Progressive MS

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Disclosures

None
Learning Objectives

Phenotypic studies on progression

Pathology and mechanisms

Imaging correlates

Treatments
Key Messages

There is a ‘window of opportunity’ for anti-inflammatory/anti-immune therapies for MS to affect progression

In early disease peripheral adaptive immune system activation predominates, while in late disease innate immune system activation within the CNS predominates

Number of cortical lesions and deep gray matter volume on brain MRI as well as spinal cord volume correlate with disability progression

Treatment with DMTs delays progression

There are new treatments available that affect disability progression
EDSS

Onset of progressive MS is age-sensitive & independent of pre-progression disease course

Onset of progressive MS is age-sensitive & independent of pre-progression disease course

Koch et al. J Neurol Sci. 2007
Onset of progressive MS is age-sensitive & independent of pre-progression disease course

- SPMS (420); SAPMS (112); PPMS (322)
- Mean age at progressive MS onset: 45 ± 10 yrs
- 99% of conversion to progressive MS < 75 yrs age

Tutuncu et al, MSJ 2013.
What does this tell us

• Once a certain threshold of disability has been reached disease progression is uninfluenced by relapses, either those that have occurred previously or those which have occurred subsequently.

• Almost complete suppression of relapses with Alemtuzumab in patients that have already entered the progressive phase of MS had little effect on subsequent disease progression.

• Use of Alemtuzumab at earlier disease stages (before onset of progressive disease) has demonstrated that the drug may have effects on preventing or delaying onset of disease progression.

• These observations suggest a ‘window of opportunity’ for anti-inflammatory/anti-immune therapies for MS and that once a clinical level of disability has been reached these therapies become less effective.
Can we change the natural history of progressive MS?

• No drug has been proven to prevent progressive MS
• Sustained moderate to severe disability is due to progressive phase of MS
• Absolute life time risk of SPMS starts dropping after age 45 in a patient that still continues to have RRMS
• 7% > age 60
• Prevention of relapses can prevent additional disability
• Most patients stop having relapses after age 59
• 14% of SPMS patients have ongoing relapses
<table>
<thead>
<tr>
<th>50% chance of progression at age 45 (odds of no progression = 1.0)</th>
<th>Age (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 45</td>
</tr>
<tr>
<td>Chance of SPMS</td>
<td>35%</td>
</tr>
<tr>
<td>odds of no progression</td>
<td>2.9</td>
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<table>
<thead>
<tr>
<th>Duration from MS onset (yrs)</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>&gt; 15</td>
</tr>
<tr>
<td>Chance of no progression</td>
<td>60%</td>
</tr>
<tr>
<td>odds of SPMS</td>
<td>1.6</td>
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</table>
• Rate of disease progression appears to correlate with the severity of cortical inflammation

• Cortical lesions have reduced levels of inflammatory cellular infiltrate and pure intracortical lesions typically have low levels of inflammation

• In both SPMS and PPMS there appears to be a correlation between the degree of subpial demyelination and leptomeningeal inflammation, suggesting a potent driver for the process

• However, the association between meningeal inflammation and cortical demyelination remains unclear

• How do cortical lesions induce neuronal cell body injury?
Potential Mechanisms Of Axonal Injury

- Abnormal axonal proteins
- Ion channel changes
- Inflammation
- Demyelination
- Mitochondrial/energy failure
- Axon transport failure
Non-disease-related Factors For Remyelination Failure

The efficiency of remyelination is affected by the non disease related factors age, sex and genetic background.

The efficiency of remyelination decreases with age this is compounded by an age associated increase in the vulnerability of demyelinated axons to atrophy.

The age associated effects on remyelination are due to a decrease in the efficiency of both OPC recruitment and OPC differentiation.

The impairment of OPC differentiation with age mirrors the failure of oligodendrocyte lineage differentiation that is associated with many chronically demyelinated MS plaques.

The decline in remyelination efficiency occurs more rapidly in males than in females.

There is a critical age associated change in the epigenetic regulation of OPC differentiation during remyelination.
Disease-specific Factors For Remyelination Failure

MS lesions fail to remyelinate not because of a shortage of available precursor cells but rather because of a failure of OPC recruitment, involving proliferation, migration and repopulation of areas of demyelination.

