Disclosures

- I have nothing to disclose

Objectives

- Participants will be able to:
  - Describe the different mechanisms of action of the disease modifying therapist (DMTs)
  - Recognize the safety concerns versus the efficacy of the new DMTs
  - Understand the use of these DMTs in clinical practice.

History

- Multiple Sclerosis was first recognized as a disease 1869 when it was named by Jean-Martin Charcot
  - Sclerose en plaque disseminee
  - Insular sclerosis, cerebrospinal sclerosis and ultimately multiple sclerosis
  - Assumed to be infectious initially but in the 1920s it was recognized as an inflammatory reaction
  - The importance of myelin, myelin basic protein and oligoclonnal bands were identified in the 1940s
- Initial treatments
  - Initial studies in 1960s showed ACTH was superior to placebo in speeding recovery
  - Steroids were found to help as well.
  - Focus was on both inflammation and infection
  - Interferons that were known to modulate the immune system and a copolymer made up of myelin protein fragments could protect patients against the disease and were the first medications approved in the 1990s

- Murry, TJ. Multiple Sclerosis: a history of a disease. Demos Medical Publishing.New York, New York. 2005

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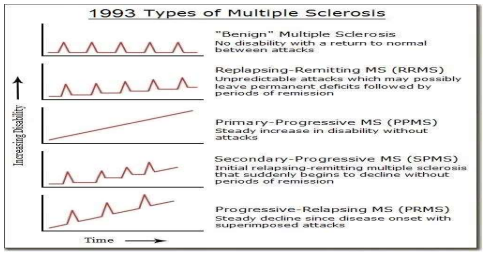
Clinical Course



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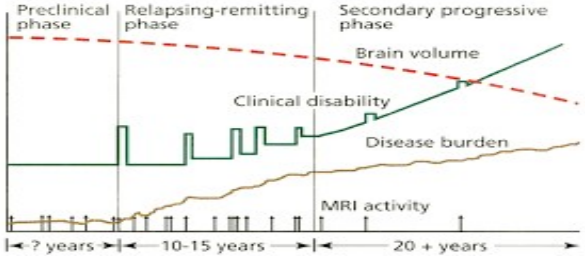
Natural History of Relapsing Remitting Disease



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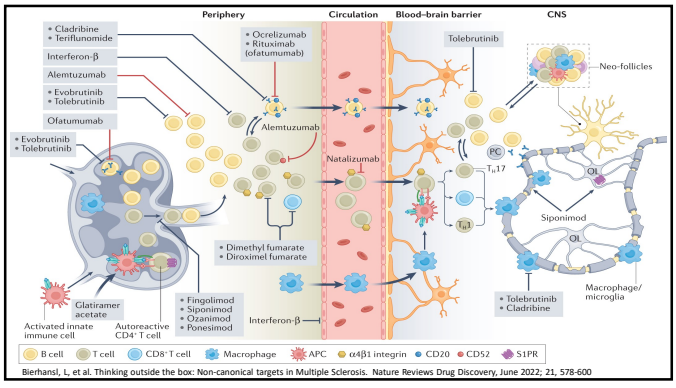
Advantages of Disease Management

- Reduced disease activity
- Delayed transition to secondarily progressive disease
- Reduced disability
- Decreased brain atrophy
- All of our treatments are designed to prevent active inflammation

