Treatment and outcomes in anti-HMG-CoA reductase-associated immune-mediated necrotising myopathy. Comparative analysis of a single-centre cohort and published data

J.-G. Rademacher[1], S. Glaubitz[2], S. Zechel[3], M. Oettler[1], B. Tampe[1], J. Schmidt[2,4,5], P. Korsten[1]

[1]Department of Nephrology and Rheumatology, University Medical Centre Göttingen, Germany; [2]Department of Neurology, University Medical Centre Göttingen, Germany; [3]Institute of Neuropathology, University Medical Centre Göttingen, Germany; [4]Department of Neurology and Pain Treatment, Immanuel Klinik Rüdersdorf, University Hospital of the Brandenburg Medical School Theodor Fontane, Rüdersdorf bei Berlin, Germany; [5]Faculty of Health Sciences Brandenburg, Brandenburg Medical School Theodor Fontane, Rüdersdorf bei Berlin, Germany.

Abstract

Objective

Anti-hydroxy-methyl-glutaryl-coenzyme A reductase (HMGCR) antibody-associated myopathy was recognised as a new form of immune-mediated necrotising myopathy (IMNM) a decade ago. Due to the rarity of the disease, only limited data on clinical manifestations and therapeutic outcomes are available.

Methods

We retrospectively analysed a monocentric cohort of HMGCR-associated IMNM patients treated at the University Medical Centre Göttingen. Clinical, laboratory, and biopsy data, as well as treatment outcomes, were analysed. In addition, a literature search was performed on published HMGCR IMNM cohorts in Medline and Web of Science.

Results

We identified nine patients; five were female. The median age was 68 years (47-77). Six were statin-exposed and older than statin-naive patients (71 years [65-77] vs. 51 years [47-67]). All had muscle weakness, seven myalgias. Strength (MRC sum score) was 53/65 (46-61) at baseline and increased to 63/65 (50-65) with therapy. Creatine kinase (CK) levels decreased from a median level of 12837 U/L (range 6346-25011) to 624 U/L (35-1564 U/L). All received glucocorticoids (GC) and at least one immunosuppressive therapy. The literature review identified 26 studies comprising 691 patients. 57.9% were female, 61.3% statin exposed. 95.2% had weakness, 39.1% myalgia. Dysphagia affected 28.8%. 84.9% received GC and a median of 1.5 additional immunosuppressants. Compared to published data, our patients had higher baseline CK values (12837 [6346-25011] vs. 6951 [2539-10500], $p<0.001$), and we used azathioprine and intravenous immunoglobulins ($p<0.001$) more frequently but methotrexate and rituximab less frequently ($p<0.001$).

Conclusion

HMGCR-associated IMNM is a rare subset of myositis. With systemic treatment, patients usually achieve partial or complete remission. Optimal treatment has not been established, but glucocorticoids, azathioprine, and methotrexate are generally effective with or without intravenous immunoglobulins.

Key words

myositis, HMG CoA reductase inhibitors, immunosuppressive agents, immune-mediated necrotising myopathy, myopathy

Jan-Gerd Rademacher, MD
Stefanie Glaubitz, MD
Sabrina Zechel, MD
Manuela Oettler, MD
Björn Tampe, MD
Jens Schmidt, MD
Peter Korsten, MD

Please address correspondence to:
Peter Korsten,
Department of Nephrology and Rheumatology,
University Medical Centre Göttingen,
Robert-Koch-Strasse 40,
37075 Göttingen, Germany.
E-mail:
peter.korsten@med.uni-goettingen.de

Received on October 28, 2021; accepted in revised form on December 6, 2021.

Funding: S. Glaubitz is supported by the Deutsche Forschungsgemeinschaft (DFG) within the Clinician Scientist Program "Cell Dynamics in Disease and Therapy" at the University Medical Center Goettingen (project number 413501650). The funding body did not influence the writing of the manuscript. J.G. Rademacher, S. Glaubitz, S. Zechel, J. Schmidt and P. Korsten are members of the European Reference Network for Rare Neuromuscular Disorders (ERN EURO-NMD).

Competing interests: J. Schmidt has received payments for advisory boards, speakers honoraria, travel expenses, research projects from Alnylam, Argenx, Biotest, CSL Behring, Euroimmun, Janssen, Kezar, LFB, Novartis, Octapharma, UCB. P. Korsten has received honoraria or travel support from Abbvie, Boehringer Ingelheim, BMS, Chugai, Gilead, GSK, JAnssen-Cilag, Lilly and Sanofi Aventis, and research grants from GSK and Diamed Medizintechnik GmbH, all unrelated to this paper.
The other authors have declared no competing interests.

Introduction

Idiopathic inflammatory myopathies (IIM) represent a group of chronic muscle diseases of varying severity. In addition to polymyositis, dermatomyositis, overlap myositis, and inclusion body myositis, immune-mediated necrotising myopathies (IMNM) have become characterised better in recent years. IMNM is histologically characterised by muscle fibre necrosis, and myophagocytosis of varying extent in the absence or infrequent presence of lymphocytic infiltrates (1). Based on associated antibodies, subtypes are classified according to the 2017 European Neuromuscular Centre criteria: IMNM with positive anti-SRP or anti-hydroxy-methyl-glutaryl-coenzyme A reductase (HMGCR) antibodies are distinguished from seronegative IMNM (2). HMGCR is a crucial enzyme of cholesterol synthesis and the target enzyme of statins in treating hypercholesterolemia (3). Statin-associated muscle disease is a common side effect in some individuals, most often reported as muscle cramping, myalgia, or muscle weakness. In addition, rhabdomyolysis can also represent a rare but serious side effect (4). While these symptoms generally resolve after the discontinuation of these drugs, about 2-3/100.000 statin users develop therapy-induced anti-HMGCR-associated IMNM (4). Nevertheless, the disease can also occur without statin exposure, particularly in younger patients (5). A decade ago, anti-HMGCR antibodies were identified from preserved IIM patient sera with unknown antibody status (6). Subsequently, anti-HMGCR-associated IMNM has been characterised (6). Nevertheless, due to its rarity, the optimal treatment approach has not been entirely determined in anti-HMGCR+ IMNM. Here, we analysed patients from our centre with anti-HMGCR+ IMNM and provide a comparative analysis of published cohorts using an extensive literature search.

