Multiple Sclerosis: Essentials for the Family Physician

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Objectives

- Review common subtypes of Multiple Sclerosis (MS) as well as their immunopathogenesis
- Contrast the treatment strategies of escalation and induction
- Discuss risks and benefits of continuous immune-suppression vs immune reconstitution

Disclosures

- Receipt of speaking or consultation fees: Actelion, Alexion, Biogen, Celgene, EMD Serono, Genzyme-Sanofi, Novartis, Pendopharm, Roche, and Teva
- Member of a company advisory board: Actelion, Alexion, Biogen, Celgene, EMD Serono, Genzyme-Sanofi, Novartis, Pendopharm, Roche, and Teva

Recent Changes in Practice Landscape

- 14 currently approved DMTs (9 new therapies since 2010 alone!)
- Likely at least 3 more imminently arriving
- Injectables, oral agents and infusion based therapies
- Paradigm shift of treating earlier with higher efficacy agents
- Aiming for NEDA (no evidence of disease activity)
- First approved therapy for progressive MS, with several other therapies in late stage development (Biotin, Siponimod, etc.)

Prevalence of MS

- Canada has the **highest rate** of MS in the world[6]
  - An estimated 100,000 Canadians live with the disease[6]
- The prevalence of MS is increasing worldwide[7]

