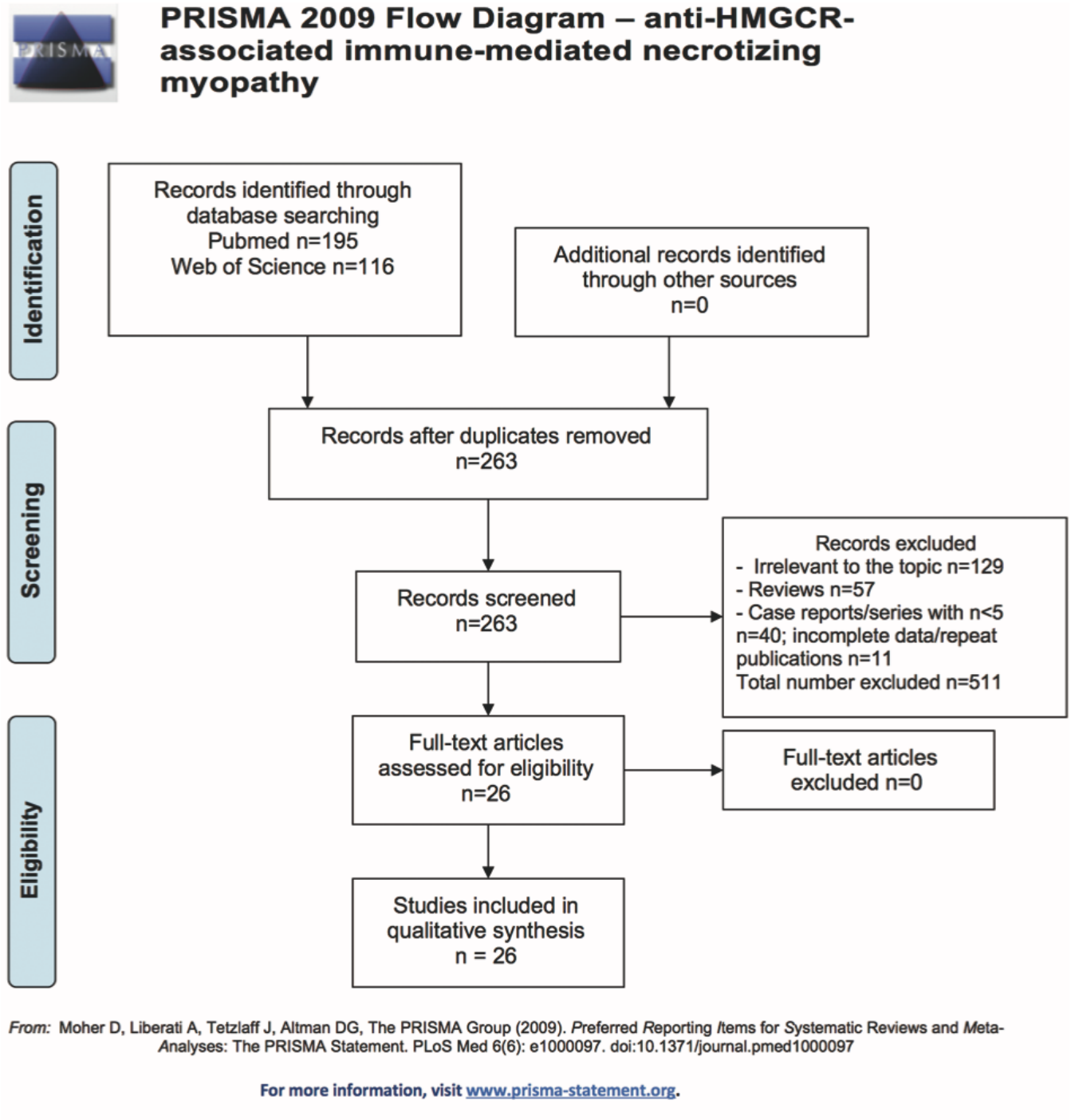

Supplementary Fig. S1. PRISMA flow chart of literature search.

Supplementary file S2. Search strategy for the literature review and data extraction.

