BIOLOGIC DRUGS IN THE TREATMENT OF MYOSITIS

Professor David Isenberg
University College London, UK
• Incidence of PM/DM/IBM 1.9-7.7 million

• Prevalence in the UK = 8/100,000

• Affects all ages but 2 peaks of onset; childhood onset 5-15 and adult onset 40-60. IBM peaks after 50 years.

• DM/PM overall F:M ratio = 2-3:1
KEY FACTS – 2 – CLINICAL CLASSIFICATION

- Adult onset idiopathic polymyositis
- Adult onset idiopathic dermatomyositis
- Childhood onset myositis (invariably dermatomyositis)
- Myositis associated with other autoimmune rheumatic disease
- Inclusion body myositis
- Rare forms: focal, ocular, eosinophilic, granulomatous myositis
- Cancer associated myositis
KEY FACTS – 3 – A MULTISYSTEM DISEASE

- Constitutional – fever, wt loss, nodes, fatigue
- Joints – arthralgia, arthritis
- Gastrointestinal – dysphagia, abdo pain
- Cardiovascular – palpitations, chest pain
SKIN – RASHES, ERYTHEMA, ULCERATION AND ERYTHRODERMA
MUSCLE – MYALGIA, WEAKNESS
Polymyositis: histopathological features
Dermatomyositis: histopathological features
Respiratory – dysphonia, dyspnoea
TRADITIONAL METHODS OF ASSESSING MYOSITIS

- Clinical
- Enzymes
- EMG
- Biopsy
ASSESSMENT OF OUTCOME

ACTIVITY-MITAX

PATIENT’S PERCEPTION-SF-36

DAMAGE-MYODAM

Idiopathic Inflammatory myopathies
<table>
<thead>
<tr>
<th></th>
<th>Activity</th>
<th>Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td>rash, arthritis, fever, MMT, myalgia</td>
<td>Atrophy, contractures</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td>↑ Muscle enzymes (CK, LDH, AST, ALT)</td>
<td>↓ Creatinine, normal enzymes</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td>RFTs, HRCT, barium swallow</td>
<td>RFTs, HRCT, barium swallow</td>
</tr>
<tr>
<td><strong>EMG</strong></td>
<td>↑ fibrillations</td>
<td>normal</td>
</tr>
<tr>
<td><strong>Biopsy</strong></td>
<td>Inflammatory cells, necrosis, MHC staining</td>
<td>Little cells, atrophy, fibrotic tissue</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td>↑ signal suggesting inflammation</td>
<td>Fat replacement, atrophy</td>
</tr>
</tbody>
</table>
- Retrospective study (1976 → 2013)

- 97 patients followed up during this period (72F, 25M)

![Diagram with categories: Adult-onset Polymyositis [APM] (n=35), Adult-onset Dermatomyositis [ADM] (n=37), Overlap syndrome [OS] (n=25).]
<table>
<thead>
<tr>
<th>Category</th>
<th>All Patients</th>
<th>Those Who Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>97</td>
<td>24</td>
</tr>
<tr>
<td>ADM</td>
<td>38%</td>
<td>37%</td>
</tr>
<tr>
<td>APM</td>
<td>36%</td>
<td>33%</td>
</tr>
<tr>
<td>OS</td>
<td>26%</td>
<td>29%</td>
</tr>
<tr>
<td>Female</td>
<td>74%</td>
<td>58%</td>
</tr>
<tr>
<td>Male</td>
<td>26%</td>
<td>42%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>64%</td>
<td>67%</td>
</tr>
<tr>
<td>Afro-Caribbean</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>South Asian</td>
<td>10%</td>
<td>8%</td>
</tr>
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</table>
### All Patients