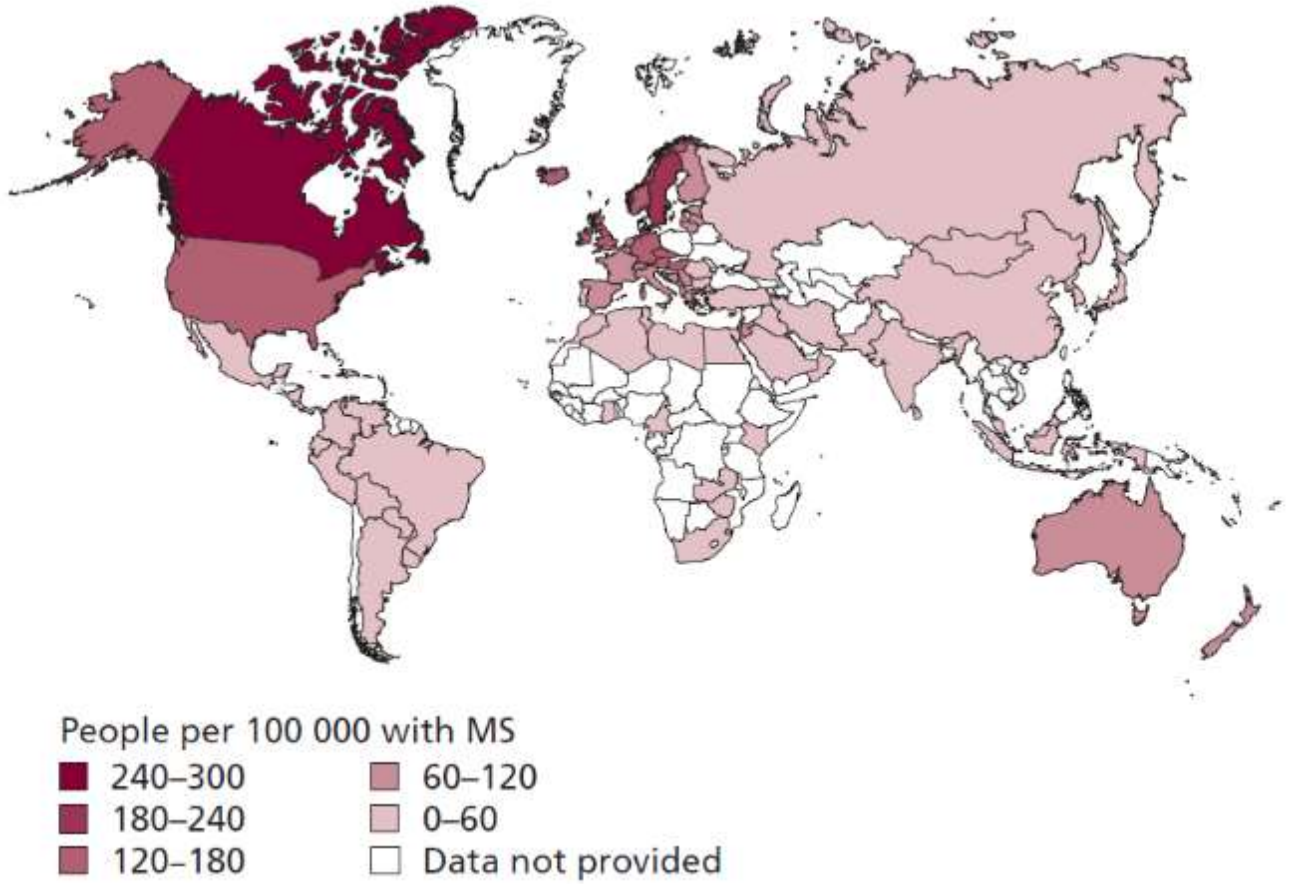
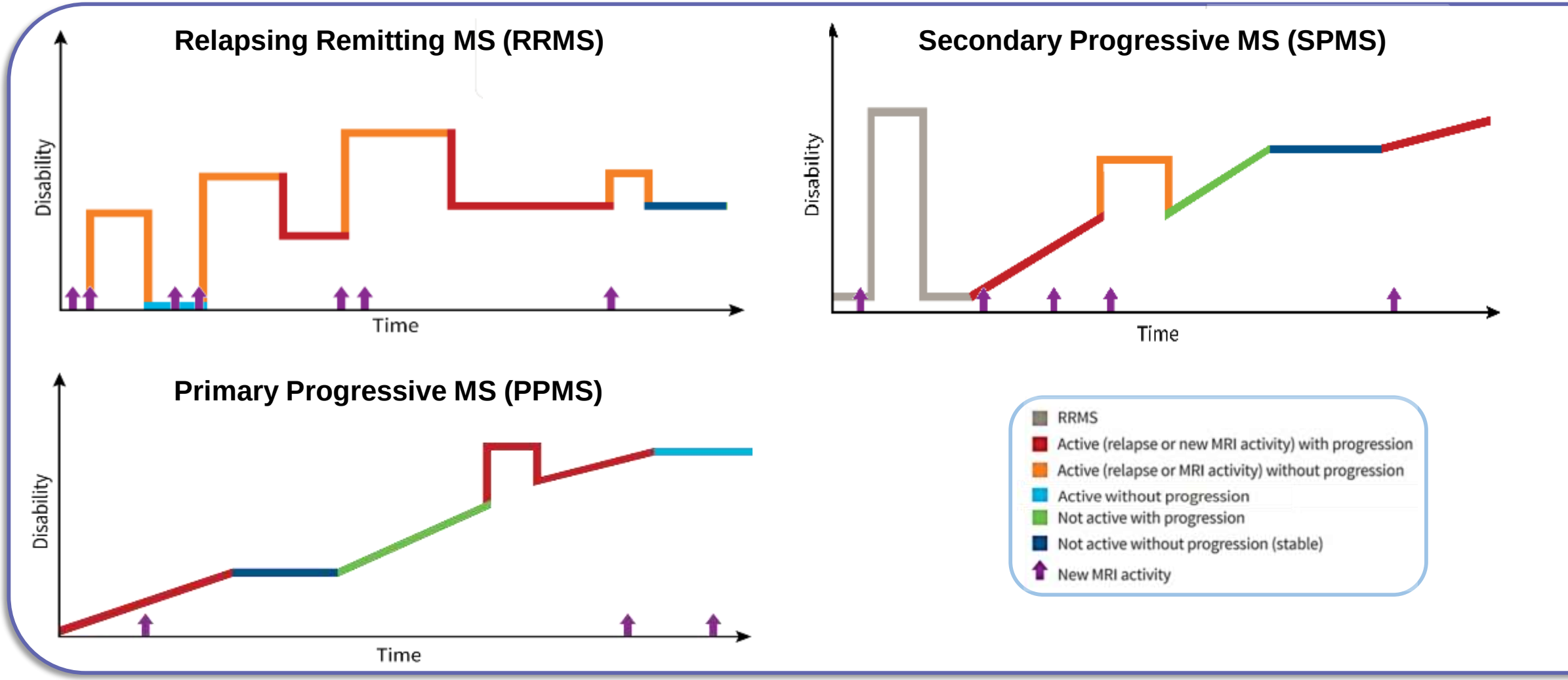


