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DOI: 10.3899/jrheum.171495
http://www.jrheum.org/content/early/2018/12/10/jrheum.171495

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ABSTRACT. ***Objective.*** A pathogenic role of anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) antibodies has been proposed. Our objective was to assess efficacy of rituximab (RTX) in anti-HMGCR immune-mediated necrotizing myopathy.

Methods. All patients who had been treated with RTX were retrospectively reviewed to assess features and outcome.

Results. Three of 9 patients demonstrated stable or improved muscle strength ± decline in creatine kinase levels, or T2/short-tau inversion recovery hypersignal decrease on magnetic resonance imaging following RTX treatment. RTX permitted intravenous immunoglobulin discontinuation and corticosteroid reduction to low dose in 2 patients.

Conclusion. One-third of patients with refractory anti-HMGCR had improved strength or other evidence of improved disease activity following RTX treatment. (J Rheumatol First Release December 15 2018; doi:10.3899/jrheum.171495)

Key Indexing Terms:
MYOSITIS IMMUNE-MEDIATED NECROTIZING MYOPATHY
ANTI-3-HYDROXY-3-METHYLGLUTARYL-COENZYME A REDUCTASE RITUXIMAB

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Dr. Landon-Cardinal is the recipient of Clinical Fellowship awards from the Université de Montréal Rheumatology Program, Abbvie Educational Grant and the Association des médecins rhumatologues du Québec, Visithan-Khy Educational Grant.

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Accepted for publication September 11, 2018.

Anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) antibodies are recently identified myositis-specific antibodies[1,2] associated with a severe form of immune-mediated necrotizing myopathy (IMNM) with poor muscle strength recovery at 4 years[3] and early severe muscle damage identification on magnetic resonance imaging (MRI)[4]. Reported findings support a pathogenic role of anti-HMGCR antibodies[5,6,7].

Overall, these patients tend to require aggressive immunosuppressive therapy and present relapsing disease course, yet older statin-exposed patients may have a more favorable prognosis than younger patients[3]. B cells play a prominent role in the antibody production and the chimeric monoclonal antibody targeting CD20+ B cells [rituximab (RTX)] has been reported in the treatment of refractory myositis[8]. Yet, there was no separate consideration in this study of patients having an anti-HMGCR antibody[8a]. Moreover, only a few case reports and case series have reported this therapeutic strategy in anti-HMGCR IMNM[9,10].

In this case series, we report the characteristics and outcome of patients with anti-HMGCR IMNM who were treated with RTX.

MATERIALS AND METHODS

Design. This is a retrospective case series of 9 patients with anti-HMGCR IMNM who were treated with RTX between 2009 and 2017.

Subjects. All patients had been evaluated as part of routine clinical care in the outpatient clinic or during hospitalization.

Assessment of muscle disease. Strength was assessed by manual muscle

testing and graded using the Medical Research Council–5 scale. Electromyogram, muscle MRI with T1- and T2- weighted short-tau inversion recovery (STIR), muscle biopsies, and serum creatine kinase (CK) levels were reviewed.

Detection of anti-HMGCR antibodies and titers. Serum samples had previously been collected and banked from all patients with a diagnosis of IMNM according to the European Neuromuscular Centre Workshop criteria[11]. Anti-HMGCR antibodies were identified using ELISA (Inova Diagnostics Inc.) or addressable laser bead immunoassay (ALBIA). Sera collected within 3 months prior to and during the RTX treatment period were retrospectively retrieved and sent for anti-HMGCR titer measurement using the ALBIA-HMGCR assay.

RTX treatment. Most patients were administered a standard protocol of 1 g of intravenous RTX, infused once, followed by a second dose repeated after 2 weeks. One patient received a dose of 375 mg/m^2/body surface area once weekly for 4 weeks. Patients were subsequently re-perfused with RTX 1 g every 6 months at the discretion of the treating physician.

Response criteria. Patients were considered responsive to treatment if (1) CK level was reduced to ≤ twice the upper limit of normal (adjusted for ethnicity) and/or T2/STIR hypersignal on MRI was resolved, (2) no muscle testing deterioration was observed, and (3) corticosteroids could be tapered to low dose (≤ 15 mg/day) and intravenous immunoglobulin (IVIG) discontinued.