Why?

1- OPCs are direct targets of the disease process in the lesion
2- OPC recruitment into areas of demyelination may fail owing to disturbances in the local expression of the OPC migration guidance cues semaphorin 3a and 3F
3- failure of differentiation and maturation. Several studies have shown that OPC availability is not a limiting factor for remyelination in MS lesions
   - chronically demyelinated lesions contain factors that inhibit precursor differentiation
   - the absence of positive factors
Differentiation block of oligodendroglial progenitors is a major determinant of remyelination failure in chronic multiple sclerosis lesions
Imaging correlates of progression
Cortical Lesions In MS

Cortical lesions were detected by MRI in the majority (64%) of patients with relapsing remitting (RRMS) and secondary progressive (70%) MS (SPMS), as well as in more than one-third (36.8%) of patients with clinically isolated syndromes (CIS) suggestive of MS.

A recent study based on 5-year longitudinal observations of more than 300 MS patients with different clinical phenotypes showed that patients with a high cortical lesion load at baseline had the worst clinical evolution and the fastest progression of cortical atrophy after 5 years.

Cortical lesion volume was an independent predictor of disability progression.

Interestingly, RRMS and SPMS patients were found to accumulate new cortical lesions at a similar rate.

Patients suffering from RRMS with cognitive deficits had more cortical lesions and atrophy than cognitively normal MS patients.
Normalized Thalamic Volume Decline

Healthy Controls
(n=81)

Multiple Sclerosis
(n=520)

Estimated rate of decline:
-0.28% per year

Estimated rate of decline:
-0.71% per year

ANN NEUROL 2018;83:223–234
DGM volume predicts future progression of EDSS

(A) Baseline DGM volume, but not baseline lobar cortical grey matter or whole brain volumes, can predict future EDSS progression. Predictive value of DGM volume is independent of clinical phenotypes.

HR (95% CI) for the model with continuous volume 0.73 (0.55-0.96)  
\( p<0.05 \)

HR (95% CI) for the model with continuous volume 0.72 (0.62-0.82)  
\( p<0.001 \)
Conclusions

Baseline thalamic volume had the highest predictive value of EDSS progression.

No significant differences in rates of loss in patients who were receiving disease-modifying drugs and those who were not.

The pathological events that underpin DGM atrophy are not known, but this is generally interpreted as the result of neurodegeneration.

In healthy controls, rate of DGM atrophy was faster than that in other regions, suggesting that it may be a hotspot for both age- and disease-related atrophy in the human brain.

Whereas lower thalamic volume and higher rates of atrophy were associated with worse disability in these studies, the effect size was small.

Given the constancy of atrophy rates over disease epochs and in different MS clinical phenotypes, it seems likely that any therapy targeting atrophy should be started at the time of clinical presentation to achieve maximal benefit.
Spinal Cord Volume Loss
A marker of disease progression in multiple sclerosis

Neurology® 2018;91:e349-e358
What’s the effect of treatment on disease progression
Patients with MS were assessed for eligibility

- 44217 MSBase
- 43048 Untreated
- 1091 Non-MSBase alemtuzumab

Excluded
- 34765 Did not receive DMT during follow-up in MSBase cohort
- 14001 <3 EDSS scores (including 1 before baseline)
- 7171 <4 y clinical follow-up (3364 started DMT within 4 y of data extract; 2887 missing data)
- 6251 Not classified as relapsing-remitting MS at baseline
  (2676 primary progressive MS; 1003 secondary progressive MS)
- 3679 Received ≥1 DMTs but each treatment <6 mo
- 1996 Received ineligible treatment
- 1633 Participated in a randomized clinical trial

9452 Eligible for matching

- 92 Treated with alemtuzumab at anytime
- 1182 Treated with natalizumab at anytime
- 605 Treated with fingolimod at anytime
- 8353 Treated with glatiramer acetate at anytime
- 275 Untreated