Material and methods

Patient population and data collection

We screened all available muscle biopsies at our centre for the presence of necrotising myopathy. Next, we screened the electronic medical records of all patients treated for IMNM in the Department of Neurology and the Department of Nephrology and Rheumatology for the presence of anti-HMGCR antibodies. From the patient records, we collected data on demographic, clinical, and laboratory parameters as well as non-invasive and invasive assessments (electromyography [EMG], nerve conduction studies [NCS], and magnetic resonance imaging [MRI]). Finally, we assessed treatments and outcomes. In addition, all patients were evaluated for past or present statin exposure. The study was approved by the local ethics committee and informed consent was obtained from all included patients.

Antibody testing

Quantitative antibody testing against HMGCR was performed at an external laboratory (Labor Volkmann, Karlsruhe, Germany). In all patients, standard antibody testing included myositis-specific and myositis-associated antibodies (Mi-2α, Mi-2β, TIF1γ, MDA5, NXP2, SAE1, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, and Ro-52 using the Myositis 16 antigen panel, Euroimmun, Lübeck, Germany).

Outcome data

As outcome data, we assessed the Medical Research Council-sum score (MRC sum score). This commonly used muscle strength score evaluates the muscle strength of six muscle groups on both sides, including shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion. In addition, neck bending was added for a more precise information value in this study. Strength was measured on a scale ranging from 0 to 5, where 0 corresponds to complete plegia, and 5 corresponds to full strength against resistance. The addition of each muscle value equals the MRC sum score (7). Therefore, the score can range from 0 (complete plegia) to 65 (normal muscle strength). Serum levels of creatine kinase (CK) at baseline and during follow-up were recorded. Complete remission was defined as the normalisation of CK and

muscle strength, in line with the definitions proposed at the 224th ENMC International Workshop (2).

Muscle biopsies

Muscle biopsies were snap-frozen in isopentane, cooled by liquid nitrogen for one minute, sectioned on a cryostat at 6 µm thickness, and air-dried for 20 minutes (min) at room temperature (RT). Standard histological (Haematoxylin-eosin [HE], trichrome, oil red) and enzymatic analyses (NADH, MAD, MAG, SDH, COX/SDH, acid phosphatase, non-specific esterase, ATPase pH 4,3; 4,6 and 10,4) were performed. For immunohistochemistry, six-micrometer sections were fixed in acetone at -20ºC for 10 min, blocked in H_2O_2 for 10 min, and incubated in primary antibody (diluted in 10% foetal calf serum) for 90 min at RT. Stainings were visualised with biotinylated secondary antibodies and finally developed in diaminobenzidine (DAB). Nuclei were counterstained in haematoxylin. The HE stained cross-sections from six patients were scanned, and regenerative and necrotic fibres were counted using cellSens software (Olympus, Japan).

Literature review

A review of the literature on anti-HMGCR-associated IMNM was performed using Medline and Web of Science databases up to July 2021. Search terms included "anti-HMGCR myopathy," "statin-induced autoimmune necrotising autoimmune myopathy," "immune-mediated necrotising myopathy," and articles including the keywords "myositis" and "myopathy" in combination with "statin." English articles with available clinical and laboratory data were included. Case series were included if they reported at least five patients. Histopathologic features, treatment modalities, and outcomes were extracted when available. Some studies retrospectively analysed cohorts published previously; these were excluded from further review to avoid double-reporting of data.

Statistical analysis

Demographic data were analysed descriptively. The Shapiro-Wilk test was used for the assessment of normality. As appropriate, parametric and non-parametric baseline and follow-up data were compared using either the paired t-test or Wilcoxon signed-rank test. Categorical outcomes of frequency data were analysed using Pearson's chi-square test. *p*-values <0.05 were considered statistically significant.

Available epidemiologic, clinical, and laboratory parameters from the literature search were also presented descriptively. Mean values of CK were derived from publications or calculated from pre-existing data sets. In studies where only median values were reported, the mean value was estimated using a publicly available calculator configured according to Luo *et al*. (8). Data analyses were performed with GraphPad Prism version 9.1 (GraphPad, La Jolla, California, USA).

