RemyelINation

Sat 16-SEP-2023, 18:30-18:50
axel petzold

Expertisecentrum Neuro-ophthalmology Amsterdam UMC
Disclosures

NIHR UK, UCSF
Stichting MS Research NL
Novartis, Heidelberg Academy
To be covered

- Background on remyelination
- The key trial in humans
- Novel outcomes
- Novel trials
- Summary
Remyelination in mice and men

Klotz, L et al Nat Rev Neurol 2023

**Disease course**

- Mouse: Severity increases over time and then decreases.
- Human: Severity increases periodically.

**Resolution versus persistence of inflammation**

- Mouse: T cell and macrophage-microglia in active lesion resolve weeks after onset.
- Human: Mixed lesion with partial remyelination and no remyelination.

<table>
<thead>
<tr>
<th>Intrinsic repair capacity</th>
<th>Mouse</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In mice: remyelination success

A

AAV-MBP::mTdTmato

Immunization

7d

pre c-MS

c-MS d3

c-MS d16

Cytokines

B

pre c-MS

c-MS d3

c-MS d16

Internodes:

Green: New

Orange: Remaining

C

In vivo

LM

c-MS d16

CLEM

UCL Mezydlo, A et al Neuron 2023 Expertisecentrum Neuro-ophthalmology Amsterdam UMC
In men: remyelination failure

Tonietto, M et al. Brain 2023
Remyelination strategies

- Repurposing of safe drugs
- Novel compounds
- Stem cells
- Genetic
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Preparing the stage
Choosing the drug
Clemastine fumarate:

- Hay-fever tablet
- > 700,000,000 tablets (1979 to 1992, FDA data)
- 1.4/100,000 AE (mainly fatigue)
Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial

Ari J Green, Jeffrey M Gelfand, Bruce A Cree, Carolyn Bevan, W John Boscardin, Feng Mei, Justin Inman, Sam Arnow, Michael Devereux, Aya Abounasr, Hiroko Nobuta, Alyssa Zhu, Matt Friessen, Roy Gerona, Hans Christian von Büdingen, Roland G Henry, Stephen L Hauser, Jonah R Chan

Summary

Background Multiple sclerosis is a degenerative inflammatory disease of the CNS characterised by immune-mediated destruction of myelin and progressive neuroaxonal loss. Myelin in the CNS is a specialised extension of the oligodendrocyte plasma membrane and clemastine fumarate can stimulate differentiation of oligodendrocyte precursor cells in vitro, in animal models, and in human cells. We aimed to analyse the efficacy and safety of clemastine fumarate as a treatment for patients with multiple sclerosis.

Methods We did this single-centre, 150-day, double-blind, randomised, placebo-controlled, crossover trial (ReBUILD) in patients with relapsing multiple sclerosis with chronic demyelinating optic neuropathy on stable immunomodulatory therapy. Patients who fulfilled international panel criteria for diagnosis with disease duration of less than 15 years were eligible. Patients were randomly assigned (1:1) via block randomisation using a random number generator to
Patients in both groups exhibited shortening of P100 latency while on the active compound. The primary prespecified efficacy endpoint for the trial was met with reduction of latency delay of $1.7 \text{ ms/eye}$ (95% CI 0.5–2.9; $p=0.0048$) in the crossover model.
Limitations of (most) trials

- One model: Optic Neuritis
- Outcome measure: VA, pVEP
Treatment failures

- Issues with primary outcome measure
  - In ON this is high contrast VA (ceiling effect)
- Non-responders
  - Nothing left to remyelinate (axonotmesis)
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Myelin Water Fraction (MWF)

MWF = \frac{\text{Area A}}{\text{Area A} + (\text{Area B} + \text{Area C})}

A: \sim 10/15 \text{ ms}
B: \sim 40/70 \text{ ms}
C: > 1000 \text{ ms}

T2^*

\begin{tabular}{|c|c|}
\hline
\textbf{GROUP 1} & \textbf{GROUP 2} \\
\hline
\hline
\text{ON THERAPY} & \text{NO THERAPY} \\
\text{(baseline to 3 months)} & \text{(3 to 5 months)} \\
\text{OFF THERAPY} & \text{ON THERAPY} \\
\hline
\end{tabular}
A novel eye-movement impairment in multiple sclerosis indicating widespread cortical damage
Table 1 Demographic and clinical characteristics of the healthy controls and patients with MS

<table>
<thead>
<tr>
<th></th>
<th>Patients with MS</th>
<th>Healthy controls (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n = 210)</td>
<td>INO (n = 71)</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>142 (68)</td>
<td>40 (56)</td>
</tr>
<tr>
<td>Age, y</td>
<td>54.5 (±10.8)</td>
<td>56.7 (±9.7)</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>21.0 (±8.5)</td>
<td>23.5 (9.0)</td>
</tr>
<tr>
<td>EDSS, median (IQR, total range)</td>
<td>3.5 (3.5, 0.0–8.5)</td>
<td>4.0 (3.0, 1.5–8.5)</td>
</tr>
</tbody>
</table>
# INO in population based birth cohort (1966)

## INO prevalence in MS 24%

### Table 1

Demographic and clinical characteristics of individuals with MS and healthy controls.