- 57 Treated with alemtuzumab only
- 100 Treated with natalizumab only
- 88 Treated with fingolimod only
- 3715 Treated with glatiramer acetate only

431 Patients treated and followed up before fingolimod, alemtuzumab, and natalizumab were available for escalation
A. The median follow-up was 7.6 years (interquartile range [IQR], 5.8-9.6); B. 4.5 years (IQR, 4.3-5.1); C. 4.9 years (IQR, 4.4-5.8); and D. 7.4 years (IQR, 6.8-8.6) years. HR indicates hazard ratio.
A. Treatment with glatiramer acetate or interferon beta ≤5 y vs >5 y of onset

B. Treatment with glatiramer acetate or interferon beta within 5 y vs no treatment

C. Treatment with glatiramer acetate or interferon beta between 5 y and 10 y vs no treatment

D. Escalation from glatiramer acetate or interferon beta treatment to fingolimod, alemtuzumab, or natalizumab treatment ≤5 y vs >5 y of onset

A. The median follow-up was 13.4 years (interquartile range [IQR], 11-18.1); B. 7.5 years (IQR, 5.7-9.8); C. 7.7 years (IQR, 5.8-9.7); and D. 5.3 years (IQR, 4.6-6.4).

HR indicates hazard ratio.
Comparison of Cumulative Hazard of Conversion to Secondary Progressive Multiple Sclerosis for Initial Treatment With Glatiramer Acetate or Interferon Beta vs Fingolimod, Alemtuzumab, or Natalizumab
Conclusions

The current understanding of the disease pathogenesis assumes that inflammation is closely associated with demyelination and with irreversible axonal and cortical damage, thus reduction of neurodegeneration should be a logical consequence of stopping inflammation.

Early treatment is better than late, but late treatment is better than never.

Early aggressive treatment is better than escalation.
### Modifiable Risk Factors For Progression

<table>
<thead>
<tr>
<th>Risk factor and outcome measure</th>
<th>Study design, number of studies</th>
<th>Findings: direction, magnitude of effect</th>
<th>QoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D: correlation 25(OH)D level and EDSS</td>
<td>11 concurrent, 2 retrospective, 2 prospective studies</td>
<td>Weak correlation ($r = -0.22; CI = -0.28, -0.10; 11 studies$) indicating that lower levels of vitamin D are associated with higher EDSS scores</td>
<td>Moderate (indirect)</td>
</tr>
<tr>
<td>Sun exposure: no outcome assessed in &gt;1 study</td>
<td>5 retrospective studies</td>
<td>Association but predictor and outcome measures varied (see text)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Sunscreen use: no outcome assessed in &gt;1 study</td>
<td>2 retrospective studies</td>
<td>No association but predictor and outcome measures varied (see text)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Month of birth: no outcome assessed in &gt;1 study</td>
<td>3 retrospective studies</td>
<td>No association but outcome measures varied (see text)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Smoking: risk of progression comparing smokers and nonsmokers</td>
<td>1 concurrent, 9 retrospective, 4 prospective studies</td>
<td>Smoking is associated with an increased risk of progression ($HR = 1.55; CI = 1.10, 2.19; 7 studies$)</td>
<td>Moderate (heterogeneity)</td>
</tr>
<tr>
<td>Fish consumption: no outcome assessed in &gt;1 study</td>
<td>2 concurrent, 3 retrospective studies</td>
<td>Conflicting results (see text)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Alcohol-related predictors: no outcome assessed in &gt;1 study reporting on the same operationalization</td>
<td>3 concurrent, 2 retrospective studies</td>
<td>Association but predictor and outcome measures varied (see text)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Exercise: no outcome assessed in &gt;1 study</td>
<td>2 retrospective, 3 prospective studies</td>
<td>Conflicting results (see text)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Brain trauma: no outcome assessed in &gt;1 study</td>
<td>2 retrospective studies</td>
<td>No association but predictor and outcome measures varied (see text)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Epidural analgesia: EDSS scores</td>
<td>2 prospective studies, 1 retrospective study</td>
<td>1 study showed no association with EDSS (sign. N/A), 1 study no association with 3 EDSS score categories ($p&gt;0.1$); 1 study no association with EDSS or DSS ($p=0.66$)</td>
<td>Low (exploratory design, no effect estimate)</td>
</tr>
<tr>
<td>Oral contraception: no outcome assessed in &gt;1 study</td>
<td>3 retrospective studies</td>
<td>Conflicting results (see text)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Geographic region: no outcome assessed in &gt;1 study</td>
<td>1 retrospective, 1 prospective study</td>
<td>Conflicting results (see text)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Education: no outcome assessed in &gt;1 study</td>
<td>2 retrospective studies</td>
<td>Conflicting results (see text)</td>
<td>Insufficient</td>
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</table>