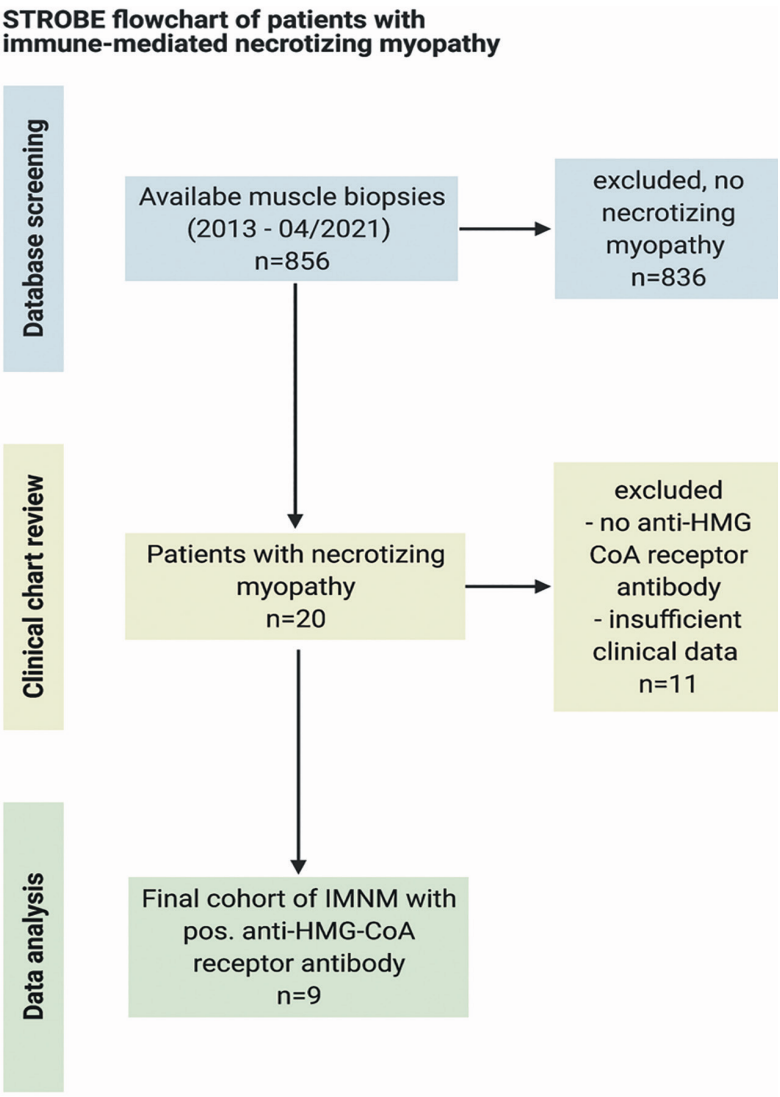

Fig. 1. STROBE flowchart of patient disposition.

Results

Patient cohort

Eight hundred and fifty-six muscle biopsies available from 2013 to April 2021 were screened for the presence of necrotising myopathy. Twenty biopsies were identified, and six patients with positive anti-HMGCR antibodies were analysed. Three additional seropositive patients with histologically proven IMNM whose muscle biopsies were performed at external centres were also included in the analysis (Fig. 1). Five patients were women, and the median age of the cohort was 68 years (47–77). Six patients (66.6%) had been

Table I. Baseline data of the cohort.

Demographic characteristics	n=9
Median age at diagnosis, years (range)	68 (47-77)
Females, n (%)	5 (55.6)
Statin exposure, n (%)	6 (66.7)
Atorvastatin, n (%)	4 (66.6)
Simvastatin, n (%)	2 (33.3)
Median age of statin-users, years (range)	71 (65-77)
Median-age of statin-naive patients, years (range)	51 (47-67)
Median time of follow-up, months (range)	33 (5-168)
Laboratory and clinical features	
Median CK, U/L (range)	12837 (6346-25011)
Median MRC sum score, value (range)	53 (49-61)
Myositis features on MRI, n (%)	8 (100)
Necrotising myositis in biopsy, n (%)	9 (100)
Malignancy, n (%)	0

CK: creatine kinase; HMGCR: hydroxy-methyl-glutaryl-coenzyme A reductase; MRC sum score: medical research council manual-muscle-testing for six bilateral muscles and neck bending; MRI: magnetic resonance imaging.

statin-exposed, four of whom were taking atorvastatin (66.6%), and two were taking simvastatin (33.3%). The demographic characteristics of the patient cohort are shown in Table I.

The median length of follow-up for all patients was 33 months (5–168 months). Unfortunately, one patient died from an aortic rupture unrelated to IMNM. The clinical data and individual treatment regimens are presented in Table II. No malignant disease was observed during follow-up.

Electromyography and magnetic resonance imaging findings

Electromyography (EMG) was performed in nine patients showing a myopathic pattern. Eight patients (88.9%) received an MRI scan, of which two were examined with whole-body MRI. Muscle oedema was present in all patients. Six patients had muscle oedema of the ischiocrural muscles; two had an affection of the M. quadriceps femoris. Two scans demonstrated fatty infiltration, while one patient had muscular atrophy.

Pathohistological features of the muscle biopsies

Evaluation of the six locally available muscle biopsies demonstrated necrotising myopathy in all cases. These were characterised by a coexistence of necrotic and regenerating myofibres, as shown in Figure 2. Lymphocytic infiltrates were mild in three biopsies and more prominent in two samples. Endomysial fibrosis was seen in 50% (3/6). Trichrome stain showed a single ragged-red fibre in two cases and myofibres with rimmed vacuoles in one specimen. Immunohistochemical analysis showed an upregulation of MHC-I in myofibres of all biopsies. $CD3^+$ and $CD8^+$ T cells were present in six and five biopsies, respectively. Single $CD20^+$ B cells were detectable in two specimens. KiM1P showed abundant myophagia in all muscle sections examined. CD56 was also noticeable in numerous fibres (in 5 of 5 biopsies evaluated for CD56). C5b-9/membrane attack complex (MAC) deposits were evident in necrotic myofibres (in 5 of 5 biopsies evaluated for MAC deposits).

Treatments

All patients received glucocorticoids (GC) as induction and maintenance therapy, including initial high-dose

Table II. Clinical characteristics, treatment regimens, and outcomes of the Göttingen cohort.

No	Sex	Age at Dx	Statin exposure	Glucocorticoids (dose, mg)		Immunosuppression		Outcome*
				Pulse	Maintenance	1st line	2nd/3rd line	
1	f	77	Atorvastatin	Pred 1 mg/kg	2 mg	AZA + IVIg	-	Partial remission
2	f	65	Simvastatin	Pred 1 mg/kg	0	AZA + IVIg	MTX + IVIg	Partial remission
3	f	47	-	MP 1000 mg x 1	0	AZA + IVIg	-	Partial remission
4	m	68	Atorvastatin	MP 500 mg x 5	10 mg	AZA	-	Complete remission, GC monotherapy
5	m	74	Atorvastatin	MP 500 mg x 3	50 mg	AZA + IVIg	-	CK↓, mild improvement 3 months after Dx
6	m	72	Simvastatin	Pred 100 mg x 1	30 mg	-	-	Partial remission, died from aortic rupture
7	f	51	-	MP 500 mg x 3	5 mg	AZA + IVIg	MMF + IVIg	Complete remission
8	m	70	Atorvastatin	MP 500 mg x 3	5 mg	AZA + IVIg	AZA	Partial remission
9	f	67	-	-	2 mg	AZA, MTX, MMF + IVIg	IVIg	Partial remission, GC monotherapy

*Outcome definitions: complete remission was defined as normalisation of CK and strength according to the 224th ENMC International Workshop. Partial remission refers to an improvement to mild weakness and/or near-normal CK.
AZA: azathioprine; CK: creatine kinase; Dx: diagnosis; f: female; FU: follow-up; GC: glucocorticoids; IVIg: intravenous immunoglobulins; m: male; MMF: mycophenolate mofetil; MP: methylprednisolone; MTX: methotrexate; Pred: prednisolone.

