Management of Relapsing-Remitting MS in a Changing Therapeutic Landscape

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Disclosures

Dr. Cameron has consulted for Adamas Pharmaceuticals and Greenwich Biosciences

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Learning Objectives

- Summarize the new therapies available for patients with RRMS and the therapies under investigation
- Select the most appropriate therapy for patients with RRMS
- Outline a patient-centered plan by collaborating with patients with RRMS
- Identify patients who will benefit from an initially more aggressive therapy

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Outline

Clinical case

MS background

History of MS Disease Modifying Therapies – The "Old" DMTs, the "Newer" DMTs

Where we are today – The "Newest" DMTs

How to choose a DMT *with* our patients with RRMS

Who is likely to benefit from an initially more aggressive therapy?

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Clinical Case

Date of visit: 8/2/20

CC/ID: 25 yo male presents with recent episode of diplopia concerning for MS

HPI: Diplopia onset 6/8/20, worst looking down and to the right, now almost fully resolved. MRI brain showed ~ 1 dozen T2 hyperintense lesions, supra and infratentorial, 2 enhancing.

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History

About 1 month of right facial numbness in 2019

About 1 month of bilateral hand numbness in 2017

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Exam

WNL except for bilateral brachioradialis hyperreflexia

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Diagnosis of MS

Clinical history

MRI brain

Other supportive testing

- MRI spine
- CSF
- VEEP

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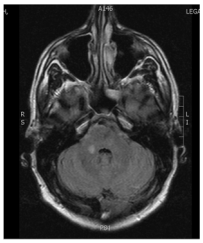
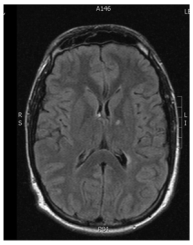
MRI brain 6/10/10

FLAIR (fluid attenuation inversion recovery)





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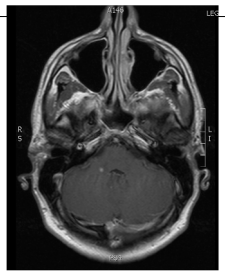
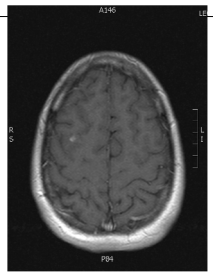
MRI brain 6/10/10: T1 contrast

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MS

Multiple scars in the CNS, optic nerves

Neurological symptoms separated in time and space

No better explanation

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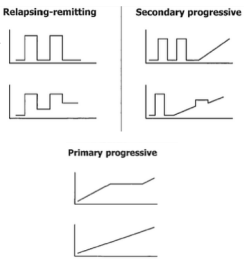
Course of MS

Types of MS

- Relapsing remitting (~85% at onset)
- Secondary progressive (~50% of RRMS at 10-15 years from onset)
- Primary progressive (~ 15% at onset)



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Who gets MS

F>M, 2-4:1

Young adult onset, lifelong disease

Beyond the 40° latitude (Portland is 45°)

Genetic predisposition

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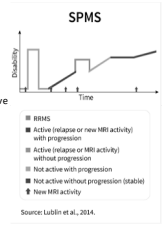
Treatment/Management

Disease modifying therapies (>20)

- Reduce relapse rate
- Slow accumulation of disability
- Approved for relapsing forms of MS
  - Clinically isolated syndrome,
  - Relapsing-remitting disease,
  - Active (with relapses or new MRI activity) secondary progressive
- NONE approved for *inactive* secondary progressive MS
- 1 approved for PPMS (Ocrelizumab)

Relapse management – high dose steroids

Symptom management



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DMT history, the "old" DMTs – pre 2010

DMT	Approval	Likely MOA	Route	Considerations
Interferon Beta	1993 - 2014	Reduced T cell activation/proliferation, secretion of MMPs, expression of HLA, inhibit IFN gamma	Injection	Leukocytopenia, increased LFTs, flu-like symtoms, ? Depression, modest efficacy ~↓ ARR ~30%
Glatiramer Acetate	1996 - 2014	Th1 to Th2 shift; block MHC peptide antigen	Injection	Injection site lipoatrophy, high safety and tolerability, modest efficacy ~ ↓ ARR ~ 25% **3 generics now available** (2015, 2017, 2018)
Natalizumab	2004	Binds Alpha-4 integrin on immune cells preventing interaction with vascular endothelium and transmigration to CNS	Infusion	PML (~ 1/250), high efficacy ~ ↓ ARR 60-70%

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DMT history, the "middle" DMTs –2010 - 2015

