Discussing Disease Modifying Therapies for Progressive Multiple Sclerosis

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CMSC, June 2015

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Talk Overview

- Do disease modifying therapies help progressive MS?
- How do we discuss disease modifying therapies with people with progressive MS?
- What does the future hold for effectively treating progressive MS?

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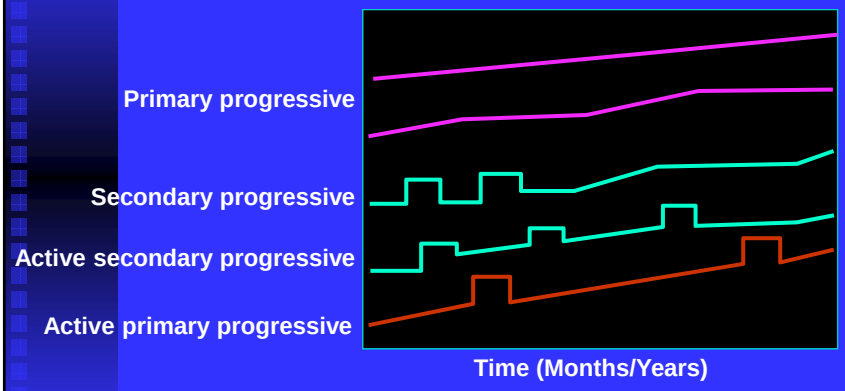
Progressive Forms of MS



Adapted from Lublin et al. *Neurology*. 1996;46:907.

"Active" Progressive MS

Progressive MS in which there is evidence of inflammatory disease activity

- clinical relapses
- new MRI lesions
- Gad + lesions on MRI

Adapted from NMSS Consensus statement, 2014

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DMT and Progressive MS

- With one exception, all FDA approved DMT are for relapsing forms of MS
- Mitoxantrone is approved for treating rapidly worsening secondary progressive MS
  - Effectiveness is limited
  - Cardotoxicity and treatment related acute leukemia is a major deterrent to use
- Use of DMTs in progressive MS is “off-label”

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Interferon beta-1b for Secondary Progressive MS

- European trial[1] but not North American trial[2] met primary endpoint of delay in worsening in EDSS
- Secondary endpoints
  - Decreased relapses
  - Decreased new T2 lesions on brain MRI

1. European Study Group in IFN beta-1b in SPMS. Lancet 1998; 352:1491-7
2. Panitch H et al. Neurology 2004; 63:1788-95

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Interferon beta-1a IM in Secondary Progressive MS

- Dose was 60 mcg once a week
  - Met primary endpoint of delay in worsening on MSFC (driven by 9HPT and PASAT)
  - Did not delay worsening on EDSS
- Secondary endpoints
  - Decreased relapses
  - Decreased new T2 lesions on brain MRI

Cohen JA et al. Neurology 2002; 59:679-87.

Glatiramer acetate for Primary Progressive MS

- Trial did not meet primary endpoint of delay in worsening on EDSS
- Secondary endpoint
  - Decreased new T2 lesions on brain MRI

Wolinsky JS et al. Ann Neurol 2007; 61:14-24

Rituximab for Primary Progressive MS

- Trial did not meet primary endpoint of delay in worsening on EDSS
- Secondary endpoint
  - Decreased new T2 lesions on brain MRI

Hawker K et al. Ann Neurol 2009; 66:460-71.

Other Trials

- Fingolimod trial for PPMS
  - Negative trial announced this year
- Natalizumab for SPMS
- Ocrelizumab for PPMS
- Ibudilast for Progressive MS
- Masitinib for Progressive MS
- Others

Summary

- To date, anti-inflammatory DMT have been ineffective at significantly slowing progression in SPMS and PPMS
- Anti-inflammatory DMT can decrease risk of relapses and formation of new T2 lesions

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Counseling Patients Regarding DMT

- Patients who develop SPMS while on DMT started when they had RRMS
- Patients not on a DMT with progressive MS who have “active” disease
- Patients not on a DMT with progressive MS who do not have “active” disease

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Patients who develop SPMS while on DMT started when they had RRMS

- We do not have strong evidence to guide us
- Need open discussion about lack of evidence regarding risks of stopping and benefits of continuing
- If decision is made to stop DMT, monitoring plan should be made
- Escalating to more intensive immunosuppressant generally is not indicated

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Patients not on a DMT with progressive MS who have “active” disease

- If they are eligible for accessible clinical trial, encourage participation
- Explain that initiating a DMT will only control the “active” component of their MS; they should not expect DMT to stop progression
- If decision is made to use DMT, use safest medication available

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Patients not on a DMT with progressive MS who do not have “active” disease

- If they are eligible for accessible clinical trial, encourage participation
- Explain status of evidence, which currently does not justify use of DMT
- If decision is made to use DMT, use safest medication available; recognize that this is “off-label” treatment

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Future Therapies

- Early, effective treatment of RRMS may reduce risk of SPMS
- Neuroprotective therapies
  - Sodium channel blockers
  - Anti-oxidants
  - Mitochondrial protection
- Remyelination therapies