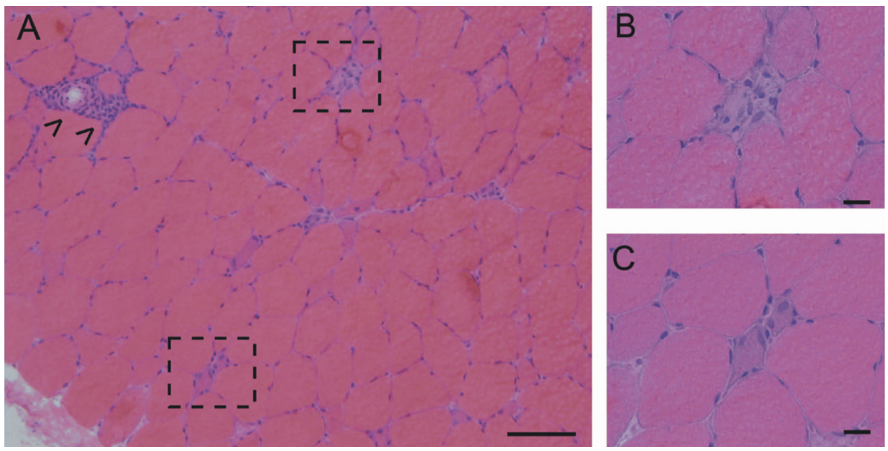

Fig. 2. Muscle biopsy analysis.
(**A**) HE stained section of muscle biopsy showing abundant necrotic fibres (**B**) and regenerative fibres (**C**). Also, note the perivascular infiltrate (arrowheads) **A**. overview, **B+C.** Higher magnification of area depicted in **A**. Scale bar: **A**: 50 µm, **B+C**: 20 µm.
HE: haematoxylin-eosin.

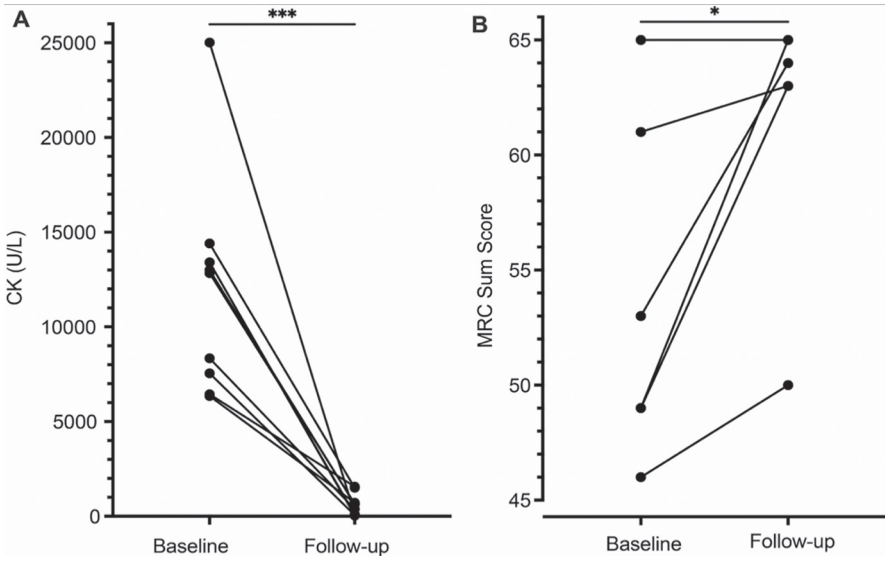

Fig. 3. CK (A) and MRC sum score (B) at baseline and follow-up in our cohort.
(**A**) Elevated baseline CK significantly decreased with immunosuppressive therapy. (**B**) Reduced strength recovered to normal function or mild persisting weakness. One patient with severe weakness showed mild improvement after three months of therapy. ***p<0.001, *p=0.035.
CK: creatine kinase; MRC sum score: medical research council manual-muscle-testing for six bilateral muscles and neck bending.

therapy in nine patients. Five of these patients were treated with methylprednisolone as intravenous pulse therapy (500-1000 mg per day), three patients were treated with 1 mg/kg oral prednisolone. One patient was still in steroid taper after induction therapy at the time of data analysis; eight were already receiving or had a history of additional immunosuppression (IS) as GC-sparing therapy. The median GC maintenance dose was 5 mg (0-50 mg) daily. Two patients were treated without GC; three required more than 5 mg of prednisolone equivalent per day. Azathioprine (AZA; 8/9) was the most frequently used IS at our centre. One patient was on monotherapy with low-dose GC therapy after therapy with AZA. Seven patients were treated with additional intravenous immunoglobulins (IVIg). In addition, mycophenolate mofetil (MMF) and methotrexate (MTX) were prescribed in two patients each. Rituximab (RTX) or other more intense immunosuppressive therapies, such as cyclophosphamide (CYC), were not applied to any patient in our cohort. Individual treatment strategies are shown in Table II.

Outcome parameters

The median CK at baseline in our cohort was 12837 U/L (6346-25011 U/L). With treatment, CK levels fell to median levels of 624 U/L (35-1564 U/L). Strength (MRC sum score) was documented in seven patients at baseline and during follow-up. All had relevant muscle weakness (median 53 [46-61]/65). Two patients had muscle weakness that was not further specified. Muscle strength increased to a median score of 63/65 (50-65/65) at follow-up. Two patients achieved complete remission (normalisation of CK and full muscle strength), the other patients had mild persisting weakness and/or moderately elevated CK (partial remission). Baseline and follow-up levels of CK and strength scores are shown in Figure 3. CK levels and MRC sum scores improved statistically significantly after treatment (p<0.001 and p=0.035, respectively).

