Anti-SRP and anti-HMGCR myopathies

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Four major types of myositis

- Inclusion body myositis
- Dermatomyositis
- Antisynthetase syndrome
- Immune-mediated necrotizing myopathy
Three subtypes of IMNM*

- **Anti-HMGCR myopathy**
  - High CK and proximal weakness
  - Anti-HMGCR+

- **Anti-SRP myopathy**
  - High CK and proximal weakness
  - Anti-SRP+

- **Antibody-negative IMNM**
  - High CK and proximal weakness
  - No MSA
  - Necrotizing muscle biopsy

*Allenbach et al., Neuromuscular Disorders, 2018*
Clinical features: anti-SRP vs. anti-HMGCR myopathies at Hopkins\textsuperscript{1,2}

<table>
<thead>
<tr>
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<th>Anti-SRP n=37 (95% CI)</th>
<th>Anti-HMGCR N=104 (95% CI)</th>
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<tbody>
<tr>
<td>Age of onset, years</td>
<td>38.4 (33.8, 43.0)</td>
<td>55.0 (52.4, 57.6)</td>
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<tr>
<td>Female sex, %</td>
<td>78 (63, 89)</td>
<td>59 (49, 68)</td>
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<tr>
<td>Caucasian, %</td>
<td>54 (38, 69)</td>
<td>72 (63, 80)</td>
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<tr>
<td>Black, %</td>
<td>41 (26, 57)</td>
<td>19 (13, 28)</td>
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<tr>
<td>Necrotizing biopsy, %</td>
<td>78 (63, 89)</td>
<td>77 (68, 84)</td>
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<tr>
<td>Skin involvement, %</td>
<td>3 (0, 14)</td>
<td>5 (2, 11)</td>
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<tr>
<td>ILD, %</td>
<td>22 (11, 37)</td>
<td>4 (2, 9)</td>
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<tr>
<td>Statin exposure, %</td>
<td>5 (1, 18)</td>
<td>75 (66, 82)</td>
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Compared to anti-HMGCR myopathy patients, anti-SRP myopathy patients are more likely younger, female, black, to have ILD, and to be statin-naive.

\textsuperscript{1}Pinal-Fernandez, AC&R, 2017
\textsuperscript{2}Tiniakou and Pinal-Fernandez, Rheumatology, 2017
Current treatments for anti-HMGCR and anti-SRP myopathy

- Steroids
- Methotrexate, azathioprine, mycophenolate
- IVIG (especially for anti-HMGCR)
- Rituximab (especially for anti-SRP)
IMNM patients have severe and persistent proximal weakness

![Graph showing strength over years from first visit for AS, DM, and IMNM patients.](image-url)

Unpublished data
Anti-SRP and anti-HMGCR myopathy patients recover strength slowly

Older anti-HMGCR patients recover faster

Old and young anti-SRP patients recover at same rate
Incomplete response to therapy in anti-SRP and anti-HMGCR myopathy: the Hopkins experience

- **Anti-HMGCR**
  - 50 patients followed > 2 years
  - 22 reached full-strength
    - Mean age at onset 56 years
    - Only 3 could be tapered off meds
    - 12 with CK > 500
  - 15 strength less than 8/10
    - Mean strength 5.8/10
    - Median most recent CK: 1401 IU/L
    - Mean age at onset 48 years (vs 56. p=0.02)

- **Anti-SRP**
  - 21 patients followed > 2 years
  - 10 reached at least 8/10 strength
    - Only 1 could be tapered off meds
    - 4 with CK > 500
  - 11 strength less than 8/10

Tiniakou and Pinal Fernandez et al, Rheumatology, 2017
Necrotizing Myopathy

Degeneration, regeneration, and minimal lymphocytic inflammation
Complement deposition on surface of myofibers in anti-SRP and anti-HMGCR myopathies

Anti-SRP

Anti-HMGCR

Christopher-Stine, A&R, 2010
Muscle biopsy of anti-SRP and anti-HMGCR: scattered necrotic and regenerating fibers

Allenbach and Arouche-Delaperche, Neurology, 2018
Muscle biopsy: more necrotic fibers in anti-SRP

Allenbach and Arouche-Delaperche, Neurology, 2018
Complement deposition correlates with necrosis in anti-HMGCR and anti-SRP myopathy

Allenbach and Arouche-Delaperche, Neurology, 2018
Anti-SRP and anti-HMGCR IgG causes hypotrophy of human myotubes and decreased myotube formation \textit{in vitro}.