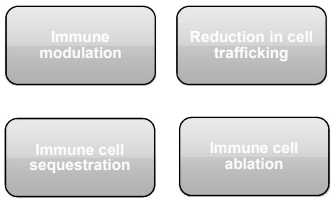
Current Treatment Options

- 26 medications are now available on the market including generic formulations
- One has been removed from the marketplace due to side effects
- Self injectable medications
  - Interferon Beta 1B (Betaseron/Extavia)
  - Interferon Beta 1A IM(Avonex)
  - Interferon Beta 1A SQ (Rebif)
  - Peginterferon (Plegridy)
  - Glatiramer Acetate (Copaxone/Glatopa/generic formulation)
  - Ofatumumab (Kesimpta)
- Oral medications
  - Terfludimide (Aubagio/generic formulation)
  - Fingolimod (Gilenya/generic formulation)/Siponimod (Mayzent)/Ozanimod (Zeposia)/Ponesimod (Ponvory)
  - Dimethyl Fumarate (Tecfidera/generic formulations)/Diroximel Fumarate (Vulmerity)/Monomethyl Fumarate (Bafiertam)
  - Cladrabine (Mavenclad)
- Infusion medications
  - Natalizamab (Tysabri)
  - Ocrelizamab (Ocrevus)/Ublituximab (Briumvi)
  - Alemtuzamab (Lemtrada)
  - Mitaxantrone (Novantrone)



Bierhansl, L, et al. Thinking outside the box: Non-canonical targets in Multiple Sclerosis. Nature Reviews Drug Discovery, June 2022; 21, 578-600

RRMS treatment: Different mechanistic approaches[1-6]



1. Weber MS, et al. *Neurotherapeutics*. 2007;4(4):647-653. 2. Aharoni R, et al. *Proc Natl Acad Sci U S A*. 2008;105(32):11358-11363. 3. Betaseron prescribing information. Bayer HealthCare Pharmaceuticals Inc. 4. Tysabri® prescribing information. Biogen Idec Inc. 5. Lopez-Diego RS, et al. *Nat Rev Drug Discovery*. 2008;7(11):909-920. 6. Giovannoni G, et al. *N Engl J Med*. 2010;362(5):416-426.

Disease Modifying Medications

- Self Injectable medications
  - Interferons (Betaseron, Avonex, Rebif, Plegridy)
    - MOA: Reduces antigen presentation and T-cell proliferation, alters cytokine and matrix metalloproteinase (MMP) expression, and restores suppressor function
    - Pros: 30-40% reduction in relapse rate, no new safety signals, multiple injection types and frequencies
    - Cons: Flu-like symptoms, injection reactions, depression, thyroid dysfunction, liver dysfunction
  - Glatiramer Acetate (Copaxone, Glatopa)
    - MOA: shifts the population of T cells from proinflammatory Th1 T-cells to regulatory Th2 T-cells that suppress the inflammatory response
    - Pros: 30% reduction in relapse rate, no new safety signals, variable dosing schedule, no flu-like reactions
    - Cons: Injection reactions, immediate post dose reactions
  - Ofatumumab (Kesimpta)
    - MOA: targets the CD20-positive B-cells protecting the nerve cells from mediated damage caused by CD20-positive B lymphoma cell lines
    - Pros: 50% efficacy, monthly self injection, also approved for active secondary progressive disease
    - Cons: injection reactions, immunosuppression, breast cancer and infections

Disease Modifying Medications

- Oral medications
  - Fingolimod/Siponimod/Ozanimod/Ponesimod
    - MOA: a sphingosine 1-phosphate receptor modulator binding with high affinity to sphingosine 1-phosphate receptors 1, 3, 4, and 5 blocking the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood
    - Pros: 50% reduction in relapse rate, no injections, once a day, Siponimod also tested in secondary progressive disease with a 20% reduction in the rate of disability
    - Cons: Pre and post dose monitoring for heart (newer formulations do not require this), eye and skin conditions,, infection risk including rare cases of PML,
  - Dimethyl Fumarate/Diroximel Fumarate/Monomethyl Fumarate
    - MOA: activates the Nrf2 transcriptional pathway resulting in intraneuronal synthesis of the antioxidant glutathione (GSH) mediated through the Nrf2; additional immunomodulatory actions for dimethyl fumarate mediated through nitric oxide, interleukins, tumor necrosis factor (TNF-α), or other cytokines.
    - Pros: 50% reduction in relapse rate, no injections, no significant monitoring needed
    - Cons: twice a day, GI upset, flushing, low lymphocyte count, rare cases of PML
  - Teriflunimide
    - MOA: inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis.
    - Pros: 30% reduction in relapse rate, no injections, once a day
    - Cons: Hair loss, liver function abnormalities, contraindicated in pregnancy

