Update on New MS Therapeutics

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AAN August 2017 Meeting

MULTIPLE SCLEROSIS CENTER

Disclosures

Clinical Trial Involvement:

- SPRINT-MS Trial – MediciNova, ibudilast
- LemCog – Sanofi/Genzyme, alemtuzumab
- N-MOmentum – AstraZeneca, MEDI-551

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Objectives – Update on New MS Therapeutics

- Briefly review DMDs approved prior to 2014
- Discuss MS DMDs approved since 2013
- Therapies on the horizon
- Present treatment choice guiding principles

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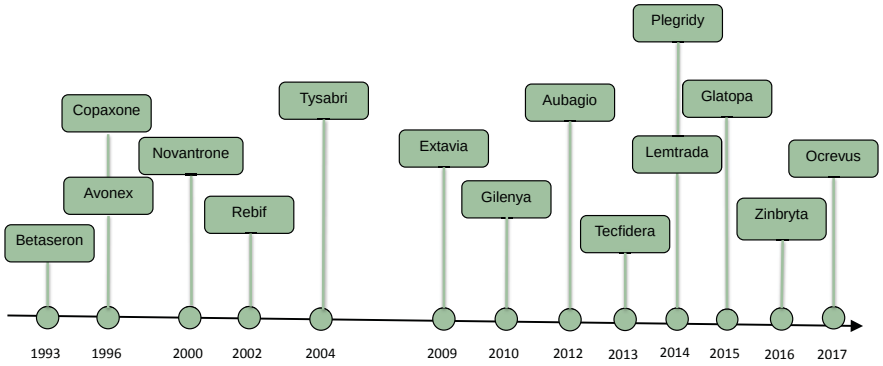
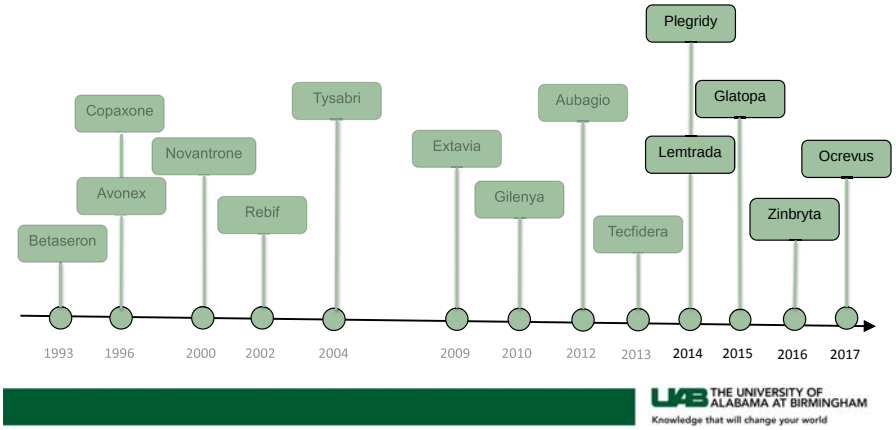
Ever-expanding landscape



Ever-expanding landscape



Not New MS Therapeutics

DMDs 1993-2002

	↓ARR	Indication (s)	Monitoring	Common Side Effects	Advantages
IFN-1b (Betaseron)	34%	RRMS, CIS	CBC, LFT, TFT	Flu-like symptoms (FLS), injections site reactions (ISR), transaminitis	Long-term safety
IFN-1a IM (Avonex)	32%	RRMS, CIS	CBC, LFT, TFT	FLS, ISR, transaminitis	Weekly dosing, long-term safety
glatiramer acetate (Copaxone)	30%	RRMS, CIS	None	ISR, systemic reaction	No monitoring, long-term safety
mitoxantrone (Novantrone)	63%	RPMS, SPMS	CBC, LFT, hCG, TTE	Cardiomyopathy/CHF, myelosuppression, secondary leukemia	Only approved med for SPMS
IFN-1a SC (Rebif)	32%	RRMS	CBC, LFT, TFT	FLS,ISR, transaminitis	Lower rates of FLS, Long-term safety

Respective FDA PIs. Modified.