Query Pubmed/MEDLINE
(SINAM OR Statin-induced myopathy AND/OR HMG-Coa myopathy AND/OR HMGCR myopathy AND/OR necrotizing myositis AND/OR immune mediated necrotizing myopathy AND/OR autoimmune mediated necrotizing myopathy AND/OR (statin AND myositis))) AND ((humans[Filter]) AND (english[Filter] OR german[Filter]))

Query Web of Science
TS=(HMGCR AND myopathy)

Refined by: DOCUMENT TYPES: (ARTICLE OR MEETING ABSTRACT OR EARLY ACCESS OR LETTER) AND LANGUAGES: (ENGLISH)
Timespan: All years.
Indexes: SCI-EXPANDED, SSCI.

Supplementary Table S1. Literature review of reports of anti-HMGCR-antibody associated necrotising myositis. For incomplete datasets, characteristics are indicated in relation to the available number of the criterion (*e.g.*, 5/20 = 5 out of 20).

First author	Year	N	Type	Statin exposure	Age (years)	Sex	CK levels (U/L)	Clinical features	Histology	Therapeutic regimen	Outcome/additional insights	Ref
Mammen	2011	45	MC RA of BS	30 (66%) (24/26 >50 ys)	Non-statin 37 ±17 *vs*. statin 59±9	n.a.	Non-statin 13392±8839 *vs*. statin 7881±5875	Prox. weakness 95.6% MUP in EMG 97,3%	40/40 NM; 8 inflammatory infiltrates, 1 rimmed vacuoles	n.a.	Race: Non-statin 46.7% *vs*. statin 86.7% white	(1)
Werner	2012	55	RA	40	24 - 72	35 f 20 m	3675±3649 (51)	Symmetrical prox. weakness (52)	53/55; NM (38); endomysial/ perivascular inflammation, necrosis (10), necrosis w/ vacuoles (2); mild myofiber necrosis (2); normal (1)	GC Heterogenous: AZA, MMF, MTX, IVIG, tacrolimus	**Overall greater benefit for statin-exposed patients** Arm abduction strength ↑ Hip flexion strength ↑ CK ↓ anti-HMGCR level ↓	(2)
Drouot	2014	37	MC RA of BS	15 (40%)	44 ± 19	25 f 12 m	6974±4970	Unspecified muscle weakness 92%	37/37 NM, 10 w/ perivascular inflammatory infiltrates	n.a.	n.a.	(3)
Allenbach	2014	45	MC RA of BS	20 (44,4%) 10 Atorva 4 Rosuva	Non-statin 36.6±21.7 *vs*. statin 64.4±6.8	33 f 22 m	6941 ±8802	Prox. weakness 97.7%, myalgia 53.3%, dysphagia 26.7%, atrophy 22.2%, weight loss 20%, arthralgia 11.1%, RP 11.1%	42/43 NM	39 received therapy: GC (37), MTX (20), AZA (10), MMF (6), CsA (2), CYC (2), IVIG (17), RTX (9), PLEX (2). Treatment 34.1 ± 40.8 months	3 African, 1 Asian 5 patients with cancer after Dx of NM (2 months – 19y) 1 patient died due to aspiration pneumonia No information on overall outcome	(4)