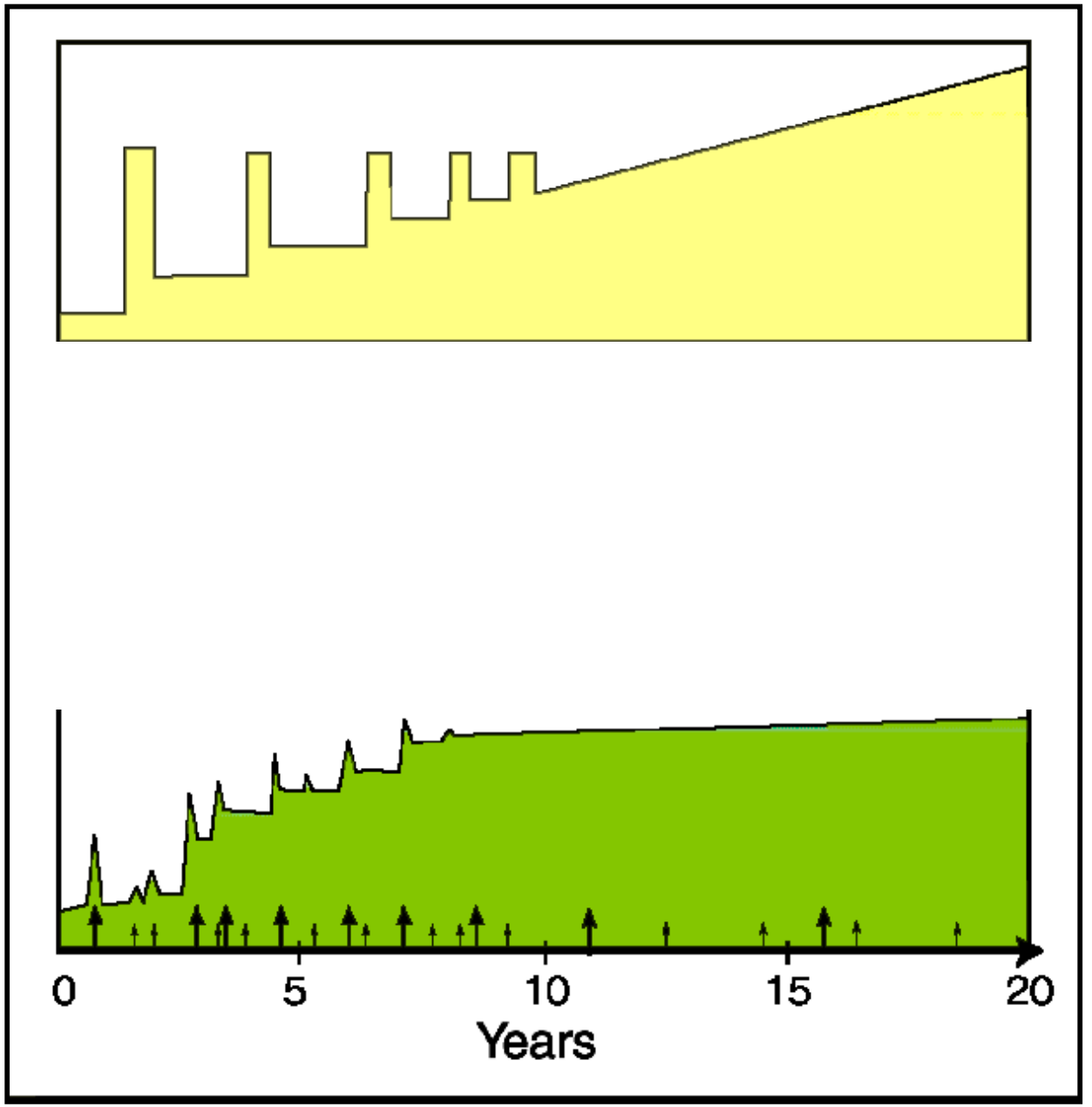
Figure source: Atlas of MS Database. Multiple Sclerosis. International Federation, 2013.

MS Society of Canada. About MS. 2017. Available at: https://mssociety.ca/about-ms.
Malik O, et al. Fast Facts: Multiple Sclerosis. 3rd ed. Oxford, UK: Health Press Limited; 2014.