<table>
<thead>
<tr>
<th>Age at Diagnosis</th>
<th>41 years</th>
<th>42 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Duration of Symptoms (IQR)</td>
<td>6 (9)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td>Highest CK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 X ULN</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>&gt; 10 x ULN</td>
<td>63%</td>
<td>67%</td>
</tr>
<tr>
<td>ANA +ve</td>
<td>49%</td>
<td>58%</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Those Who Died</th>
<th>n = 24</th>
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<tbody>
<tr>
<td>Age at Diagnosis</td>
<td>42 years</td>
</tr>
<tr>
<td>Median Duration of Symptoms (IQR)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td>Highest CK</td>
<td></td>
</tr>
<tr>
<td>&lt; 2 X ULN</td>
<td>0%</td>
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<tr>
<td>&gt; 10 x ULN</td>
<td>67%</td>
</tr>
<tr>
<td>ANA +ve</td>
<td>58%</td>
</tr>
<tr>
<td>Condition</td>
<td>All Patients</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td></td>
<td>n = 97</td>
</tr>
<tr>
<td></td>
<td>%</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>25</td>
</tr>
<tr>
<td>Lung involvement</td>
<td>32</td>
</tr>
<tr>
<td>Malignancy</td>
<td>12</td>
</tr>
<tr>
<td>Infection</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>All Patients</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------</td>
</tr>
<tr>
<td></td>
<td>n = 97</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>7%</td>
</tr>
<tr>
<td>Steroids + 1 IS</td>
<td>27%</td>
</tr>
<tr>
<td>Steroids + 2 IS</td>
<td>26%</td>
</tr>
<tr>
<td>Steroids + 3 IS</td>
<td>11%</td>
</tr>
<tr>
<td>Steroids + 4 or more IS</td>
<td>29%</td>
</tr>
<tr>
<td><strong>Disease Course</strong></td>
<td></td>
</tr>
<tr>
<td>Monophasic</td>
<td>36%</td>
</tr>
<tr>
<td>Relapsing/remitting</td>
<td>34%</td>
</tr>
<tr>
<td>Chronic Persistent</td>
<td>30%</td>
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</table>
Statistically significant factors associated with ↓survival

<table>
<thead>
<tr>
<th>Univariate Analysis</th>
<th>Hazards Ratio</th>
<th>Confidence Interval</th>
<th>p =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Involvement</td>
<td>1.78; 95%</td>
<td>1.13 – 2.82</td>
<td>0.013</td>
</tr>
<tr>
<td>Infection</td>
<td>4.18; 95%</td>
<td>1.61 – 10.91</td>
<td>0.003</td>
</tr>
<tr>
<td>Upper and Lower Limb Involvement</td>
<td>0.13; 95%</td>
<td>0.03 – 0.62</td>
<td>0.010</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Multivariate Analysis</th>
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</thead>
<tbody>
<tr>
<td>Infection</td>
<td>3.68; 95%</td>
<td>1.38 – 9.82</td>
<td>0.009</td>
</tr>
<tr>
<td>Upper and Lower Limb Involvement</td>
<td>0.16; 95%</td>
<td>0.03 – 0.81</td>
<td>0.027</td>
</tr>
<tr>
<td>Causes Of Deaths</td>
<td>n =</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-----</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other:-</strong></td>
<td></td>
<td></td>
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<tr>
<td>Trauma</td>
<td>1</td>
<td></td>
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<tr>
<td>GI bleeding</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncertain</td>
<td>3</td>
<td></td>
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</tr>
</tbody>
</table>
OUTCOME UCL MYOSITIS COHORT (1979 – 2015)
n = 97
CELL DEATH

Necrosis

Apoptosis
(programmed cell death)
First observed histochemically by Kerr (Australia) in 1965

Was referred to as ‘shrinking necrosis’ in 1971

‘Apoptosis’ first used in 1972

Now thought to be the major mechanism of normal cell death in complex organs

Characterised by an orderly sequence of well-defined biochemical events
MORPHOLOGY OF APOPTOSIS

Viable cell

Apoptosis
CELL DEATH

UV Light → Keratinocytes → Apoptotic cells

Larger Apoptotic Blebs
Nucleosomes
Ro (60kD)
La
Sm
PARP
UI-70kD
Mi-2

Small Blebs
Ro (52kD)
Ribosomal P
Calreticulin

Fodrin
Jo-1
CELL DEATH

APOPTOSIS

Clq deficiency

UV irradiation

Infection

Anti-Clq antibodies

Nuclear material

DNA histones enzymes

B

Clq R

Phagocytes

Clq R

Plasma cell

Memory B cell

Anti Jo-1 antibodies

T

CD 40

CD 40 L

CD 40

Memory B cell

Phagocytes

Clq R

Clq R

Anti-Clq antibodies

Infection

UV irradiation

Clq deficiency

DNA histones enzymes

CD 40

CD 40 L

CD 40

Memory B cell

Anti Jo-1 antibodies
CORTICOSTEROIDS AND MYOSITIS

- Have never been tested adequately in randomised, placebo-controlled trials

- *Carpenter (1977)* compared 20 mg + prednisolone vs < 10 mg /day over an 8 week period