Limaye	2015	19	MC RA of BS	16/17 (2 n.a.)	Mean 70 (55 – 89)	8 f 11 m	n.a.	Prox. weakness n.a., diabetes mellitus (8), AHT (11), malignancy (5), ischemic heart disease (3)	PM (8), IBM (6), idiopathic (2), NM (2), DM (1), other (1)	n.a.	**DR11⁺ and statin-use association** (9/10 anti-HMGCR antibody positive)	(5)
Klein	2015	15	RA	15	55 – 67 (11)	7 f 4 m	24 - 211 µkat/l (11); 6960 U/L	Decreased MMT-8 (11/11; 62.5 - 91.3%), myalgia (4/11)	NM (11), PM (4)	n.a.	Most patient characteristics available for NM (11 patients)	(6)
Ge	2015	22	RA	3	41.1 ±14.4	16 f 6 m	2539 ±3048 (18/21)	6/20 Subacute onset (<12m), 14/20 progressive onset (>12m), myalgia (14/20), Dysphagia (10/20) Anti-Jo-1 and ILD in 3/22	12/22; NM (8), significant inflammation + necrotic myofibers (2), inflammatory cell infiltration (2)	11/22 available: GC (63.1 mg qd) and/or other immunosuppressants	RA of 405 Chinese IIM patients 70% progressive onset >12m **No correlation between antibody level and disease activity** Strength improvement, CK ↓, Follow-up median 9m (2.5 – 24m)	(7)
Watanabe	2016	8	RA of BS	3/8 Atorvastatin	Mean 66 (49-79)	3 f 5 m	7738 (3028 – 10452)	Symmetrical prox. weakness (≥III/V) MUP in EMG (7)	NM	Immunotherapy (7) + IVIG (4)	Improvement and no relapse after 2 ys., CK ↓ (7)	(8)
Ashton	2016	14	SC RA	12	Statin 65 (53-78); non-statin 44 (37-51)	8 f 6 m	7189 (1000 - 17000)	Symmetrical prox. weakness (≥II/V, hip flexion MRC non-statin 3-; statin 4-), myalgia (4), dysphagia (5)	13/14; NM (13), mild perivascular inflammatory cell infiltrates (3), mild endomysial inflammation (4), MHC-I pos. (10), MAC pos. (2)	GC (13), MTX (10), IVIG (5), RTX (5), AZA (5), MMF (1)	Average therapy 7m in non-statin, 32m in statin-users Complete remission (4), ongoing immunotherapy (9), ongoing symptoms (5)	(9)
Kadoya	2016	33	SC RA	7 (21%)	Statin 71±8; non-statin 56 ±16	23 f 10 m	9761±8131	Severe muscle weakness MRC ≤III (25), myalgia (14), dysphagia (8), skin rash (5), arthralgia (2), ILD (1); asymptomatic CKemia (4)	32/33; NM (21), NSM (9), DM (2); moderate/severe necrosis/ regeneration (31), absent/mild inflammation (23), moderate/severe inflammation (8), MHC-I pos. (16), C5b-9 deposition on sarcolemma (23)	Non-cancer (10/18): CS (10), IVIG (4), MTX (7), AZA (3), TAC (2), CYC (1) Cancer prior myopathy (3): CS (3), IVIG (3), MTX (1) Cancer+ (12): GC (12), IVIG (5), MTX (1), CYC (2)	**Cancer association and poor prognosis**: 12/33 patients with cancer, detection within 1.3 ys. of myopathy diagnosis. Mortality rate 9/12 during max. 3ys follow-up	(10)