<table>
<thead>
<tr>
<th></th>
<th>Individuals with MS</th>
<th>INO, N = 53</th>
<th>Non-INO, N = 167</th>
<th>p-value</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, female</strong></td>
<td>Overall, N = 220(^a)</td>
<td>160 (73%)</td>
<td>30 (57%)</td>
<td>130 (78%)</td>
<td>80 (73%)</td>
</tr>
<tr>
<td><strong>Disease course</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPMS</td>
<td>32 (15%)</td>
<td>9 (17%)</td>
<td>23 (14%)</td>
<td>0.129</td>
<td>NA</td>
</tr>
<tr>
<td>SPMS</td>
<td>48 (22%)</td>
<td>16 (31%)</td>
<td>32 (19%)</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>RRMS</td>
<td>138 (63%)</td>
<td>27 (52%)</td>
<td>111 (67%)</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td><strong>Disease duration, y</strong></td>
<td>16 (9)</td>
<td>16 (10)</td>
<td>16 (9)</td>
<td>0.915</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Current DMT use</strong></td>
<td>95 (43%)</td>
<td>27 (51%)</td>
<td>68 (41%)</td>
<td>0.190</td>
<td>NA</td>
</tr>
<tr>
<td><strong>EDSS</strong></td>
<td>3.5 (2.5–4.0)</td>
<td>4.0 (3.0–4.5)</td>
<td>3.5 (2.5–4.0)</td>
<td>0.044</td>
<td>NA</td>
</tr>
<tr>
<td><strong>SDMT</strong></td>
<td>52 (10)</td>
<td>49 (10)</td>
<td>53 (10)</td>
<td>0.046</td>
<td>NA</td>
</tr>
<tr>
<td><strong>NHPT (sec)</strong></td>
<td>21.59 (19.41–24.37)</td>
<td>22.20 (20.50–26.27)</td>
<td>21.41 (19.00–24.02)</td>
<td>0.015</td>
<td>NA</td>
</tr>
<tr>
<td><strong>T25-FW (sec)</strong></td>
<td>4.85 (4.15–6.20)</td>
<td>5.15 (4.40–7.11)</td>
<td>4.80 (4.05–6.12)</td>
<td>0.136</td>
<td>NA</td>
</tr>
<tr>
<td><strong>HCVA, mean ODS</strong></td>
<td>54 (50–60)</td>
<td>54 (48–58)</td>
<td>54 (50–60)</td>
<td>0.270</td>
<td>NA</td>
</tr>
<tr>
<td><strong>LCVA, mean ODS</strong></td>
<td>29 (22–35)</td>
<td>26 (20–34)</td>
<td>29 (22–35)</td>
<td>0.325</td>
<td>NA</td>
</tr>
<tr>
<td><strong>History of optic neuritis</strong></td>
<td>86 (39%)</td>
<td>25 (47%)</td>
<td>61 (37%)</td>
<td>0.167</td>
<td>NA</td>
</tr>
<tr>
<td><strong>History of vascular risk factors</strong></td>
<td>50 (23%)</td>
<td>9 (17%)</td>
<td>41 (25%)</td>
<td>0.252</td>
<td>22 (20%)</td>
</tr>
<tr>
<td><strong>History of vascular events</strong></td>
<td>5 (2.3%)</td>
<td>1 (1.9%)</td>
<td>4 (2.4%)</td>
<td>&gt;0.999</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Can we predict remyelination treatment response?

(A) **VDI peak velocity**
- Placebo
- Fampridine

(C) **VDI peak velocity, non-INO eyes**
- Placebo
- Fampridine

Data from Kawita, M.S.K. et al. CNSNT 2018
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RESTORE trial

Screening Week -4 to -2
Baseline Day -7 to -3

Start treatment

T0
Month 0

T1
Month 3

Clemastine 4mg
2 capsules per day

End treatment

T2
Month 6

T3
Month 12

T4
Month 24

T5
Month 36

End study

Placebo
2 capsules per day

Wash Out

Fampridine response

EudraCT: 2021-003677-66
ClinicalTrials.gov: NCT05338450

Hof, S et al. [under revision]
**RECOVER trial**

- **Screening Period**: All patients undergo assessments to ensure eligibility for participation.

- **Treatment Period 1**: Baseline to 1 week
  - **GROUP A**: Clemastine 12mg (6mg 2x/day)
  - **GROUP B**: Placebo (6mg 2x/day)

- **Treatment Period 2**: 1-week to 3-month
  - **GROUP A**: Clemastine 8mg (4mg 2x/day)
  - **GROUP B**: Placebo (4mg 2x/day)

- **Treatment Period 3**: 3-month to 9-month
  - **GROUP A**: Off treatment
  - **GROUP B**: Off treatment

ClinicalTrials.gov: NCT00896220

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RemyelINatiON

- Drug discovery strategy (high throughput)
- Chose a safe option (clemastine)
- Afferent visual pathway model (VEP)
- Efferent visual pathway model (VDI)
- Two model confirmation (RCT)
- Re-consider role for PET-MRI
Wielkie dzięki