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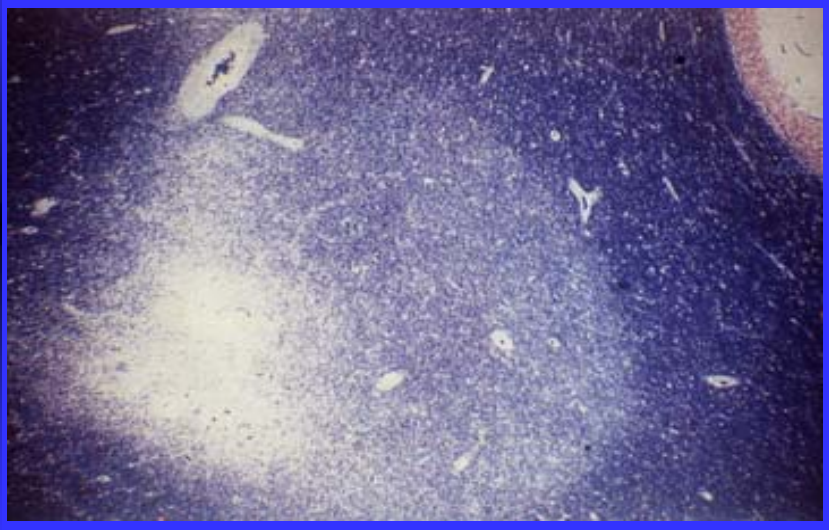
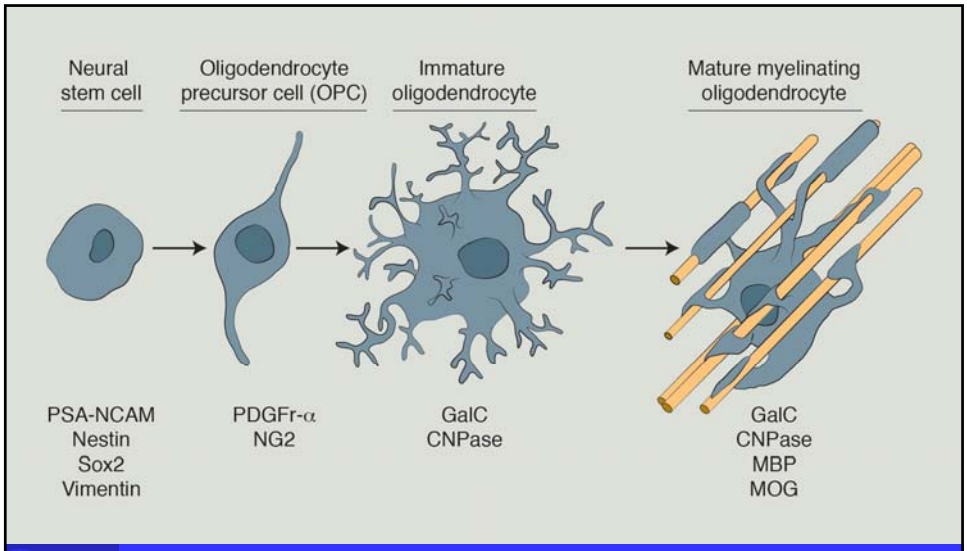
MS and Remyelination

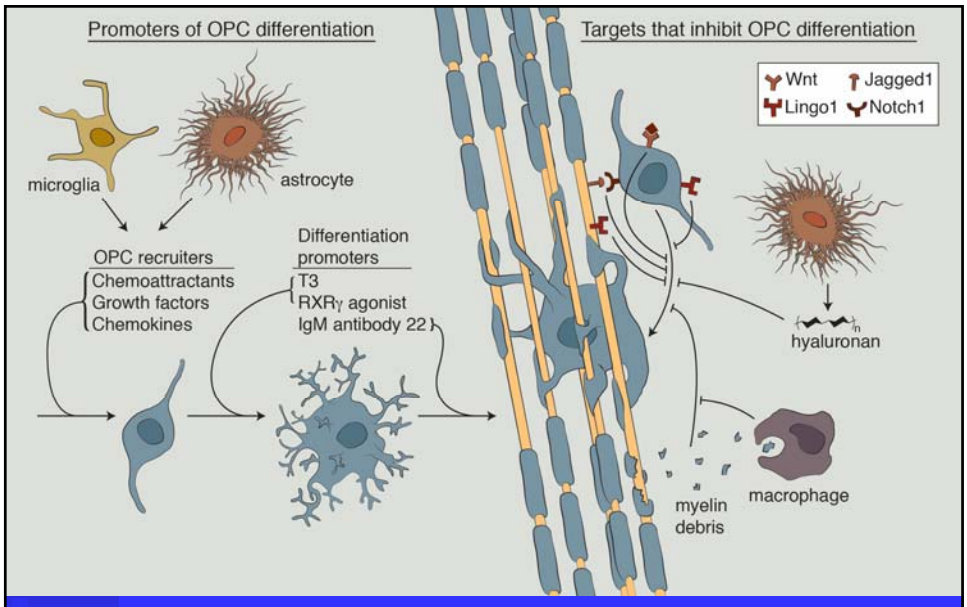


Consequences of Chronic Demyelination

- Chronically demyelinated axons utilize more energy and accumulate Ca^{++}
- Increased susceptibility to noxious substances released by microglia
- Loss of trophic influences of oligodendrocytes
- Cumulative effect is axonal degeneration and progressive worsening



Hartley MD et al. Curr Neurol Neurosci Rep. 2014;14:485-93



Hartley MD et al. Curr Neurol Neurosci Rep. 2014;14:485-93

Remyelination Therapies

- Oligodendrocyte precursor cell (OPC) injections
- Block inhibitors of remyelination
  - Anti-LINGO monoclonal antibody
- Stimulate OPC differentiation
  - Human IgM22
  - Thyromimetic drugs
  - Other small molecule drugs

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Conclusions

- Current DMT for RRMS are largely ineffective in treating progressive MS
- There are many clinical trials underway in progressive MS
- Treatments that promote remyelination may prove to be the most effective way to prevent and treat progressive MS

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