First author	Year	N	Type	Statin exposure	Age (years)	Sex	CK levels (U/L)	Clinical features	Histology	Therapeutic regimen	Outcome/additional insights	Ref
Kennedy	2016	9	MC RA, CR	7 4 Atorva 5 Simva (1.5 – 12ys)	Mean 67.8 (56 - 81)	4 f 5 m	10500 (4200 – 21800)	Weakness prox. limbs (6/9), prox. legs (3/9) MUP in EMG (4/4) Dysphagia (1)	8/8 NM	GC (9), MTX (3), IVIG (1), AZA (1), CYC (1)	Est. incidence in New Zealand 1.7/million/year and 1/90.000 statin-users Outcome n.a.	(11)
Alvarado-Cardenas	2016	23	RA	14/17 10 Simva 4 Atorva	63 ±18	7 f 7 m	6391 (Q1-Q3 6428–9596)	Prox. weakness (14/14), myalgia (7/14)	15/17 NM, 1 PM, 1 DM	14/17: 14 GC, 8 IVIG, 8 AZA, 4 MTX, 1 MMF	Clinical data available for statin-users (14): 12/14 complete response, 2 partial response	(12)
Liang	2016	9	RA	0	10m – 13ys	5 f 4 m	Mean 6617 (918 – 10891)	4 subacute (<6m), 5 chronic onsets Prox. weakness (8), fatigue + skin rash (2), myalgia (2)	9 NM	GC (9), MTX (5), IVIG (5), MMF (2), CsA (1), AZA (1), CYC (1)	Paediatric cohort, initial diagnosis IM (4), muscular I dystrophy (5). Strength improvement and CK ↓ (8 of whom 4 GC monotherapy), Persisting weakness and CK- elevation (1)	(13)
Shovman	2017	12	RA	12	n.a.	n.a.	2700 - 12200	Prox. weakness (12) MUP in EMG	12 NM	n.a.	Comparison of ELISA and CIA for the detection of anti-HMGCR antibodies	(14)
Kishi	2017	5	MC RA	0	8.1 (7 – 12)	3 f 2 m	435 - 30300	Severe prox. and distal weakness (5), falling episodes (5), muscle atrophy (5), Myalgia (2), arthralgia (5), contractures (5), skin rash (3), arthritis (2), dysphagia (3), weight loss (4), fever (2), adenopathy (2)	2/5 (patients without DM-rash); NM (2), MHC-I pos. (2)	GC (5), MTX (5), IVIG (4), CYC/AZA/MMF/CsA (3), RTX/ABA/TNF (2)	**Paediatric cohort**; DRB1*07:01 in juvenile anti-HMGCR-myopathy (5/5). Partial response: chronic (4), polycyclic (1) course; mild/moderate weakness (3), CK↑ (2), wheelchair use (2/5)	(15)
Tiniakou	2017	104	SC RA	80	55 (52.4 – 57.6)	63 f 44 m	Mean 4146 in black patients, 2161 in white patients	Prox. weakness (100/104), 27% dysphagia (28/104), 6% cancer-associated myositis (6/104), 5% skin involvement, 4% ILD	77% NM	74% GC, 50% MTX, 39% IVIG, 23% AZA, 18% MMF, 15% RTX	**Younger patients with more severe weakness, higher CK. Better strength improvement in older patients.** 65% normal strength within 4ys, one third refractory disease >2ys	(16)
Troyanov	2017	12	MC RA	12 Atorva 20 mg (6) 40 mg (5) 80 mg (1) Mean 38.8 m	66 (43 - 81)	6 f 6 m	Mean 7661	Prox. weakness onset <12m (9), myalgia (8), dysphagia (3), myopathic EMG (9)	12 NM	12/12; GC (11), Long-term GC (2), MTX (10), IVIG (8), AZA (2), MMF (2) ABA (1)	Evaluation of **Atorva+**, anti- HMGCR+ **myositis**. Exclusion of DM, CTD, overlap abs and non-responder. Follow-up >3ys: Tapering of GC and normal/near-normal strength (8), absence of dysphagia	(17)
Jiao	2018	21	SC RA	0	(6 – 67)	14 f 7 m	7968.6±4408.7	Prox. weakness (20), neck flexion weakness (19), MRC <III (12), myalgia (10), muscle atrophy (9), skin rash (8), dysphagia (4), weight loss (4); Myopathic EMG (18/18)	21 NM, 15 with lymphocytic infiltration	GC (20), IVIG (3), MTX (6), AZA (7), CYC (3) TAC (2), HCQ (2), RTX (2), LEF (1)	Analysis of statin-naïve patients. higher CK, poorer response to treatment, more recurrent weakness in <50 years-old	(18)