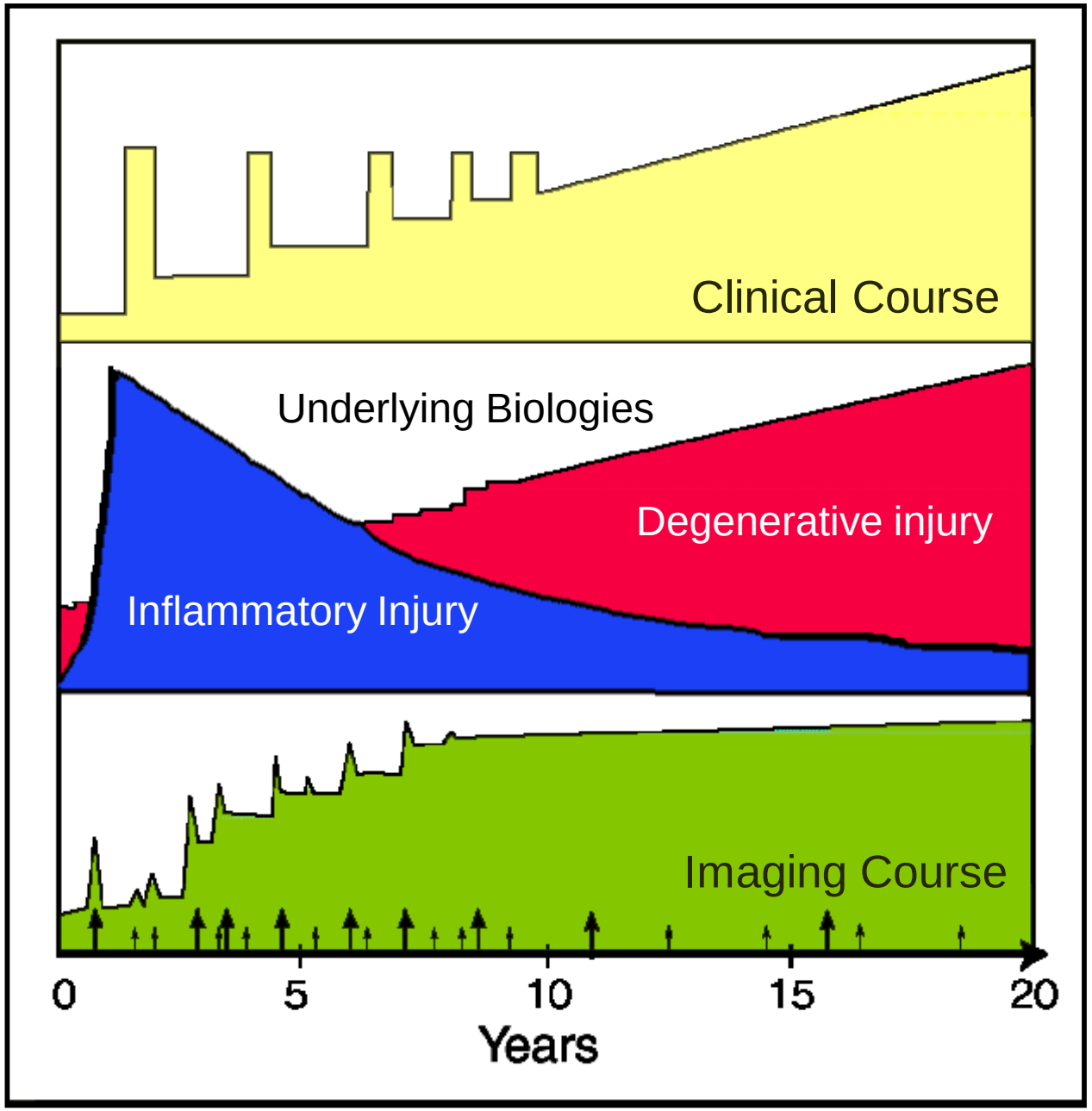
MS disease subtypes



Adapted from: Lublin FD, et al., 2014.