DMT	Approval	Likely MOA	Route	Considerations
Fingolimod (Gilenya®)	2010	Sphingosine 1-phosphate receptor modulator; prevents activated lymphocyte egress from secondary lymphoid organs to circulation	Oral	First dose bradycardia. HTN, macular edema, increased LFTs, lymphopenia, ocular melanoma (PML total ~ 15), fairly high efficacy ~↓ARR 50%
Teriflunomide (Aubagio ®)	2012	Inhibits dihydro-orotate dehydrogenase; decreases proliferation of activated immune cells	Oral	Hair loss, teratogenicity (men and women), "category X", screen for TB, modest efficacy ~↓ARR ~25%
Dimethyl fumarate (Tecfidera ®)	2013	Th1 to Th2 shift; activates NrF2 transcription	Oral	Early GI sx, flushing, lymphopenia (PML total ~ 10 with MS), fairly high efficacy ~↓ARR 50%
Alemtuzumab (Lemtrada®)	2014	Antibody-dependent cell-mediated lysis following binding of drug to CD52 antigen present on immune cells	Infusion	Infusion reactions, autoimmune thyroid disease in ~ 25%, ITP in ~1-3%, Goodpasture's syndrome in ~1%, high efficacy ~↓ARR 70%

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The "new" DMTs – approved 2015-2019

DMT	Approval	Likely MOA	Route	Considerations
~~Daclizumab~~	~~2016~~	~~Targets CD25, prevents T cell activation~~	~~Injection~~	~~Withdrawn 2018~~
Ocrelizumab (Ocrevus®)	2017	Anti-CD20, targets B cells	Infusion	IV Q6 months, approved for PPMS, high efficacy ~↓ARR 70%
Cladribine (Mavenclad®)	2019	Interfere with DNA synthesis and repair in B and T cells	Oral	Short course 1x/year, lymphopenia,infection, incr LFTs, black box warning for malignancy, fairly high efficacy ~↓ARR 50%
Siponimod (Mayzent®)	2019	Sphingosine 1-phosphate receptor modulator	Oral	Genotype sequencing CYP2C9 for dosing, titration but no first dose observation
Diroximel fumarate (Vumerity®)	2019	Th1 to Th2 shift; activates NrF2 transcription	Oral	Bioequivalent to DMF but with less GI side effects, $88k

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The "newest" DMTs – approved so far in 2020

DMT	Approval	Likely MOA	Route	Considerations
Monomethyl fumarate (Bafiertam®)	2020	Th1 to Th2 shift; activates NrF2 transcription	Oral	Active metabolite of dimethyl and diroximel fumarate
Ozanimod (Zeposia®)	2020	Sphingosine 1-phosphate receptor modulator	Oral	Interaction w/ foods w/ high tyramine and MOAI (SSRI, SNRI), titration but no first dose observation or genetic testing
Ofatumumab (Kesimpta®)	2020	Anti-CD20, targets B cells	Injection	SQ, monthly at home, fairly high efficacy ~↓ARR 50%

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Soon to come?

SQ rituximab for MS

S1PR modulators – Ponesimod, Amiselimod

Lipoic acid

Tyrosine kinase inhibitors – Evobrutinib, Masitinib

Stem cell therapy (HSCT) (BEAT MS)

Discontinuation trial ongoing (DISCO MS)

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Choosing a DMT *with* our patients with RRMS

By route of administration
- Injectable
- Oral
- IV

By "benefit"

By "risk"

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Route of administration: Impacts adherence and monitoring

Injectable
- Rarely the patient's preferred route
- Have a long history of safety that may be preferred
- No reason to change legacy patients who are doing well
- Glatiramer probably has the best pregnancy safety

Oral
- The easiest
- But there are often challenges with adherence, adherence monitoring and safety monitoring
- A misperception that easy = safe

Infusion/IV
- Adds another cost
- Takes coordination
- Travel considerations
- Easy to monitor adherence and check labs with infusions

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Benefit – high efficacy vs low efficacy

Range from ~ 25% to 70%+ ↓ ARR

What does your patient need?

What does your patient want?

At what risk?

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Risk – high risk vs low risk

Probability – range of PML risk with tysabri and others

Severity – Herpes zoster vs PML vs malignancy

Timing – early flu-like side effects with IFNs, early GI sx with DMF vs long term PML risk with natalizumab

Risk vs tolerability – PML, malignancy, infection Vs. GI sx, flushing

Prevention/risk reduction

- e.g. JCV Ab testing for PML, Hepatitis B testing before ocrelizumab, CBC with diff and LFT monitoring

Treatable?

- e.g. thyroid dysfunction, herpes zoster, malignancy, PML, UTI, URI

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What about the cost?

1993 - ~$10k/year

2004 average price $16k/year

2013 average price $61k/year

2017 average price $83k/year (even generics are > $60k/year)

2019 median price $88k/year

2020 …

40% of people with MS alter or stop taking medications due to high cost (NMSS)

11% could easily afford the cost of their medication without financial assistance

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Who is likely to benefit from an initially more aggressive therapy?

Early predictors of more aggressive disease

At diagnosis
- Bowel and bladder symptoms at disease onset
- Male sex
- Older age at onset
- More lesions, more Gd+ lesions

Over the first few years
- Persistent disease activity on less aggressive therapy
- Higher relapse rate
- Poorer recovery from relapses
- Gd enhancing lesions
- New T2 lesions

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Conclusions

These are exciting times in MS care
- 20+ DMTs and more all the time

These are complex times in MS care
- 20+ DMTs and more all the time
- Different benefits and risks
- "Me too" drugs
- Cost

Decision whether to take a DMT, and if so which DMT, are made collaboratively and evolve over time

The future is bright

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Thank You

Q & A

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