Arouche-Delaperche, Annals of Neurology, 2018
Anti-HMGCR and anti-SRP aAbs cause weakness in vivo

C57BL/6

D1
D2
D3
D4
D5
D6
D7
D8

Grip training

Grip test

CYC

Plasma (400µl) or IgG (2 mg)

SRP

HMGCR

△ Grip strength (g)

-60
-40
-20
0

○ Control IgG
○ IgG-depleted plasma (P3)
● Anti-SRP⁺ IgG (P3)

△ Grip strength (g)

-60
-40
-20
0

○ Control IgG
○ IgG-depleted plasma (P4)
● Anti-HMGCR⁺ IgG (P4)

Bergua et al. Ann Rheum Dis, 2019
Anti-HMGCR and anti-SRP aAbs cause myofiber necrosis *in vivo*

**Control**

**Anti-HMGCR**

**Anti-SRP**

Necrotic fibres / section

**Bergua et al. Ann Rheum Dis, 2019**
Pathogenicity of anti-SRP/HMGCR autoantibodies requires the complement system

**Figure Description**: The diagram illustrates the experimental protocol and outcomes for C3^wt and C3^-/- mice. The protocol includes the following steps:

- **C3^wt** and **C3^-/-** mice are used.
- **C3^-/-** mice lack complement component C3.
- Mice receive CYC (cyclophosphamide) on day 1 (D1).
- Plasma or IgG injections are administered on days D2 to D7.
- Grip test blood samples are collected on D1 and D7.
- Grip training and muscle strength assessments are performed.

**Results**:

- Muscle strength (g) is measured for **Anti-SRP+ IgG (P3)** in C3^wt and C3^-/- mice.
- Muscle strength (g) is measured for **Anti-HMGCR+ IgG (P4)** in C3^wt and C3^-/- mice.

**Statistical Significance**:

- Significant differences (**) are observed in muscle strength for **Anti-SRP+ IgG (P3)** in C3^-/- mice compared to C3^wt mice.
- Significant differences (**) are observed in muscle strength for **Anti-HMGCR+ IgG (P4)** in C3^-/- mice compared to C3^wt mice.

**Source**: Bergua et al. Ann Rheum Dis, 2019
Exogeneous complement exacerbates pathogenicity of anti-SRP/HMGCR autoantibodies

Bergua et al. Ann Rheum Dis, 2019
Phased 2 Clinical Trial Will Evaluate the Potential of Zilucoplan for the Treatment of IMNM

Randomized, double-blind, placebo-controlled, multi-center study, followed by an open-label, long-term extension

**Broad Patient Population**
- Clinical diagnosis of IMNM
- Autoantibody positive (HMGCR, SRP)
- MRC weakness of ≤ 4/5 in at least 1 proximal muscle group
- CK >1000 IU/L
- Stable doses of corticosteroids, immunosuppressants, or IVIg
- Vaccinated against meningococcus

**Endpoints**
- Primary endpoint: Change from baseline to week 8 in CK
- Secondary endpoints include functional assessments using validated measures, such as:
  - Triple Timed Up and Go (3TUG) Test
  - Proximal Manual Muscle Testing (MMT)
  - Physician and Patient Global Activity Visual Analogue Scales (VAS)
  - Health Assessment Questionnaire (HAQ)
  - Myositis Disease Activity Assessment Tool (MDAAT)

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<th>Screening</th>
<th>1:1 Randomization</th>
<th>Long-Term Extension (Active Drug)</th>
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<tr>
<td>Placebo + Standard of Care (n=12)</td>
<td>0.3 mg/kg SC + Standard of Care (n=12)</td>
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