Courtesy of Amit Bar-Or



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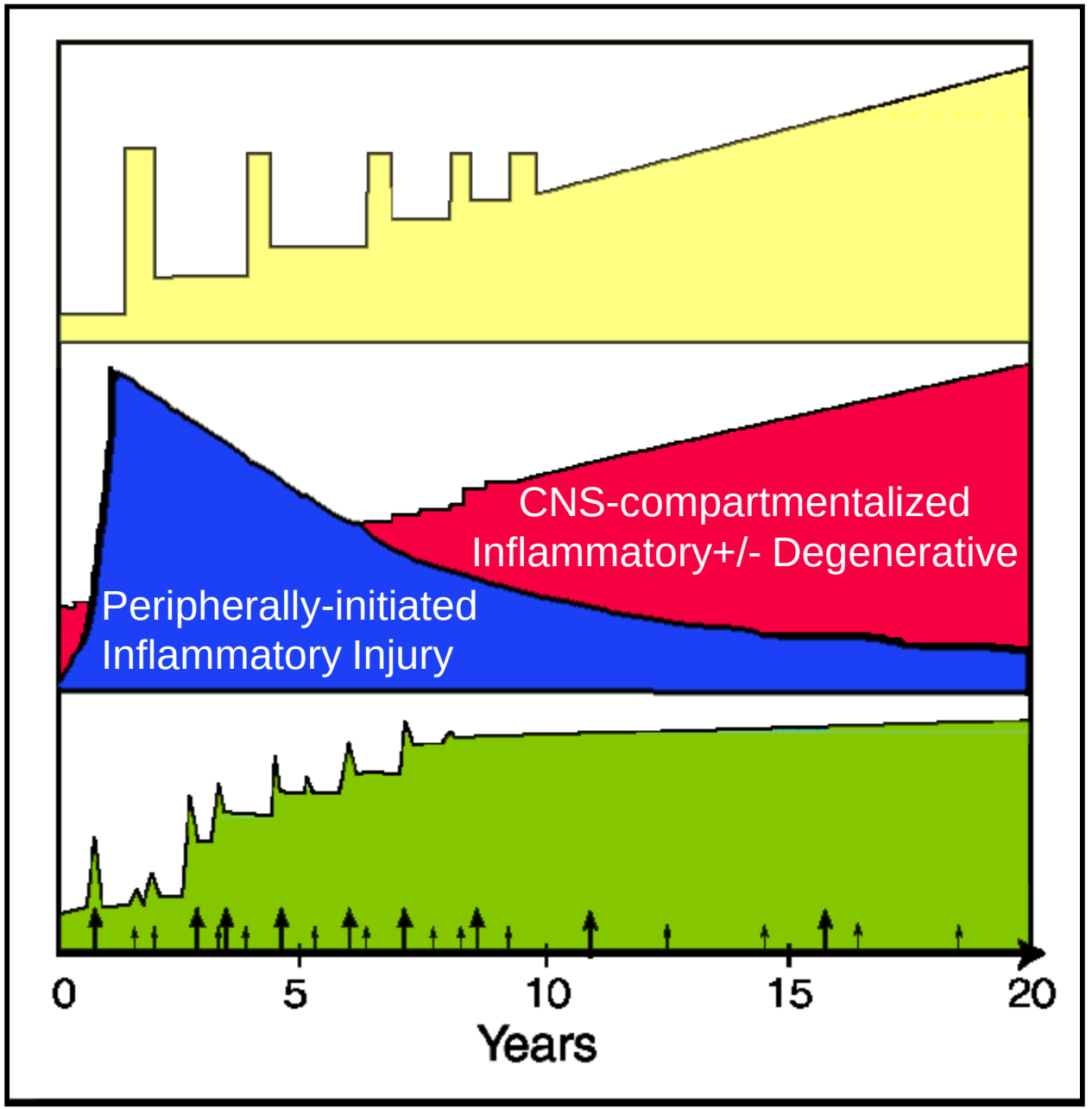

Courtesy of Amit Bar-Or

Prognosis and prognostic factors of MS

- Patients experience increased disability over time
  - Walking impairment within ~10 years
  - Unilateral walking support ~15 to 20 years
- Life expectancy is reduced by ~7–10 years
- Main causes of death:
  - Medical complications (50% of patients)
  - Suicide
  - Causes similar to the general population

Factors that influence prognosis in multiple sclerosis
(validated mainly in RRMS)

Better prognosis	Worse prognosis
• Young age of onset • Female sex • Presentation with optic neuritis • Isolated sensory symptom • Full recovery from attack • Long interval to second relapse • No disability after 5 years • Low lesion load • Caucasian • Low relapse rate in first 2–5 years • Early good response to first-line DMT • Low rate of brain atrophy	• Older age of onset • Male sex • Multifocal onset • Motor/cerebellar system affected • High relapse rate in first 2–5 years • Substantial disability after 5 years • Large lesion load • African American • + CSF OCB with high WBC • Smoking and obesity • Sub-optimal response to first-line DMT • Rapid rate of brain atrophy

Milo R, Miller A. *Autoimmun Rev*. 2014;13:518-524.
Malik O, et al. Fast Facts: Multiple Sclerosis. 3rd ed. Oxford, UK: Health Press Limited; 2014.
Gauthier SA, et al. *Arch Neurol*. 2009;66(2):234-237