Disease Modifying Medications

- One additional oral medication
- Cladribine (Mavenclad): Study focused on relapsing remitting disease (impacts both T and B cells)
  - MOA: helps in the rapid reduction of natural killer cells with minimal impact on neutrophils, platelets and monocytes.
  - Pros: 50% reduction in relapse rate, yearly treatment cycles only, only two years of treatment
  - Cons: increased infection risk, questionable cancer risk

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Disease Modifying Medications

- Infusions
  - Natalizumab (Tysabri)
    - MOA: reduce the transmission of immune cells into the central nervous system by interfering with the α4β1-integrin receptor molecules on the surfaces of cells expressing the VCAM-1 gene
    - Pros: 67% reduction in relapses, once a month, well tolerated
    - Cons: PML, JCV testing every six months, can't take immunosuppressants
  - Alemtuzumab (Lemtrada)
    - MOA: targets CD52, a protein abundant on T and B cells which depletes circulating T and B lymphocytes after each treatment course
    - Pros: 49-55% efficacy, Once a year dosing, only two years of required treatment, slowed disability
    - Cons:infusion reactions, thyroid, platelet and kidney dysfunction, prolonged immunosuppression, infections
  - Ocrelizumab (Ocrevus)/Ublituximab (Briumvi)
    - MOA: targets the CD20-positive B-cells protecting the nerve cells from mediated damage caused by CD20-positive B lymphoma cell lines
    - Pros: 54% efficacy, twice a year dosing, also improved for primary progressive disease
    - Cons: infusion reactions, immunosuppression, breast cancer (?) and infections
  - Mitaxantrone (Novantrone)
    - MOA: intercalation with the DNA molecule potently inhibiting proliferation of B and T lymphocytes as well as macrophages.
    - Pros: Slows disability, once every three months treatments
    - Cons: Maximum of 2 years of treatment due to cardiomyopathy

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How to chose the right treatment

- Individualized management
  - Consideration of prognostic factors
  - Consideration of personal patient concerns
- Prognostic Factors (for a poor prognosis)
  - Male gender
  - African heritage
  - Older age of onset
  - Motor symptoms or ataxia at onset
  - Incomplete recovery from relapses
  - Frequent relapses (2 or more in 2 years)
  - Brainstem or spinal cord lesions at onset
- Patient Concerns
  - Safety
  - Pregnancy plans
  - Lifestyle

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Other factors found to predict prognosis

- Presenting initially with optic neuritis instead of other symptoms has a better longterm outcome.
- Having OCB in the spinal fluid had a medium impact on prognosis
- Having more than 10 lesions on MRI at presentation increased the risk of progression in disability by 3 fold.
- Starting DMTs early reduced the risk developing CDMS or progressing

Tintore, M et al. Defining high, medium and low impact prognostic factors for developing MS. Brain. 2015; 138 : 1863-1874

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Induction vs Escalation Therapy

- Definition
  - Escalation Therapy: Starting with the lowest efficacy but best safety profile medications and changing to a higher efficacy medication only with evidence of breakthrough disease
  - Induction therapy (now called immune reconstitution therapy): Starting with a high efficacy medication from the start to induce remission and prevent breakthrough disease and the need for a new therapy
- Rationale for escalation therapy
  - No good unbiased head to head studies to prove differences in efficacy
  - Many patients do well on their first medication so why risk safety
- Rationale for induction therapy
  - Relapses and new MRI changes are greatest at the onset of MS when patients are youngest
  - Failure rates and intolerance of the older injectables are high enough that many patients will transition to a more tolerable and efficacious product anyway.