- Most authors have suggested a starting dose of 1-2 mg/kg prednisolone but this has never been validated

- Efforts have been made to show that lower doses (0.5 mg/kg) may be sufficient e.g. *Nzeusseu et al. Clin Exp Rheum 1999; 17,441-6.*
IMMUNOSUPPRESSIVES (AZATHIOPRINE) AND STEROIDS (DOUBLE-BLIND PROSPECTIVE TRIAL)

16 patients

- 8 patients
  - 60 mg prednisolone
  - 2 mg/kg azathioprine

- 8 patients
  - 60 mg prednisolone placebo

IMMUNOSUPPRESSIVES (AZATHIOPRINE) AND STEROIDS (DOUBLE-BLIND PROSPECTIVE TRIAL)

16 patients

60 mg prednisolone
2 mg/kg azathioprine

60mg prednisolone placebo

8

3 months

No significant difference between regimes

8

Conclusions: 

Followed by an open 3 year study

‘the distinct impression one perceived at the end of the 3 years was that the group on azathioprine was stronger and required less prednisolone than the group on prednisolone alone’

Bunch. A & R; 1981: 24-45
• Of 25 patients with steroid resistant myositis given oral methotrexate 88% had significant disease improvements and 43% reduced their steroids.

  Bohan et al. Medicine 1977; 56:25

• A randomised control trial in 36 patients of methotrexate and cyclosporin A showed equivalent clinical improvement and decreased CK.

  Venkovsky et al. Scand J Rheum 2000; 29:95
In a randomised trial of 30 patients with treatment resistant myositis an intention to treat analysis showed a trend to improvement \((p=0.025)\) for those given oral azathioprine and methotrexate compared to IV methotrexate.

Villaba et al. A & R 1998; 41: 392
• Several cases reports suggesting benefit

• In a double blind placebo-controlled trial of 15 patients, 8 given IVIg (and continuing oral prednisolone) showed significant improvement in muscle strength ($p < 0.018$) and symptoms

• ($p < 0.035$) whereas the 7 given the placebo showed no benefit.

• Dalakas et al. N Engl J Med 1993; 32
In spite of some optimistic case reports a controlled trial involving 39 patients of leukaphoresis and plasma exchange was no more effective than sham apheresis


Whole body irradiation, total lymphoid irradiation, thymectomy, extracorporeal photochemotherapy have never been subjected to adequate control trials.
WHAT TREATMENT FOR MYOSITIS HAS FAILED TO ACHIEVE!
- Use sunscreens

- Consider topical steroids

- Hydroxychloroquine can improve the rash and lower steroid requirement

- **BUT** no method of treating subcutaneous calcification is of proven benefit
ARTICULAR

Co-existent polyarthralgia quite common

Usually steroid responsive

PULMONARY

Interstitial lung disease common

Response to immunosuppression variable

CARDIAC

Up to 70% of patients involved

Mostly asymptomatic

GASTRO-INTESTINAL

Dysphagia is up to 30%

Cricopharyngeal myotomy occasionally needed (Kagen et al. 1985)
Active exercise is discouraged during acute inflammation.

Start passive range of motion exercises early to avoid joint contractures.

Active exercise can be introduced when inflammation subsides (Hicks 1988), start with isometric exercises.

Active resistive exercises can be considered in stable patients even if some disease activity persists (Escalante et al. 1993).
PREDNISOLONE (0.5 – 0.75mg/kg)

Improvement

Prednisolone (0.5-0.75mg/kg)

↓prednisolone by 15-25%/month

Maintenance steroids likely to be required for 2 years
**PREDNISOLONE (0.5 – 0.75mg/kg)**

- **Improvement**
  - ↓prednisolone by 15-25%/month

- **Poor response**
  - Add
    - Azathioprine
      - 2 mg/kg (less toxic)
  - or
    - Methotrexate
      - Up to 25 mg/wk (higher response rate)
  - or both

- **Maintenance steroids likely to be required for 2 years**

- **Wait 4 - 6 months**

- **If poor response… consider:**
  1. Is the diagnosis correct?
  2. Other drugs neoral/cyclophosphamide/Anti-TNF
  3. IvIg - can be used in severe cases much earlier
- Before corticosteroids and immunosuppressives the mortality rate was 50-70%
  
  eg Medsger et al 1971

- Even after their introduction the outlook was far from ‘stellar’ eg.