DMDs 2006-2013

(all RRMS)

	↓ARR	Monitoring	Side Effects	Advantages
natalizumab (Tysabri)	67%	MRI, LFT, CBC	PML, fatigue, infusion reactions	High efficacy, early effectiveness, monthly dosing
fingolimod (Gilenya)	55%	HR, BP, CBC, LFT, ECG, Ophtho, VZV IgG	Initial bradycardia, macular edema, skin malignancy, lymphopenia, de novo HTN	High efficacy, early effectiveness, oral
teriflunomide (Aubagio)	32%	hCG,CBC, LFT,PPD,BP	GI symptoms, hair thinning, transaminitis, Category X in pregnancy (women AND men)	Oral, daily dosing, disability data
dimethyl fumarate (Tecfidera)	53%	CBC	Flushing, GI symptoms, leukopenia	High efficacy, oral

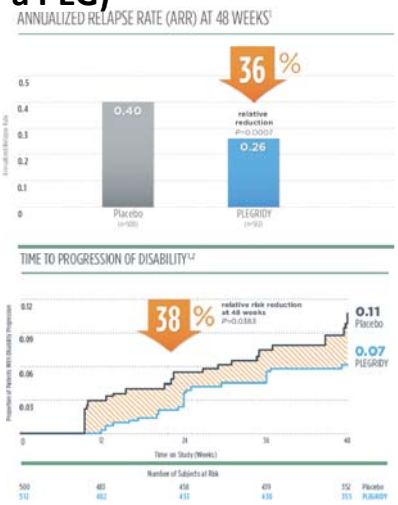
Respective FDA PIs. Modified.

Newer

- Plegridy
- Lemtrada
- Glatopa
- Zinbryta
- Ocrevus

Plegridy (interferon beta 1-a PEG)

- Pegylated to extend ½ life
- Dosed every 14 days
- Common adverse events:
  - ISR – 66% v 11%
  - FLS – 47%
  - Decreased blood counts



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ADVANCE Trial data

Newer

- Plegridy
- Lemtrada
- Glatopa
- Zinbryta
- Ocrevus

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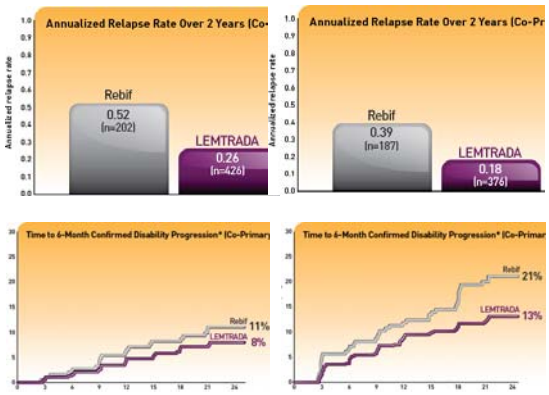
Lemtrada (alemtuzumab)

- CD52 mAb
  - B and T lymphs
- 5 days year one, 3 days year two
- Pretreatment, monitoring



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CARE-MS I, CARE-MS II Trial data

Lemtrada (alemtuzumab)

- Common AEs:
  - Infusion reactions (92%)
  - Thyroid disorders (34%)
  - Rash (53%)
  - Headache (52%)
  - Pyrexia (29%)
  - Nausea (21%)
- Serious AEs:
  - Infusion reactions (3%)
  - ITP (2%)
  - Neoplasms (1%)
    - Thyroid cancer (0.3%)
    - Melanoma (~0.3%)
    - Lymphoproliferative Dz
  - Nephropathies (0.3%)

CARE-MS I, CARE-MS II Trial data

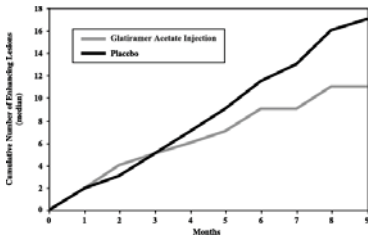
Newer

- Plegridy
- Lemtrada
- Glatopa
- Zinbryta
- Ocrevus

Glatopa (glatiramer acetate)

- First 'generic' DMD
- 20mg GA subQ daily
- AEs:
  - ISR, SOB, palpitations, vasodilation
- ANDA

	GA 20mg QD	Placebo	P-value
Mean Relapses	1.19/2yrs	1.68/2yrs	0.055
% Relapse Free	34%	27%	0.25