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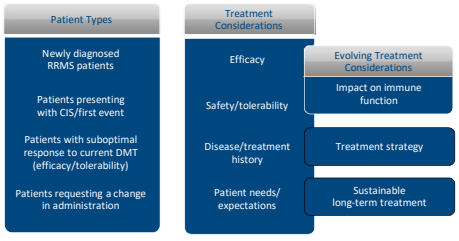
Matching patients and treatment: Changing considerations



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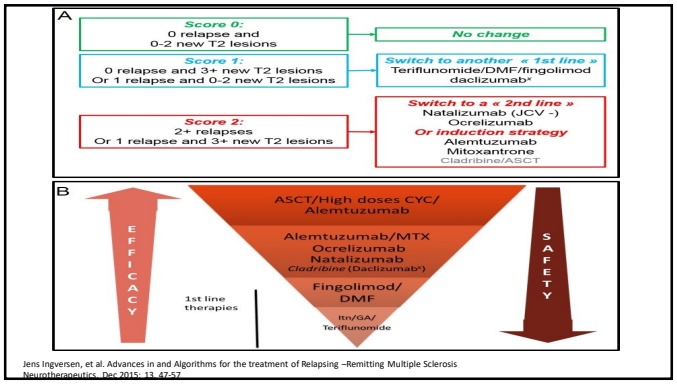

Jens Ingversen, et al. Advances in and Algorithms for the treatment of Relapsing –Remitting Multiple Sclerosis Neurotherapeutics. Dec 2015; 13, 47-57

New targets in trials

- BTK inhibitors
- CD40/CD40L inhibitors.
- Stem Cells.
- Nutritional and repurposed medications.

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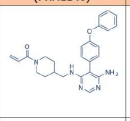
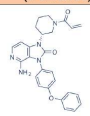
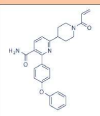
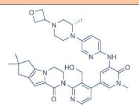
Burton Tyrosine Kinase Inhibitors (BTKi)

- BTK is implicated in peripheral and central inflammation in MS
  - Therapeutic target
- Cytoplasmic tyrosine kinase
  - Phosphorylates tyrosine from ATP
- Signal transducer of B cell receptors, chemokines, cytokines, Fc receptors (not T cells)
  - Antigen binding to BCR leads to BTK activation and leads to B cell proliferation, maturation, differentiation, cytokine expression

TABLE. COMPARISON OF BRUTON TYROSINE KINASE INHIBITOR PHARMACOLOGY

	Evobrutininb (M-251) (PRN2246)	Tolebrutinib (SAR442168)	Orelabrutinib (ICP-022)	Fenebrutinib (GDC-0853)
Structure				
Molecular weight	429.51[24]	455.51[24]	427.9[25]	664.80[24]
Chemical bond with BTK10	Covalent, irreversible	Covalent, irreversible	Covalent, irreversible	Noncovalent, reversible
Inhibition site	Kinase domain C481 residue	Kinase domain C481 residue	Kinase domain C481 residue	SH2 domain K430 residue, kinase domain M 477 and D539 residues
IC50 (nM)[a]	37.97	0.4-0.79	1.6	2.37
Inhibition of other tyrosine kinases	Minimal, targets BTK selectively[7]	Binds 12 of 250 tyrosine kinases at 1 mcMol[9]	Best selectivity, BTK only; > 90% inhibition[25]	Targets 2 of 286 kinases[7]

Abbreviations: BTK, Bruton tyrosine kinase; BTKI, BTK inhibitor; IC50, half-maximal concentration. [a]The IC50 for the BTKIs of interest vary depending on the type of used cells to determine the inhibition constant; however different papers report comparable values.