Results of the literature review

Overall characteristics of the included studies

Our literature search revealed 263 articles; of these, 26 articles were included in the final analysis. Details of the search process are shown in the flow chart (Supplementary file S1). All publications reviewed were retrospective analyses. Five publications reported on patients with available preserved blood samples who were formerly classified as seronegative myositis (6, 9-12). The clinical manifestations and immunosuppressive therapies used in the respective studies are provided in Supplementary File S2. The included articles analysed a total number of 639 patients. There was a slight female predominance with 57.9% women (327/565); two studies did not report gender (6,13). In addition, 61.3% were statin-exposed (392/639), with the limitations that some authors intentionally included paediatric (14-16), only statin-exposed (13, 17, 18), or explicitly statin-naive patients (19).

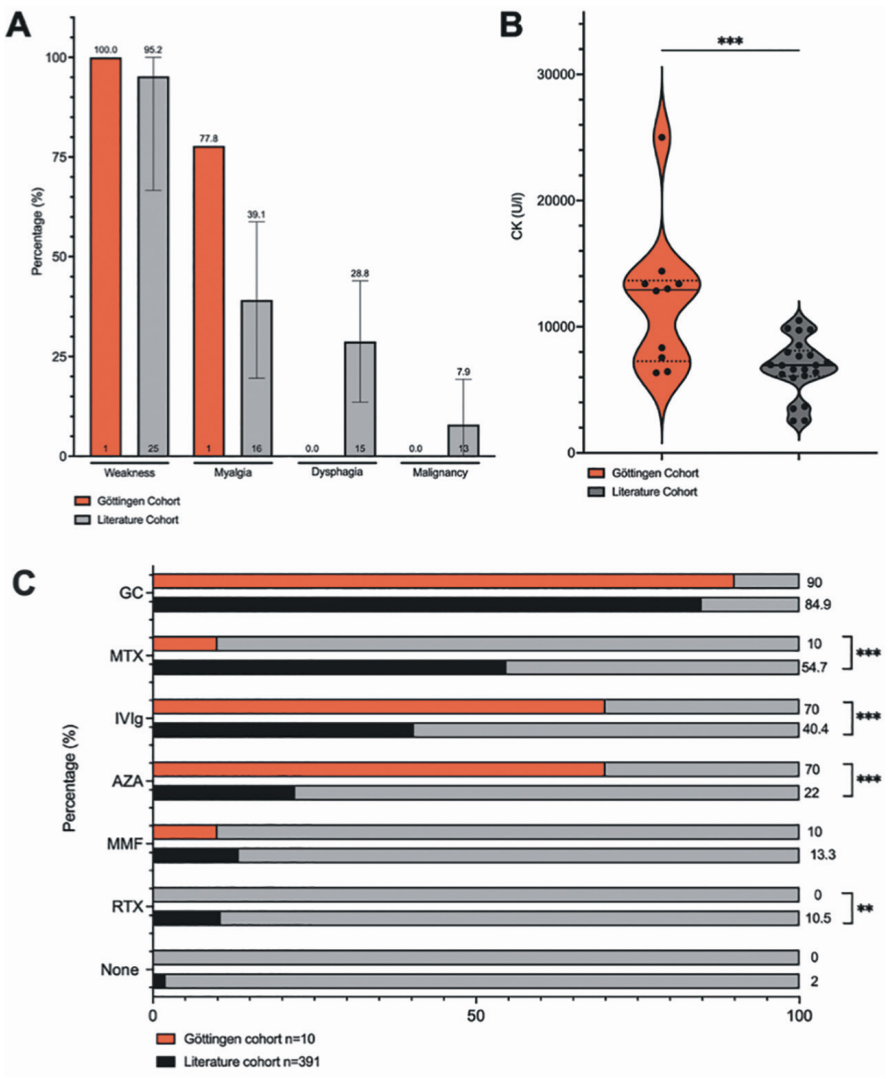

Fig. 4. Comparative analysis of the Göttingen cohort *versus* literature cohort data.
A. The most frequently reported clinical features in the literature were weakness in 95.2%, myalgia in 39.1%, dysphagia in 28.8, and malignancy in 7.9% of cases, respectively. The bottom of the column shows the overall number of evaluated patients for the symptoms/features from 26 studies.
B. Baseline CK values were higher than 5000 U/L in most studies. The CK values were statistically significantly higher in our cohort.
C. Most patients received GC. Other commonly used GC-sparing agents were MTX and IVIG. AZA, MMF, and RTX were used less often. Compared with the literature cohort, AZA and IVIg were used significantly more often, while MTX and RTX were used less frequently in our cohort (**p<0.0007; ***p<0.0001).
AZA: azathioprine; CK: creatine kinase; GC: glucocorticoids; IVIg: intravenous immunoglobulins; MTX: methotrexate; MMF: mycophenolate mofetil; RTX: rituximab.

Comparative analysis of clinical features in the Göttingen cohort versus the literature cohort

Clinical features from our cohort and the literature that could be analysed included weakness, myalgia, dysphagia, and malignancy. Weakness was the most frequently reported symptom (100% *vs*. 550/603 patients from 25/26 studies [95.2%]). Eighteen studies described a proximal symmetrical weakness, one article mentioned proximal and truncal weakness (20), and one reported proximal and distal weakness (15). Next in frequency was myalgia (77.8% *vs*. 122/303 patients [39.1%]). Dysphagia was not present in our cohort; in the literature, 15 studies reported it, affecting 107/376 patients [28.8%]. Finally, no malignancies occurred in our cohort during follow-up. In the literature cohort, malignant disease was reported in 32/369 (7.9%) of patients (Fig. 4A).

Comparison of creatine kinase in the Göttingen cohort versus the literature cohort

According to Luo *et al*., CK values were reported in 22/26 publications; the mean value calculation was applied in one study (21). The median CK was 6951 (2539-10500) U/L and averaged >5000 U/L in 18/22 studies. Thus, reported CK values of the literature were significantly lower than in our cohort (Figure 4B, p<0.001).