  5yr survival – 52%  Benbassset et al 1985

  8yr survival – 73%  Hochberg et al 1986
The common causes of death in ‘most’ series:-

- Infection
- Lung disease
- Cardiac disease
- Malignancy
All 6 achieved CD20⁺ B-cell depletion

Drug well tolerated

Improvement noted in CK (baseline range 128–5600 U/L to 57–1168 U/L); FVC (maximum improvement range 33%–44%) and muscle strength

FVC, forced vital capacity.

B-CELL TARGETED THERAPIES: DERMATOMYOSITIS

• The RIM (Rituximab in Myositis) trial involving >200 patients failed to show any benefit for Rituximab + SOC versus SOC + placebo.

• However the concomitant steroids and immunosuppressives were probably too high to make it likely that Rituximab could show benefit.
In response criteria project, examined MD assessment of improvement at week 24

Methods:

- Bibliographic search of the PubMed database using the keywords
  
  Inflammatory myopathies OR
  Anti-synthetase syndrome OR
  Polymyositis OR
  Dermatomyositis OR

  AND

  RITUXIMAB

(published up to July 2015)

Methods:

We considered case reports and open label studies and clinical trials – 2 main regimes used 1g x 2 2/52 apart or 375/m² weekly x 4

WE FOUND

46 articles

- Case report: 18
- Open label study: 4
- Case series: 23
- Major Trial: 1

≤ 4 pts: 10
> 4 pts: 13
A CAUTIOUS OVERVIEW OF THE RESULTS!

- 447 patients treated [including 151 with DM; 142 with PM; 71 with JDM]

  muscle weakness – 410 (91.7%)
  alveolitis - 70 (15.6%)
  arthritis - 14 (3.1%)

- Overall 347 (77.6%) were reported to show some form of improvement.
OTHER BIOLOGIC DRUGS THAT HAVE BEEN USED TO TREAT MYOSITIS

Abatacept

Tocilizumab

Infliximab

Anakinra

Adalimumab

Silfalimumab

Etanercept

(Fasano, Alves, Isenberg submitted)
• 3 case reports [refractory PM; JDM; myositis overlap]

• each described some clinical benefit and ↓ enzyme level in ‘hard-to-treat’ cases

• ARTEMIS Trial (ongoing phase III)
## TNF α BLOCKADE

<table>
<thead>
<tr>
<th></th>
<th>INFLIXIMAB</th>
<th>ADALIMUMAB</th>
<th>ETANERCEPT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Some encouraging early reports</td>
<td>1 case report of a hard-to-treat patient</td>
<td>Some encouraging early reports</td>
</tr>
<tr>
<td></td>
<td>2 small studies with ( n = 13 + n = 6 ) showed no benefit</td>
<td>↑ muscle strength ( \downarrow CK )</td>
<td>52 week pilot trial of 16 treatment naïve patients showed no benefits [apart from steroid sparing]</td>
</tr>
<tr>
<td></td>
<td>NOT recommended</td>
<td></td>
<td>(Ann Neurol 2011; 70; 427)</td>
</tr>
</tbody>
</table>
• 3 case reports [2PM, 1 overlap syndrome]

• In each of these hard-to-treat patients some clinical benefit and improved enzyme levels
A 12 month open-label trial reported an improvement in 7/15 patients with refractory myositis (Zong et al. Ann Rheum 2014; 75; 913).

nb the inflammatory infiltrates were still present in repeat biopsies and the IL-1 expression was not correlated to clinical responses.
• Phase 1b trial – a moderate suppression of genes induced by type 1 IFN (which is highly overexpressed in myositis patients compared to controls)

• Some improvement in muscle strength (correlated with gene neutralization) was noted (Higgs et al. Ann Rheum Dis 2014; 73; 256)
INVESTIGATOR LED STUDY

OPTIONS FOR A RITUXIMAB STUDY

- Treat at the time of the diagnosis
- Treat those who have failed steroids and 2 immunosuppressives
### PROS AND CONS