Ethics statement. Written informed consent from each study patient and approval by the local Ethics Committee [CPP Ile De France VI (2013-12-19), CCTIRS (N°14.323), and CNIL (915139)] was obtained to use medical information recorded in the myositis database for scientific purposes. Patients were reported anonymously according to French law.

RESULTS

Among 46 anti-HMGCR IMNM patients who were examined, 9 patients (20%) had been treated with RTX since 2009 (Table 1). Mean patient age at RTX initiation was 43 years and 7 patients (77%) were female. All patients presented with a history of proximal muscle weakness and 4 of them displayed a dystrophic-like presentation over a mean of 14.3 years prior to RTX introduction. Two patients had a history of statin exposure prior to myopathy. Mean peak CK level at initial presentation was 7993 IU/l (range 3324–13,537), and 1602 IU/l (range 63-3427) prior to RTX introduction. On average, patients had previously failed 3 lines of immunotherapy.

At diagnosis, muscle biopsy was performed in all cases. All biopsies displayed regenerating and necrotic fibers. MHC-I positive staining was seen in 4 cases. Three biopsies demonstrated the presence of mononuclear cell infiltrates. When performed (n = 5), biopsies demonstrated sarcolemmal C5b-9 deposition on non-necrotic muscle fibers and none in the capillaries.

One-third of patients (n = 3/9) were considered responders and all others were considered nonresponders to RTX. Responders demonstrated stable or improved strength on manual muscle testing ± decline in CK levels (Figure 1, patients A and B) or stable muscle strength and T2/STIR hypersignal decrease on MRI following RTX treatment (patient C). RTX permitted IVIG discontinuation and adjunctive corticosteroid (CS) therapy reduction to low dose in 2 patients (A and C). Three patients were clearly IVIG-dependent (D, E, and not shown) and another (not shown) with dystrophic-like presentation was also considered IVIG-dependent because IVIG tapering resulted in the patient's reported subjective muscle deterioration and functional capacity impairment together with T2/STIR hypersignal on MRI. All 4 were still receiving IVIG therapy at last followup. Of note, all 3 RTX responders were still in remission at last followup: patient A with low-dose CS and RTX, patient B with RTX and methotrexate (MTX), and patient C with MTX monotherapy.

One patient (patient F) was treated early in the course of the disease with RTX and was clearly identified as a nonresponder after 5 months of treatment. She was subsequently successfully treated with high dose CS, IVIG, and azathioprine (AZA). At last followup, this patient's CS therapy had been tapered to low dose; she was still receiving AZA and an attempt at IVIG tapering was considered. Finally, another patient (not shown) was unsuccessfully treated with RTX, because the CK level remained elevated at about 3000 IU/l without any clinical improvement (psoas 4/5) 6 months after infusion. Improvement was only observed when IVIG was subsequently initiated and the patient still received IVIG at last followup.

Table 1. Patient characteristics at RTX initiation.

Patient	Age, yrs, Sex	Statin Exposure	Disease Duration, yrs	Peak CK, IU/l	CK Prior to RTX, IU/l	Previous Treatments
A	25, M	N	1	10391	2574	PE, CYC, IVIG, AZA
B	19, F	N	10	9832	104	IVIG, MTX, AZA
C	64, M	N	23	7137	63	PE, MTX, IVIG
D	36, F	N	7	5985	1066	MTX, IVIG, AZA
E	60, F	Y	10	10050	1298	MTX, PE, IVIG
F	40, F	N	0.75	13537	3427	MTX
G	63, F	Y	5	6086	2500	MTX
H	47, F	N	17	5600	188	MTX, IVIG, AZA, MMF
I	41, F	N	3	3324	3204	IVIG, AZA, MMF, MTX

CK: creatine kinase; RTX: rituximab; PE: plasma exchange; CYC: cyclophosphamide; IVIG: intravenous Ig; AZA: azathioprine; MTX: methotrexate; MMF: mycophenolate mofetil.