Current Therapies

- Interferon-Beta (Avonex®, Rebif®, Betaseron®, Extavia®,Plegridy®)
- Glatiramer Acetate (Copaxone® and Glatect®)
- BG-12/DMF (Tecfidera®)
- Teriflunomide (Aubagio®)
- Fingolimod (Gilenya®)
- Natalizumab (Tysabri®)
- Lemtrada (Alemtuzumab®)
- Ocrelizumab (Ocrevus®)
- Cladribine (Mavenclad®)

Current Therapies: Injectables

- Interferon-Beta (Avonex®, Rebif®, Betaseron®, Extavia®,Plegridy®)
- Glatiramer Acetate (Copaxone® and Glatect®)
- BG-12/DMF (Tecfidera®)
- Teriflunomide (Aubagio®)
- Fingolimod (Gilenya®)
- Natalizumab (Tysabri®)
- Lemtrada (Alemtuzumab®)
- Ocrelizumab (Ocrevus®)
- Cladribine (Mavenclad®)

Current Therapies: Oral Medications

- Interferon-Beta (Avonex®, Rebif®, Betaseron®, Extavia®,Plegridy®)
- Glatiramer Acetate (Copaxone® and Glatect®)
- BG-12/DMF (Tecfidera®)
- Teriflunomide (Aubagio®)
- Fingolimod (Gilenya®)
- Natalizumab (Tysabri®)
- Lemtrada (Alemtuzumab®)
- Ocrelizumab (Ocrevus®)
- Cladribine (Mavenclad®)

Current Therapies: Higher Efficacy

- Interferon-Beta (Avonex®, Rebif®, Betaseron®, Extavia®,Plegridy®)
- Glatiramer Acetate (Copaxone® and Glatect®)
- BG-12/DMF (Tecfidera®)
- Teriflunomide (Aubagio®)
- Fingolimod (Gilenya®)
- Natalizumab (Tysabri®)
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One Goal: Two Therapeutic Approaches

- **Escalation**
  - Starting with a safer, first line therapy
  - Switch only if disease breakthrough
  - This approach requires meticulous monitoring (clinical, MRI)
  - Advantages: Delay and reduce risk
  - Disadvantages: Less long term efficacy
- **Induction**
  - Start with higher efficacy agent first
  - May need maintenance therapy with Immune reconstitution
  - May need to de-escalate later on to manage risk
  - Advantages: Greater long term efficacy
  - Disadvantages: May be assuming more risk than needed

Freedman, MS, Selchen, D, Prat, A., and Giacomini, PS. Canadian Journal of Neurological Sciences 2018 45(5):489-503. doi: 10.1017/cjn.2018.17.

Induction Strategies: Continuous Immunosuppression vs. Immune Reconstitution

- Recent real-world study showed favourable, long term outcomes with early intensive therapy vs first-line moderate-efficacy therapy (Harding et al.)
- **Continuous immunosuppression** – Ocrelizumab (also Natalizumab)
  - Ongoing suppression required to maintain efficacy
- **Immune reconstitution** – Alemtuzumab, HSCT and ?Cladribine tablets
  - “Bolus” dosing (reduction & reconstitution of immune cells)
  - Varying recovery of lymphocyte subsets during reconstitution phase
  - Reconstituting lymphocyte subpopulations may be less pathogenic
  - Durable response after completion of two treatment courses
  - Shorter duration of drug exposure; may have long-term safety advantages

Harding, K et al. JAMA Neurol 2019;76(5):536-541. doi: 10.1001/jamaneurol.2018.4905.

HSCT: hematopoietic stem cell transplantation

Treatment of Primary Progressive MS

Ocrelizumab

- An anti-CD20 monoclonal antibody
- First approved therapy for Primary Progressive MS
- Modest efficacy (24% reduction in confirmed disability progression)
- Most common adverse events: Infusion reactions, URTI, zoster
- Potential risks: higher risk ? neoplasms (2.3% treated group vs. 0.8% of placebo group) and PML
- **Does not reverse existing deficits**
- **Clinical Considerations:** greatest benefit likely in younger progressive patients, with shorter disease duration, and more inflammation

Montalban X, et al. *N Engl J Med*. 2017;376(3):209-22

The Road Ahead…

- More therapies in progressive MS: MD1003 (high dose Biotin), Siponimod, Opicinumab (anti-lingo)
- More therapies in relapsing MS: Ozanzimod, Ponesimod, Ofatumab (anti-CD20)
- Repurposing of existing therapies (Tysabri extended interval dosing, Cladribine and Alemtuzumab for PPMS, induction therapy followed by first line DMTs)
- Many reasons for optimism
- But patients do require a lot of care and we rely on our physician colleagues to help manage this work load

Questions and Comments