Bruton Tyrosine Kinase Inhibition in Multiple Sclerosis
Practical neurology, Feb 2022

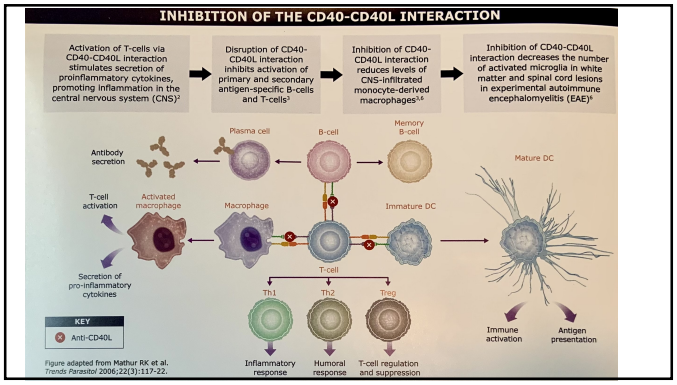
Mechanism of Action

- Preclinical studies showed benefit in EAE models
  - Decreased T-cell proliferation, inhibitions of BCR mediated B-cell activation and production of proinflammatory cytokines (interferon γ), reduce B-cell antigen presentation, inhibit BTK activity in microglia
  - Decreased B-lymphocyte maturation and differentiation in lymph nodes without affecting number
    - Less B-cell immunodeficiency
  - Promote Remyelination?
  - Decreased disease severity in a dose-dependent manner

Bruton Tyrosine Kinase Inhibition in Multiple Sclerosis
Practical neurology, Feb 2022

CD40/CD40L

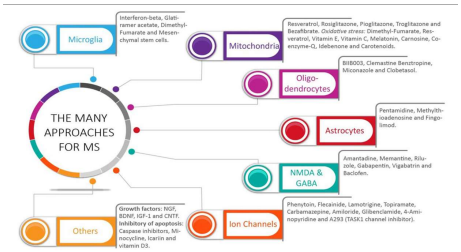
- Inhibits CD40/CD40L costimulatory signaling pathway impacting both innate and adaptive immunity.
  - Innate immune cells work as the bodies first line defense.
  - Adaptive immune cells are activated cells that recognize specific pathogens.
- Previous trials have been stopped due to blood clots/thromboembolic events.
- May impact progression as well as inflammation.
- Phase two studies show a significant reduction in Gad-enhancing and T2 lesions



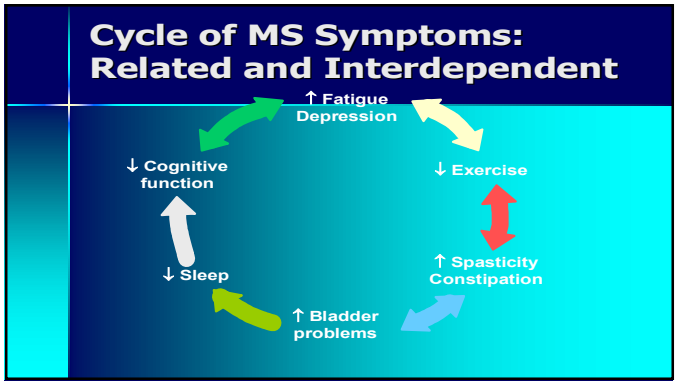
Stem cell therapy in MS

- Designed to reset the immune system to stop it from attacking the CNS
- May allow for for remyelination
- Requires immune suppression before stem cell transplantation raising the question of whether the immune suppression or stem cells are really causing the remission.
- 66% of those who underwent stem cell therapy had no activity 5 years later.
- Still considered experimental treatment.

Other Targets



LoPresti, P. Silent Free Fall at Disease Onset: A perspective on therapeutics for Progressive Multiple Sclerosis. Frontiers in Neurology, Nov 2018



Conclusions

- There are multiple mechanisms to control MS
- Decisions on treatment needs to consider prognostic factors and patient preference.
- Debate continues on whether escalation therapy or induction therapy provides the best initial treatment choice.
- New options for management undergoing study include BTK inhibitors, CD40/CD40L modulators, stem cells and even repurposed medications