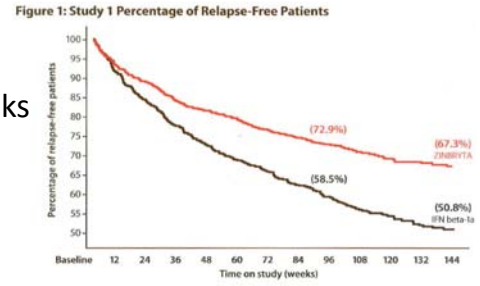
Zinbryta FDA PI

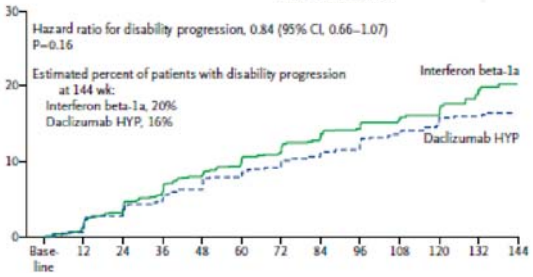
Newer

- Plegridy
- Lemtrada
- Glatopa
- Zinbryta
- Ocrevus

Zinbryta (daclizumab)

- SubQ injection Q4 weeks
- Binds CD25, alters IL-2
- Reduces T cell responsiveness





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Zinbryta (daclizumab)

- Adverse Events:
  - Skin reactions: 37% v 19% (Av)
  - Infections: 67% v 57% (Av)
  - Lymphadenopathy: 6%
  - Immune disorders: 32% vs 12% (Av)
  - Depression: 10%
- Serious AEs:
  - Hepatitis: 0.7%
  - Serious skin reactions: 2%

Hepatic Reaction	IFN-Beta 1a (IM)	daclizumab
ALT/AST >3x ULN	9%	10%
ALT/AST >5x ULN	3%	6%
ALT/AST >3xULN and Bili >2x ULN	0.1%	1%

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Newer

- Plegridy
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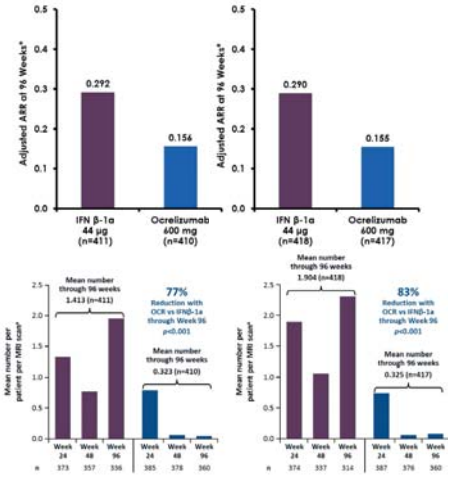
Ocrevus (ocrelizumab)

- Approved for RMS (and PMS)
- Infusion day 1, day 15, then once Q6 months

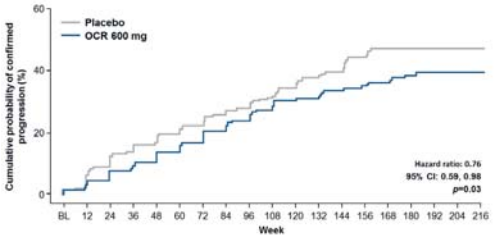


NEDA	Opera I	Opera II
Rebif	29%	25%
Ocrelizumab	48%	48%

OPERA I, OPERA II Trial data. NEDA = No Evidence of Disease Activity

Ocrevus (ocrelizumab)

- PMS data
- Infusion day 1, day 15, then once Q6 months



	Placebo	Ocrevus	P-value
Disability Progression @ 12 weeks	39.3%	32.9%	0.03
HR vs Placebo in Gd+	NA	0.65	NA
HR vs Placebo in Gd-	NA	0.84	NA

ORATORIO Trial HR = Hazard Ratio

Ocrevus (ocrelizumab)

- Any AEs (v Rebif):
  - Overall: 83% v 83%
  - Infusion reactions (34% v 10%)
  - Infections (59% v 53%)
  - Herpes infections (3% v 2.2%)
- Serious AEs:
  - Serious infections
    - 3% v 1%
  - IRRs
    - 2% on 1st infusion
    - <1% on subsequent
    - 1 life threatening
  - Malignancies:
    - 4/1000 patient years vs 2/1000 patient years
    - Breast and skin

OPERA I & II Trial Data

Treatments on the horizon

- Ponesimod – S1P1 inhibitor
- Ofatumumab – CD20 mAb
- Stem Cell

How to choose DMDs?

How to choose DMDs?

- Typical MS patients
- MS patients with little to no disability
- Patient preference

- Patients with significant disability
- Patients at risk for aggressive disease:
  - Older age of onset
  - Male sex
  - Incomplete recovery
  - High relapse frequency
  - African American race
  - Spinal cord disease
  - Severe relapses

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Please feel free to reach out!

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