MULTIPLE SCLEROSIS DISEASE MODIFYING THERAPY

Drug	Indic	Dose	Effect	Side effects	Monitoring
Self Injectables					
IFB 1A Avonex 1996	RRMS	30mic IM weekly	Modulates T-cell and B-cell	Flu-like symptoms, headaches	HGB, WBC, LFTs
IFB 1A Rebif 1998	RRMS	44mic SQ MWF	function. Down regulates	Leukopenia, anemia, depression, suicide	TSH/Free T4
IFB 1A Plegridy 2014	RRMS	125mic SQ q2w	inflammatory cytokines and T-cells	Hepatotoxicity, Thyroid dysfunction Injection site necrosis with SQ inj	Risk for Depression
IFB 1B Betaseron, Extavia, 2009	RRMS	250mic SQ EOD	↓Relapses = 30% ↓CIS to CDMS = 50%	Neutralizing antibodies, Pregnancy Class: C **Washout 1 month**	
Glatiramer acetate Copaxone 1997 Glatopa 2015	RRMS	20mg SQ daily or 40mg SQ MWF		Injection site pain & lipoatrophy Post-injection reactions: (chest/neck tightness tachycardia, diaphoresis, dyspnea, anxiety) **No Washout needed**	
Daclizumab Zinbryta, 2016 *Withdrawn in 2017*	RRMS	150mg SC monthly	CD25 blocker (IL-2 receptor)	**Withdrawn from market after patients developed fulminant hepatitis**	.
Oral					
Fingolimod Gilenya, 2010	RRMS	0.5 mg daily	**Sphingosine-1-phosphate receptor modulator**. Peripheral T-cell sequestration in lymph nodes ↓Relapses = 54% ↓EDSS = 30% ↓MRI = 74% (T2), 82% (Gd)	**Bradyarrhythmia, AV block** **Macular edema - PRES** Pulmonary function worsening Lymphopenia & PML - Transaminitis Varicella meningoencephalitis Malignancy risk Pregnancy Class: C **Washout 2 month** (t1/2 is one week)	**Pre-screen**: CBC, EKG, LFT, VZV IgG (vaccinate if negative) 1st dose monitoring (can be done at home). **Then**: CBC/LFT's q6m, fundus at 6m Beware of PML & malignancy
Siponimod Mayzent, 2018	RRMS SPMS	2 mg daily (requires titration)	**Sphingosine-1-phosphate receptor modulator**, specific to subtype 1&5, sparing subtype 3 (less cardiac side effects). **In active SPMS:**	**Bradyarrhythmia, AV block** **Macular edema in 1.8%** Pulmonary function worsening Lymphopenia & PML - Transaminitis Malignancy risk Pregnancy Class: C	**Pre-screen:** CYP2C9 testing (don't use in patients with CYP2C9 3/3) CBC, EKG, LFT, VZV IgG (vaccinate if negative) Ophthalmic fundus screening

			↓Relapses = 55% (ARR) ↓Disability progression = 21% ↓EDSS = 30% ↓MRI = 79% (T2)	**Washout:** not determined yet (t1/2 is 56h)	1st dose monitoring only for patients with bradycardia, heart block, HF or hx of MI) **Then**: CBC/LFT's q6m, fundus at 6m Beware of PML & malignanci
Teriflunomide Aubagio, 2012	RRMS	14 mg daily	Depletes pyrimidine pool Disrupts T cell interaction with APC. ↓Relapses = 31%, ↓EDSS = 30% ↓MRI = 67% (T2), 80% (Gd)	Alopecia, Hepatotoxic **Pregnancy Class: X** (Men = Women) **Washout needed till undetectable** (Oral cholestyramine or activated charcoal)	**Pre-screen:** LFT's, Pregnancy test **Then:** LFT's q6 months, HTN
Dimethyl fumarate Tecfidera, 2013	CIS RRMS SPMS	120 mg BID x 7d then 240 mg BID	Activates Nuclear related factor-like 2 (Nrf2) pathways which promotes production of anti-oxidants. Shifts Th1 to Th2 pathway. ↓Relapses = 53%, ↓EDSS = 38% ↓MRI = 85% (T2), 90% (Gd)	**Flushing** in 40% (give ASA) **GI upset** in 15% (give with Fatty foods) Transaminitis **Lymphopenia** (30% reduction), **PML** (if lymphocytic count < 500) Pregnancy Class: C - **Washout 1 months**	**Pre-screen**: CBC (lymphs > 1000), LFT **Then**: CBC q6 months, beware PML more likely if lymph < 500
Diroximel fumarate Vumerity 2019	CIS RRMS SPMS	231 mg BID x 7d then 462 mg BID	Same active metabolite as dimethyl fumarate but less GI side effects.	**Flushing** in 40% (give ASA) **GI upset** – less than reported with Tecfidera Transaminitis **Lymphopenia** (30% reduction), **PML** (if lymphocytic count < 500) Pregnancy Class: C - **Washout 1 months**	**Pre-screen**: CBC (lymphs > 1000), LFT **Then**: CBC q6 months, beware PML more likely if lymph < 500
Caldribine Mavenclad, 2019	RRMS who failed other drugs	4 cycles, 4 days each at 0, 23,43, 23 week intervals (total cumulative dose 3.5mg/kg)	Purine antimetabolite, depletes B & T lymphocytes. ↓Relapses = 58%, ↓EDSS = 33% 2-year relapse free: 83% vs 63% ↓MRI = 0 lesions	Headache, URI Lymphopenia (if dropped < 200, give prophylactic acyclovir for HSV prevention) Liver injury **Malignancy**	**Pre-screen:** CBC, LFT, HIV, TB, hepatitis panel, VZV IgG (vaccinate if negative) & Cancer screening. **Then:** cancer screening, CBC