Comparative analysis of muscle biopsies in the Göttingen cohort versus the literature cohort

Twenty-four studies presented a total number of 547 muscle biopsies. The histopathological results were described heterogeneously; therefore, all reports of myonecrosis, necrosis/regenerating fibres, and myofibre regeneration were collectively assessed as necrotising myopathy (NM). Here, 94% (514) of biopsies showed NM. Lymphocytic infiltrates were described in 30.7% (81/264), of which 70/233 (30%) were documented explicitly in combination with necrosis. Rimmed vacuoles were mentioned in five studies; here, 6.3% (8/128) of biopsies were affected (6, 11, 14, 22, 23). Three studies demonstrated mild endomysial fibrosis in 54.1% (20/37) of the specimens examined (10, 12, 14).

Immunohistochemical analyses were reported in 11 studies. The most frequently investigated feature was major histocompatibility complex (MHC)-I positivity in 58.7% (91/155) of the cases. C5b-9/membrane attack complex (MAC) deposits were found in 70.8% (85/120). MHC-II was tested in only four studies, of which one study reported positive staining in 2/13 patients (12, 14, 24, 25).

Comparison of treatment modalities in the Göttingen cohort versus the literature cohort

Treatment modalities were available for 391 patients and are depicted in Table III and Figure 4C. 84.9% (n=332) received GC as a pulse and/or maintenance therapy. Intravenous immunoglobulins were used in 158 patients (40.4%). The most frequently used IS was MTX in 54.7%

Table III. Characteristics of previously reported anti-HMGCR myopathy: results of the literature review.

Demographic characteristics	Value
Publications reviewed, n	26
Total patients, n	639
Median age at diagnosis, years (range)	58 (51-77)
Female gender, n (%)	327/565 (57.9)
Statin exposure, n (%) (n/all patients)	392/639 (61.3)
Clinical features at baseline	
CK, U/L median (range)	6951 (2539-10500)
Muscular weakness, n (%)	50/603 (91.2)
Myalgia, n (%)	122/303 (40.3)
Dysphagia, n (%)	107/376 (28.5)
Malignancy, n (%)	32/369 (7.9)
Treatment	
Therapy data available, n of patients	391
GC, n (%)	332 (84.9)
MTX, n (%)	214 (54.7)
IVIg, n (%)	158 (40.4)
AZA, n (%)	86 (22)
MMF, n (%)	52 (13.3)
RTX, n (%)	41 (10.5)
IS/patient, median (range)	1.6 (0.67-2)
No immunosuppression, n (%)	8 (2)

AZA: azathioprine; CK: creatine kinase; GC: glucocorticoids; IVIg: intravenous immunoglobulins; IS: immunosuppressive therapy; MTX: methotrexate; MMF: mycophenolate mofetil; RTX: rituximab.

(n=214) followed by AZA in 22% (n=86), and MMF in 13,3% (n=52) of cases. Rituximab (RTX) was administered in 10.5% of patients (n=41). Other immunosuppressants, such as cyclophosphamide (2.8%; n=11), tacrolimus (2.3%; n=9), leflunomide (1%; n=4), cyclosporine, and abatacept (0,8%, n=3 each) were only used in rare cases. Four patients were treated with plasmapheresis after insufficient medical therapy. Eight patients were not treated at all (2%). On average, each patient received 1.51 different non-GC immunosuppressive agents.

Outcome parameters were reported in a highly variable form. Although a good overall response to therapy was reported, precise clinical data were only available in few individual studies. Several studies described a better outcome in older and statin-exposed patients than in younger and statin-naive patients (19, 22, 24, 26). Paediatric cohorts showed a more severe and chronic disease course (14, 15).

Table IV. Comparison of histopathological features of muscle biopsies: Göttingen cohort *versus* literature cohort.

	Göttingen cohort	Literature cohort
Total biopsies, n	6	547
Histopathological features		
NM, n (%)	6 (100)	514 (94)
Inflammation, n (%)	5/6 (83.3)	81/264 (30.7)
NM + inflammation, n (%)	5/6 (83.3)	70/233 (30)
Rimmed vacuoles + NM, n (%)	1/6 (16.7)	8/128 (6.3)
Endomysial fibrosis, n (%)	3/6 (50)	29/37 (54.1)
MHC-I, n (%)	6 (100)	91/155 (58.7)
MHC-II, n (%)	n. a.	2/64 (3.1)
MAC depositions, n (%)	5/5 (100)	85/120 (70.8)

MAC: membrane attack complex; MHC: major histocompatibility complex; n.a.: not available; NM: necrotising myopathy.

Discussion

A decade ago, the discovery of anti-HMGCR antibodies directed against the 200kD/100-kD proteins in serum samples from previously seronegative IMNM patients led to discovering a new disease subtype (6, 27). Seropositivity is highly specific for anti-HMGCR-associated IMNM, and the literature reports an incidence of 1/1.000.000 per year (28, 29). About 6% of IIM patients exhibit this subtype (30). Our literature search indicates a balanced gender distribution with a slight female predominance.

Previous cohorts indicate that muscular weakness is the leading symptom in over 90% of patients. In most cases, symmetrical and proximal involvement of the muscles is clinically apparent, but a truncal distribution has also been described (20). Thus, weakness is usually the key symptom of IMNM, although the exact frequency had not been determined (31, 32). Noteworthy is the relatively frequent occurrence of myalgia and dysphagia, comparable to other IIM, such as dermatomyositis and polymyositis (33).

CK was almost universally elevated, often exceeding values greater than 5000 U/L. Our cohort had comparatively high CK, whereas only one cohort reported mean values >10000 U/L (34). However, not all studies may have reported maximum values. As our literature review indicates, about 60% of the patients had been exposed to statins. Therefore, the clinical picture may resemble statin-induced rhabdomyolysis. Differentiation can be achieved by determining myositis-specific antibodies (4), which we consider standard of care at our centre. While disease onset has been reported at any age, younger and statin-naive patients have an overall poorer treatment response and prognosis (14-16, 26). Of particular importance is juvenile anti-HMGCR-associated IMNM with a recurrent and chronic disease course and a higher disease burden than in adults. In contrast, the therapeutic response is generally favourable in statin-exposed patients older than 50 years (26). The patients of our cohort were older, and six had been exposed to statin therapy. This may explain the overall good outcome.

