody titre may help guide immunosuppression withdrawal, but further work is required.

Statins themselves have been proven to result in significant reductions in cardiovascular risk at the population level. As a result, almost 92 million people in the US in 2018 (31) are on them. Although musculoskeletal symptoms are reported, one recent study found only a small excess of mild symptoms from statins, and most reported symptoms were not due to statin. Therefore, the small risk of muscle symptoms is outweighed by the known cardiovascular benefits (32). We concur that alternative pathway lipid lowering therapies, are effective with no effect on established muscle disease (28).

There are numerous strengths to our study. Firstly, all patients receiving a biopsy are managed by our specialist neuromuscular clinic, so we can feel assured that we have captured the whole cohort of patients with confirmed IMNM myopathy in our centre. For a rare disease, as we have sampled patients over a prolonged time period, we do have experience of longer-term management including risk of malignancy, and use of biologic lipid lowering therapies in our patient cohort.

There are a few limitations of this study. Firstly, this is a single-centre retrospective study. Although this does mean that there is a uniform approach to treatment, we only have limited numbers of patients. However, given the rarity of the condition, we believe meaningful insights can be made. We have only included patients that are anti-SRP positive and anti-HMGCR positive, but there are patients who have IMNM without one of the autoantibodies. Therefore, we cannot assume our findings are relevant to all patients with IMNM. Since this is an observational study, some inferences are more descriptive, due to the limited number of patients that presented over the 13-year period, and the fact we therefore were unable to power the study for meaningful statistical significance.

As this is a retrospective study, we are not able to conclude which treatments are more effective for each antibody based on a trial, but rather describe our experience. To provide data on true effectiveness, a randomised controlled trial would need to take place.

Conclusion

We present our experience of managing anti-SRP and anti-HMGCR positive individuals with IMNM in our tertiary centre. Our findings from a diverse central London cohort of patients, were consistent with other studies. Extra-muscular features were more frequently documented in anti-SRP individuals. Long term follow-up highlighted low risk of malignancy in both cohorts. Not all individuals with antibodies for IMNM have confirmed necrosis on their muscle biopsies, consistent with the known spectrum of disease. Most patients will improve with immunosuppression, and remission off immunosuppression is feasible in carefully selected individuals confirming experience from other centres. A normal CK level, and an anti-HMGCR titre below threshold may help guide immunosuppression withdrawal, although more work is required to confirm this. Long term management of individuals positive for anti-HMGCR, who can no longer receive a statin, was successful with PCSK9 inhibitors as well as fibrates.

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