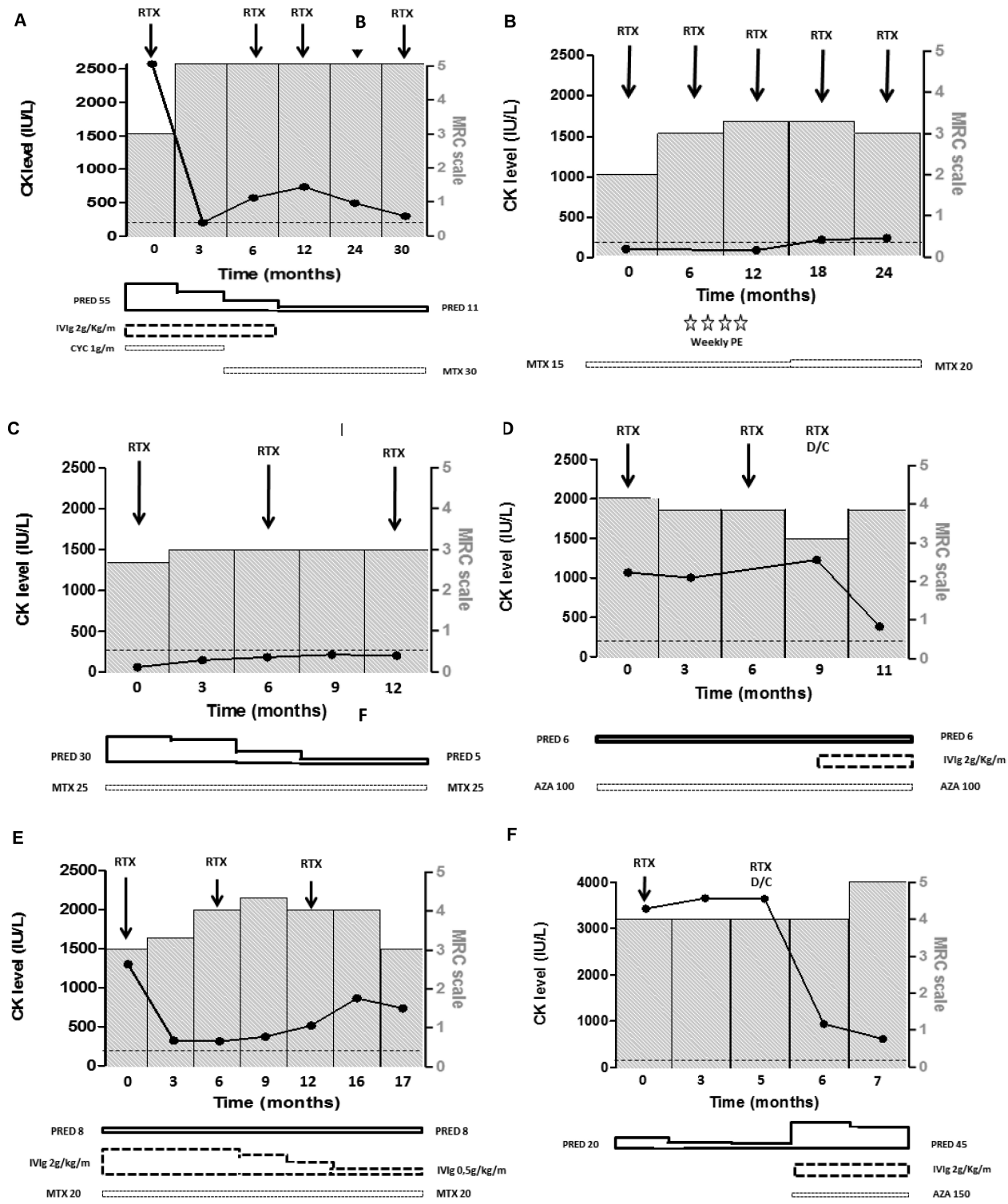

Figure 1. Clinical course of patients after rituximab initiation: CK levels (data points and lines) and MRC scale muscle strength (bar diagrams). Patients A–C are responders and D–F are nonresponders. Poorer muscle strength between psoas and deltoid was reported on a scale using an adapted MRC [(5 = 5), (5– = 4.7, (4+ = 4.3), (4 = 4), (4– = 3.7), (3+ = 3.3), (3 = 3), (3– = 2.7), (2 = 2), (1 = 1), (0 = 0)]. CK: creatine kinase; MRC: Medical Research Council; RTX: rituximab; PRED: prednisone; IVIg: intravenous Ig; CYC: cyclophosphamide; MTX: methotrexate; PE: plasma exchanges; AZA: azathioprine.