Furthermore, no malignancy was detected in our cohort. However, the literature is inconsistent in this regard. While malignancies have been described in up to one-third of anti-HMGCR-associated IMNM patients within the first 1.5 years of disease onset (11, 25), most authors did not find increased cancer rates. Thus, our reported cancer incidence may be overestimated since only studies that provided explicit information on the number of malignancies were evaluated. This contrasts with our experience, that is, no malignancies in our cohort.

Regarding treatments, GCs have been administered for induction and/or maintenance therapy in most patients in the literature. Most studies reviewed did not report the GC dose. GC doses of ≤5 mg of prednisolone equivalent in our cohort were feasible in most patients with completed induction therapy, and concomitant IS. A mean number of 1.5

different immunosuppressants were needed in combination with GC therapy, as some patients had a relapsing disease or side effects with IS. Meyer *et al*. demonstrated that in addition to initial triple therapy with GC/IVIg/IS, early dual and steroid-free induction with IS/IVIg also allowed a sufficient maintenance therapy without GC in half of the reported patients (21). On the other hand, delayed treatment was associated with worse outcomes and the need for intensive maintenance therapy (21). While AZA and IVIg were administered as first-line therapy at our centre, most patients in the literature are treated with MTX as first-line therapy, alone or in combination with IVIg (35). In the literature cohort, about 10% of patients received RTX, and some authors suggest an early application of RTX in order to prevent permanent muscle damage. Our data do not support this concept but rather suggest that an early combination therapy including GC, immunosuppressives, such as AZA, together with IVIg can be an efficient treatment strategy. This is of particular interest in view of well-known potential unwanted long-term side effects of RTX, such as persisting B cell depletion or diminished vaccine efficacy.

Due to its rarity, prospective studies on therapies of anti-HMGCR-associated IMNM are lacking (36). In addition, specific antibody testing is not ubiquitously available, and HMGCR antibodies also had to be tested in an external laboratory in our cohort. Thus, the true prevalence might be underestimated, and the disease often remains undetected. Furthermore, limited data exist regarding increasing or decreasing titres in correlation with relapses. In our experience, however, patients with a clinical relapse (rising CK levels, increased muscle pain/weakness) also show increasing levels of HMGCR antibodies. These findings have to be corroborated in further studies.

Limitations exist due to the small number of cases in our cohort. Symptoms and clinical characteristics from the literature review were collected based on non-standardised descriptions and are prone to reporting bias. The frequency of a disease characteristic, *e.g*. histochemical staining, was reported based on the population of cohorts in which it was described. However, this approach raises the possibility of overrepresenting certain aspects, as some authors may have intentionally omitted features that were not present.

Anti-HMGCR-associated IMNM is an infrequent cause of muscle weakness and rhabdomyolysis. We estimate that less than 750 reports have been published, often in small case series. The literature review of 639 patients and our cohort highlights that early immunosuppression is required in most cases and leads to muscle strength improvement and decreased CK. Therefore, correct diagnosis is essential for specific treatment and minimising the patients' disease burden. In addition to immunological laboratory analysis, representative muscle biopsy of an affected muscle is required for a correct diagnosis. Future investigations may focus on glucocorticoid-sparing or GC-free therapeutic approaches.

Conclusions

Anti-HMGCR-associated IMNM is an increasingly noticed and generally well treatable muscle disease. In case of muscle weakness and CK elevation, the condition should be considered not only in statin-exposed patients. Azathioprine and methotrexate with or without additional IVIg should be considered in all patients after remission induction with GC therapy.

References

1. WATANABE Y, URUHA A, SUZUKI S *et al*.: Clinical features and prognosis in anti-SRP and anti-HMGCR necrotising myopathy. *J Neurol Neurosurg Psychiatry* 2016; 87: 1038-44.
2. ALLENBACH Y, MAMMEN AL, BENVENISTE O *et al*.: 224th ENMC International Workshop: Clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14-16 October 2016. *Neuromuscul Disord* 2018; 28: 87-99.
3. KAPUR NK, MUSUNURU K: Clinical efficacy and safety of statins in managing cardiovascular risk. *Vasc Health Risk Manag* 2008; 4: 341-53.
4. TAYLOR BA, THOMPSON PD: Statin-associated muscle disease: advances in diagnosis and management. *Neurotherapeutics* 2018; 15: 1006-17.
5. PINAL-FERNANDEZ I, MAMMEN AL: Spectrum of immune-mediated necrotizing myopathies and their treatments. *Curr Opin Rheumatol* 2016; 28: 619-24.
6. MAMMEN AL, CHUNG T, CHRISTOPHERSTINE L *et al*.: Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. *Arthritis Rheum* 2011; 63: 713-21.
7. KLEYWEG RP, VAN DER MECHÉ FG, SCHMITZ PI: Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barré syndrome. *Muscle Nerve* 1991; 14: 1103-9.
8. LUO D, WAN X, LIU J, TONG T: Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res* 2018; 27: 1785-805.
9. DROUOT L, ALLENBACH Y, JOUEN F *et al*.: Exploring necrotizing autoimmune myopathies with a novel immunoassay for anti-3-hydroxy-3-methyl-glutaryl-CoA reductase autoantibodies. *Arthritis Res Ther* 2014; 16: R39.
10. ALLENBACH Y, DROUOT L, RIGOLET A *et al*.: Anti-HMGCR autoantibodies in European patients with autoimmune necrotizing myopathies: inconstant exposure to statin. *Medicine* (Baltimore) 2014; 93: 150-7.
11. LIMAYE V, BUNDELL C, HOLLINGSWORTH P *et al*.: Clinical and genetic associations of autoantibodies to 3-hydroxy-3-methyl-glutaryl-coenzyme a reductase in patients with immune-mediated myositis and necrotizing myopathy. *Muscle Nerve* 2015; 52: 196-203.
12. WATANABE Y, SUZUKI S, NISHIMURA H *et al*.: Statins and myotoxic effects associated with anti-3-hydroxy-3-methylglutaryl-coenzyme a reductase autoantibodies. *Medicine* (Baltimore) 2015; 94: e416.
13. SHOVMAN O, GILBURD B, CHAYAT C *et al*.: Anti-HMGCR antibodies demonstrate high diagnostic value in the diagnosis of immune-mediated necrotizing myopathy following statin exposure. *Immunol Res* 2017; 65: 276-81.
14. LIANG W-C, URUHA A, SUZUKI S *et al*.: Pediatric necrotizing myopathy associated with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies. *Rheumatology* (Oxford) 2017; 56: 287-93.
15. KISHI T, RIDER LG, PAK K *et al*.: Association of anti-3-hydroxy-3-methylglutaryl-coenzyme a reductase autoantibodies with DRB1*07:01 and severe myositis in juvenile myositis patients. *Arthritis Care Res* (Hoboken) 2017; 69: 1088-94.
16. LIANG W-C, WANG C-H, CHEN W-Z *et al*.: Treatment experience of Taiwanese patients with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase myopathy. *Kaohsiung J Med Sci* 2020; 36: 649-55.
17. KLEIN M, MANN H, PLEŠTILOVÁ L *et al*.: Increasing incidence of immune-mediated necrotizing myopathy: single-centre experience. *Rheumatology* (Oxford) 2015; 54: 2010-4.
18. TROYANOV Y, LANDON-CARDINAL O, FRITZLER MJ *et al*.: Atorvastatin-induced necrotizing autoimmune myositis: An emerging dominant entity in patients with autoimmune myositis presenting with a pure polymyositis phenotype. *Medicine* (Baltimore) 2017; 96: e5694.