#### At Diagnosis

**Pros**
- Original
  - Not confounded by previous/current immunosuppression

**Cons**
- Harder to recruit
  - Harder to fund

#### Post-Conventional Therapy

**Pros**
- Easier to recruit
  - (Probably) easier to fund

**Cons**
- Not original
  - Greater patient diversity [duration/damage/prior variable activity/therapy]
- Could be:

- In newly diagnosed, biopsy-confirmed, patients with IIM

Rituximab at time 0 and 6mns followed by Azathioprine, MTX vs Steroids and Azathioprine, MTX or MMF or MMF

Primary endpoint at one year.
- Could be:-

- In patients with established disease who have failed/done inadequately with steroids and 2 immunosuppressives eg MTX/Azathioprine

Rituximab + S.O.C.  
[viz Prednisolone (max 20mgm/dy)] vs. 
+ MMF]  
2 + 3g/dy
END POINTS – 1 YEAR END POINT

Possibilities

• Use the agreed IMACS/PRINTO myositis response criteria [quite demanding].

OR

• Agree on minimal data set viz muscle strength/CPK/patient and physician VAS.

OR

• Use the loss of MITAX As and Bs (complete or partial) as the end point.
QUESTIONS FOR DISCUSSION

• IMACS/PRINTO end points [quite demanding]

  OR

• Agree on minimal data
  – muscle strength
  – CPK
  – patient and physician VAS
  – some centres using the full MITAX end points

• Enrolment at diagnosis OR refractory disease?
Final consensus definition of improvement (Reserve Slide)

- Uses absolute % change in core set measures (CSMs)
- Conjoint analysis (1000minds) provides different weights to the various CSMs
  - MMT/CMAS > MD Global Activity > Extramuscular Global/DAS > Patient VAS > HAQ/CHAQ > Muscle enzymes/CHQ-PhS
- Uses same definition for adult DM/PM and juvenile DM
  - Different optimal cut points for each
- Defines criteria for minimal, moderate and major improvement
  - Major improvement is provisional for adult DM/PM
- Total improvement score is associated with magnitude of improvement
- Selected as a primary endpoint for future clinical trials
  - Pending approval from ACR/EULAR as final response criteria
118 patients studied

- proximal lower limb weakness = 92%
- proximal upper limb weakness = 86%
- EMG studies performed in 98 - normal in 11
- open muscle biopsies in 103 - normal in 11
FACTORS AFFECTING CREATININE KINASE LEVELS – OTHER CAUSES OF ELEVATED LEVELS – 1 -

- ethnicity
- recurrent strenuous exercise
- drugs
- endocrine/metabolic disorders
- other conditions
- other muscle diseases
- dystrophy
- rhabdomyolysis
- myocardial infarction
- metabolic
FACTORS AFFECTING CREATINE KINASE LEVELS – CAUSES OF LOW CK LEVELS IN ACTIVE MYOSITIS – 2 -

- Circulating inhibitor
- Steroid treatment without disease suppression
- Advanced disease with atrophy i.e. damage not activity
- ?? concurrent autoimmune rheumatic disease
- unexplained!
<table>
<thead>
<tr>
<th></th>
<th>Lupus + Myositis (n = 11)</th>
<th>Primary Myositis (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F:M</td>
<td>10:1</td>
</tr>
<tr>
<td>PM:DM</td>
<td>7:4</td>
<td>12:7</td>
</tr>
<tr>
<td>Age at onset</td>
<td>33 yrs (21-47)</td>
<td>36 (29-66)</td>
</tr>
<tr>
<td>Initial CK</td>
<td>11.2* (1.3-50)</td>
<td>10.7* (0.8-28)</td>
</tr>
<tr>
<td>Initial quads strength</td>
<td>49% of normal</td>
<td>52% of normal</td>
</tr>
</tbody>
</table>

*expressed as a multiple of the upper limit of normal.

Garton & Isenberg. BJR 1997; 36: 1067
MUSCLE BIOPSY - PROBLEMS

- Open vs needle vs conchotome
- Focal nature of the lesion in some cases
- Must look out for:
  - fibre hypertrophy = dystrophy
  - inclusion bodies = IBM
  - widespread necrosis with profuse regeneration = rhabdomyolysis
  (+ myoglobinuria)
INCLUSION BODY MYOSITIS
CT SCAN QUADRICEPS – 3-YEAR FOLLOW-UP