irst author	Year	N	Type	Statin exposure	Age (years)	Sex	CK levels (U/L)	Clinical features	Histology	Therapeutic regimen	Outcome/additional insights	Ref
Huang	2018	12	SC RA	0	43.1 (±13.9)	6 f 6 m	6617.2 (±8407.2)	Prox. weakness (8), myalgia (5), dysphagia (3), arthralgia, ILD (5: 4 MDA5, 1 JO-1))	6; NM (5), sole enlarged capillaries (1)	GC + immuno-suppressants	No statin-exposure detected in this Chinese cohort; Anti-MDA5-positivity and ILD (4). Good response to GC + immuno-suppressant (10). 1 cancer, 2 died.	(19)
Waters	2018	17	SC RA	8	65 (46-79)	10 f 7 m Truncal	6344 (807–11815)	Prox. weakness (15/16) RTX (2) weakness (9/16), mean MMT-8 68 (52-80)	8 NM	GC+IVIG+MTX and/or AZA (8),	Report of truncal weakness. Strength ↑, CK ↓ but worse functional assessment Karnofsky Performance Status	(20)
Mohassel	2019	6	SC RA	0	33 (12-48)	3 f 3 m	9500 (1200 – 23000)	Prox. weakness (6), Impaired walking (2) or to standing up from the ground (2), wheelchair use (1), dysphagia (1)	6; Necrosis/ regeneration (n.a.), atrophy, fiber size variability, and increased internalized nuclei (n.a.). MHC-I-pos. (6)	IVIG (6), GC pulses (1)	Anti-HMGCR myopathy mimics limb-girdle dystrophy. Strength ↑, CK ↓ (6). Walking instead of wheelchair-use (1)	(21)
Lim	2019	17	MC RA	11	Statin 63 (54–74) Non-statin 57xULN (52–65)	7 f 4 m	Statin 64 x ULN (6–114) Non-statin 90 x ULN (4–176)	Prox. weakness (17), dysphagia (6)	n.a.	GC mono (3) 2nd line (MTX/AZA and/or MMF): 10 3rd line (RTX/IVIG and/or CYC): 4	Normal strength (5), slight to moderate disability (9), severe disability (2 statin-naïve), 1 cancer	(22)
Liang	2019	5	SC RA	1	(4.5 – 69)	5 f	Mean 3502 (1430 – 6175)	Acute onset and rapid progressive weakness (3) weakness (5): Gowers' sign (4), bed ridden (1)	4; NM + MHC-I-pos. and MAC depositions (4)	GC (5), MTX/RTX (2), MTX/IVIG (1), MTX (1), AZA (1), HCQ (1), PLEX (1)	3 paediatric patients with slight to moderate disability. Normalization of strength and CK (1), impaired strength (1)	(23)
Aggarwal	2020	23	SC RA	18 Atorva (13), Simva (2), Rosuva (1), Ezetimib (1)	72 (23 – 83)	14 f 9 m	8515 ±3303	Weakness (17), myalgia/cramps (4)	23 NM	GC (23), MTX (20), IVIG (5), MMF (5), AZA (5), TAC (4), RTX (2), CYC(1), LEF (1)	Normalization of strength and CK (14), partial improvement of CK or strength (7)	(24)
Meyer	2020	55	MC RA	55 46 Atorva	67.7 (44–86.1)	25 f 30 m	5000 (554–23000)	Prox. weakness (46), Myalgia (21), dysphagia (16). 0 malignancy	54/55; necrosis/ regeneration (49), isolated sarcolemmal/ capillary MAC deposition (4), normal (1). MHC-I pos. (26/51), Sarcolemmal/ capillary MAC deposition (38/42)	GC free (14): MTX (14) + AZA (3) + GC (41): GC/SSI (19) GC/SSI/IVIG (22); MTX (25), AZA (3), MMF (7), ABA (1), MTX/AZA (2), MTX/MMF (2), MMF/ABA (1)	GC-free maintenance in >50% of statin-induced HMGCR myopathy after GC/IVIG/SSI or IVIG/SSI induction Normal strength after GC-based treatment 28/41 Normal strength after GC-free treatment in 13/14. Better Outcome in early treatment.	(25)
Treppo	2020	16	MC RA	13 12 Atorva	72.4 ±10.3	7 f 9 m	5691 (359-13171)	Prox. weakness (15), myalgia (10), dysphagia (7), myopathic EMG (14/14)	10/16; NM (9), inflammatory cell infiltrates (1)	GC/MTX/IVIG (11), GC/IVIG (2) GC mono (2), no therapy (1)	Remission in all patients after 24 months	(26)

CK: creatine kinase; CR: case report; CS: case series; IVIG: intravenous immunoglobulins; MC: multi-centre; MMT-8: eight muscle manual muscle-test; MTX: methotrexate; MMF: mycophenolate mofetil; MUP: myopathic motor unit potentials; n.a.: not available; NM: necrotising myopathy; NSM: non-specific myositis; RA: retrospective analysis; y(s): year(s); SC: single-centre.

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