The most striking effect of RTX was seen in 2 statin-naive younger patients (A and B). Of note, the first (Figure 1A) presented diffuse MHC-I overexpression and strong sarcolemmal C5b-9 deposition on his muscle biopsy. He was initially treated aggressively at diagnosis (within 2 mos of initial symptoms) with plasma exchanges (PE) in addition to high-dose CS, IVIG, and cyclophosphamide. He also presented high anti-HMGCR titer at relapse prior to RTX initiation, and displayed a dramatic titer decrease following treatment (from 1597 AU/ml at baseline to 63.8 AU/ml after 18 mos of treatment). The second (Figure 1B) also presented myofibers MHC-I overexpression (C5b-9 staining not performed) and was aggressively treated with PE within 6 months of RTX initiation. Anti-HMGCR titer prior to PE was 194.9 AU/ml and repeatedly below 40.3 AU/ml during PE treatment period. However, anti-HMGCR titer was not available prior to RTX or during RTX treatment after PE cessation. The third responder (Figure 1C) displayed a stable anti-HMGCR titer (from 107.9 AU/ml at baseline and 105.4 AU/ml after 12 mos).

Anti-HMGCR titer was not systematically correlated with clinical outcome, though it was not available for all patients (Appendix 1).

DISCUSSION

In this retrospective observational study, the beneficial effect of RTX was observed in one-third of patients with refractory anti-HMGCR IMNM.

RTX use in patients with anti-HMGCR IMNM has rarely been reported. One Australian case series of 20 patients with IMNM (13 anti-HMGCR, 2 anti–signal recognition particle, 3 connective tissue disease–associated, and 2 seronegative) reported an improvement in 2 out of 5 (40%) patients treated with RTX[10]. Of note, those 2 patients were statin-naive, younger than their statin-exposed counterparts, and both displayed myofiber MHC-I positivity; 1 had sarcolemmal C5b-9 staining and required IVIG as well. Nonetheless, they both relapsed on tapering of CS. Another Australian case series addressed 6 anti-HMGCR patients' treatment and outcome, and RTX was used in 2 refractory cases without clear benefit[9].

Most B-cell depletion therapies prevent the maturation of B cells into plasma cells, but they do not affect long-lived plasma cells[12]. Resistance of long-lived plasma cells seems to be one of the major contributors to the maintenance of autoreactive memory B cells, thereby maintaining secretion of pathogenic autoantibodies[13].

RTX is currently used mainly in refractory cases and rarely as a first-line therapy. Nonetheless, one of our patients (Figure 1F) was treated early in the course of her disease with RTX. However, no clinical and biological improvement was observed after 5 months of treatment, even though CD19 and CD20 counts remained suppressed.

Our study has some limitations. First, 1 patient (A) was initially taking multiple medications, making it impossible to definitely attribute clinical improvement to RTX. Second, while CK is usually considered a reliable marker of disease activity in IMNM, 2 patients (B and C) had normal CK levels prior to initiation of RTX therapy. However, we hypothesize that in these patients who had a chronic dystrophic-like course with significant atrophy and fatty replacement of muscle, CK levels may not have been a reliable measure of disease activity. Indeed, 1 patient had improved proximal strength from grade 2 to grade 3, and another patient had resolution of muscle edema on MRI, supporting the idea that disease activity decreased following RTX therapy in these patients.

RTX was clearly ineffective in some patients, yet may have demonstrated a beneficial effect in one-third of patients with refractory anti-HMGCR IMNM. A prospective randomized trial is needed to confirm these findings and clarify the role of RTX in the treatment of patients with shorter disease duration.

ACKNOWLEDGMENT

We thank Dr. Jean-Luc Charuel and Dr. Fabienne Jouen for anti-HMGCR titer assessment using available banked serum.

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APPENDIX 1. Anti-HMGCR titer variation following rituximab treatment.

Patient	HMGCR Titer prior to RTX, AU/ml (timing)	HMGCR Titer after RTX, AU/ml (timing)	RTX Response
A	1597 (M–1)	63.8 (M18)	Success
C	107.9 (M–2)	105.4 (M12)	Success
D	114.6 (D0)	134.5 (M9)	Failure
F	235.5 (D0)	276.5 (M4)	Failure

Anti-HMGCR: anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase; RTX: rituximab; D0: baseline; M–1: 1 month prior; M–2: 2 months prior; M4: 4 months after; M9: 9 months after; M12: 12 months after; M18: 18 months after.