19. JIAO Y, CAI S, LIN J *et al*.: Statin-naïve anti-HMGCR antibody-mediated necrotizing myopathy in China. *J Clin Neurosci* 2018; 57: 13-9.
20. WATERS MJ, LIMAYE V: Clinico-serologic features of statin-induced necrotising autoimmune myopathy in a single-centre cohort. *Clin Rheumatol* 2018; 37: 543-7.
21. MEYER A, TROYANOV Y, DROUIN J *et al*.: Statin-induced anti-HMGCR myopathy: successful therapeutic strategies for corticosteroid-free remission in 55 patients. *Arthritis Res Ther* 2020; 22: 5.
22. WERNER JL, CHRISTOPHER-STINE L, GHAZARIAN SR *et al*.: Antibody levels correlate with creatine kinase levels and strength in anti-3-hydroxy-3-methylglutaryl-coenzyme a reductase-associated autoimmune myopathy. *Arthritis Rheum* 2012; 64: 4087-93.
23. MOHASSEL P, LANDON-CARDINAL O, FOLEY AR *et al*.: Anti-HMGCR myopathy may resemble limb-girdle muscular dystrophy. *Neurol Neuroimmunol Neuroinflamm* 2019; 6: e523.
24. ASHTON C, JUNCKERSTORFF R, BUNDELL C, HOLLINGSWORTH P, NEEDHAM M: Treatment and outcomes in necrotising autoimmune myopathy: An Australian perspective. *Neuromusc Disord* 2016; 26: 734-40.
25. KADOYA M, HIDA A, MAEDA MH *et al*.: Cancer association as a risk factor for anti-HMGCR antibody-positive myopathy. *Neurol Neuroimmunol Neuroinflamm* 2016; 3: e290.
26. TINIAKOU E, PINAL-FERNANDEZ I, LLOYD TE *et al*.: More severe disease and slower recovery in younger patients with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase-associated autoimmune myopathy. *Rheumatology* (Oxford) 2017; 56: 787-94.
27. CHRISTOPHER-STINE L, CASCIOLA-ROSEN LA, HONG G, CHUNG T, CORSE AM, MAMMEN AL: A novel autoantibody recognizing 200-kd and 100-kd proteins is associated with an immune-mediated necrotizing myopathy. *Arthritis Rheum* 2010; 62: 2757-66.
28. MOHASSEL P, MAMMEN AL: Statin-associated autoimmune myopathy and anti-HMGCR autoantibodies. *Muscle Nerve* 2013; 48: 477-83.
29. CASCIOLA-ROSEN L, MAMMEN AL: Myositis autoantibodies. *Curr Opin Rheumatol* 2012; 24): 602-8.
30. HUANG L, WANG L, YANG Y *et al*.: Coexistence of anti-HMGCR and anti-MDA5 identified by an unlabeled immunoprecipitation assay in a chinese patient cohort with myositis. *Medicine* (Baltimore) 2018; 97: e13236.
31. ALLENBACH Y, BENVENISTE O, STENZEL W, BOYER O: Immune-mediated necrotizing myopathy: clinical features and pathogenesis. *Nat Rev Rheumatol* 2020; 16: 689-701.
32. PINAL-FERNANDEZ I, CASAL-DOMINGUEZ M, MAMMEN AL: Immune-mediated necrotizing myopathy. *Curr Rheumatol Rep* 2018; 20: 21.
33. GLAUBITZ S, SCHMIDT K, ZSCHÜNTZSCH J, SCHMIDT J: Myalgia in myositis and myopathies. *Best Pract Res Clin Rheumatol* 2019; 33: 101433.
34. KENNEDY N, KEATING P, O'DONNELL J: HMGCR-associated myositis: a New Zealand case series and estimate of incidence. *Intern Med J* 2016; 46: 622-5.
35. TREPPO E, INFANTINO M, BENUCCI M *et al*.: Efficacy and Safety of high-dose immunoglobulin-based regimen in statin-associated autoimmune myopathy: a multi-center and multi-disciplinary retrospective study. *J Clin Med* 2020; 9: 3454.
36. DAY JA, LIMAYE V: Immune-mediated necrotising myopathy: A critical review of current concepts. *Semin Arthritis Rheum* 2019; 49: 420-9.