*Multiple Sclerosis Journal* 2017, Vol. 23(4) 525–533
### Phase 3 Trials In PMS Since 2016

<table>
<thead>
<tr>
<th>Drug</th>
<th>Main mechanism</th>
<th>Multiple sclerosis type</th>
<th>Number of participants</th>
<th>Primary outcome for progression</th>
<th>Mean age, years (SD, active; placebo)</th>
<th>Mean duration of progression, years (SD, active; placebo)</th>
<th>Patients with baseline T1-GdE lesions, n/N (%)</th>
<th>Placebo versus active CDP, n/N (%)</th>
<th>Primary outcome HR or OR (95% CI) and result</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFORMS³</td>
<td>Fingolimod</td>
<td>PPMS</td>
<td>823</td>
<td>Composite*: time to 3-month CDP</td>
<td>49 (8-6; 8-3)</td>
<td>6 (2-5; 2-4)</td>
<td>107/820 (13%)</td>
<td>338/487 (69%) vs 232/336 (69%)</td>
<td>HR 0.95 (0.80–1.12); negative</td>
</tr>
<tr>
<td>ORATORIO⁶</td>
<td>Ocrelizumab</td>
<td>PPMS</td>
<td>732</td>
<td>EDSS: time to 3-month CDP</td>
<td>45 (7-9; 8-3)</td>
<td>7 (4-0; 3-6)</td>
<td>193/727 (27%)</td>
<td>96/244 (39%) vs 160/487 (33%)</td>
<td>HR 0.76 (0.59–0.98); positive</td>
</tr>
<tr>
<td>EXPAND⁴</td>
<td>Siponimod</td>
<td>SPMS</td>
<td>1651</td>
<td>EDSS: time to 3-month CDP</td>
<td>48 (7-8; 7-9)</td>
<td>4 (3-6; 3-3)</td>
<td>351/1599 (22%)</td>
<td>173/545 (32%) vs 288/1096 (26%)</td>
<td>HR 0.79 (0.65–0.95); positive</td>
</tr>
<tr>
<td>ASCEND⁷</td>
<td>Natalizumab</td>
<td>SPMS</td>
<td>887</td>
<td>Composite*: proportion with 6-month CDP</td>
<td>47 (7-4; 7-8)</td>
<td>5 (3-0; 3-7)</td>
<td>210/884 (24%)</td>
<td>214/448 (48%) vs 195/439 (44%)</td>
<td>OR 0.86 (0.66–1.13); negative</td>
</tr>
</tbody>
</table>


**Table:** Summary of four phase 3 trials published since 2016 in progressive multiple sclerosis
Phase II Trial Of Ibudilast In Progressive MS

• Ibudilast inhibits several cyclic nucleotide phosphodiesterases, macrophage migration inhibitory factor, and toll-like receptor 4

• It can cross the blood–brain barrier

• In a phase 2 trial involving patients with relapsing multiple sclerosis, ibudilast at a dose of 30 to 60mg per day did not prevent the development of new lesions on MRI but slowed the progression of brain atrophy in a dose-dependent fashion and decreased the proportion of GD+ lesions that converted to black holes on T1-weighted images

• 255 patients with primary or secondary progressive multiple sclerosis in a phase 2 randomized trial of oral ibudilast (≤100 mg daily) or placebo for 96 weeks. The primary efficacy end point was the rate of brain atrophy

Treatment targets in Progressive MS

- Neuroprotective therapy
- Remyelination
- Inhibition of microglia activation
References