IV infusions:					
Mitoxantrone Novantrone, 2000	SPMS (off label)	12 mg/m2 IV q3 months x2 yrs Max dose: 140 mg/m2	**T-cell killer** ↓Relapses = 67%	**Cardiotoxicity, Leukemia** GI upset, Urine color changes, Bladder infections Pregnancy Class: D **Washout 6 months**	**Pre-screen**: CBC, Echo **Before infusion**: CBC, Echo **Post-dose**: Echo annually for life
Natalizumab Tysabri, 2006 *Through MS TOUCH program*	RRMS	300 mg infusion q4w over 1 hour Max dose: 3 yrs	**Integrin Rc antagonist** Prevents CNS lymphocyte migration through the blood brain barrier (Inhibits binging of ICAM to VCAM) ↓Relapses = 68%, ↓EDSS = 42% ↓MRI = 83% (T2), 92% (Gd)	Infusion reactions: (headache 38%, fatigue 27%, erythema, nausea, dizziness) Hypersensitivity, fatigue, UTI's, pharyngitis **PML,** Neutralizing Ab's Increase number of circulating lymphocytes **Washout 3 months**	**Pre-screen:** Serum JCV Ab w/Index **On-dose**: PML screening, serum JCV Ab every 6m
Alemtuzumab Lemtrada, 2014 *Available only through Lemtrada REMS Program*	RRMS who failed 2 drugs	12 mg IV over 4h daily for 5 days then for 3 days 1 year later. Give steroids with 1st 3 infusions	**Binds to and destroys CD52 cells (**T cells, NK cells, monocytes) Compared with IFN ↓Relapses = 55%, ↓EDSS = 30% Relapse free in 2 years: 78%	Infusion reactions: (headache, flushing) **Autoimmune disorders:** (↓ Platelets in 2%, thyroid dysfunction 34%, anti-glomerular basement membrane disease 0.3%, hemolysis) **Cancer:** Thyroid, melanoma 0.3%, lymphoma **Infection: HSV/VZV** 16% Pregnancy Class: C - **Washout 3 months**	**Acyclovir** ppx (for 2 months or till CD4+ count > 200 whichever longer) **Labs:** CBC, CK, UA q1m TSH q3m (up to 2 years after last infusion) Skin exam yearly
Ocrelizumab Ocrevus, 2017	RRMS PPMS	300mg IV x2 – 2 weeks apart then 600mg IV q6m **Pre-medicate:** steroids and antihistamines	**CD20 blocker** (similar to Rituximab) Depletes B cells via antibody-dependent cell-mediated toxicity and complement-dependent cytotoxicity. Compared to rituximab, induces more ADCC and less CDC, which could reduce infusion-related toxicity	Infusion reactions (in 34%, serious reactions in 0.3%) Breast Cancer (0.7%), URTI	**Pre-Screen**: HBV **On dose**: Observe patient for 1h after infusion (allergy). - Delay infusion if active infectior - Contraindicated in active HBV - No live vaccines while on ttt

How to choose DMT:

1- According to type of MS:

RRMS /SPMS	**First line**: Interferons, glatiramer, fingolimod, siponimod, teriflunomide, dimethyl fumarate, diroximel fumarate natalizumab, ocrelizumab **Second line**: alemtuzumab, cladribine
PPMS	Ocrelizumab

2- According to pregnancy category:

Class B	Glatiramer acetate
Class C	Interferons, fingolimod, siponimod, dimethyl fumarate, natalizumab, alemtuzumab
Class D	Mitoxantrone
Class X	Teriflunomide
Not categorized	Ocrelizumab – Daclizumab

3- According to form of administration:

Oral	fingolimod, siponimod, dimethyl fumarate, diroximel fumarate, teriflunomide
IM	Interferon B1a
SC	Interferon, glatiramer acetate
Infusion	Alemtuzumab, ocrelizumab, natalizumab

4- According to side effect profile:

DMT	Limiting side effects
Interferons	Depression, hepatotoxicity, injection reaction
Fingolimod Siponimod	Bradycardia, AV block, macular edema, ↓ WBCs
Teriflunomide	Alopecia, hepatotoxicity, teratogenicity
Fumarates	GI upset, flushing (less with diroximel fumarate)
Natalizumab	PML risk
Alemtuzumab	Immune disorders, cancer, HSV/VZV infection
Ocrelizumab	Infusion related reaction
Daclizumab	Hepatotoxicity

5- According to screening measures needed:

DMT	Pre-screening	Follow up labs
Interferons	CBC, LFTs, TSH	CBC, LFTs, TSH Q6 months
Glatiramer	None	None
Fingolimod Siponimod	ECG, CBC, VZV, LFT	CBC & LFT Q6 months
Teriflunomide	HCG, LFT	LFT, BP Q6 months
Fumarates	CBC	CBC Q6 months
Natalizumab	JC Ab titer	JC titer Q6 months
Alemtuzumab	CBC, CK, TSH	CBC, CK, UA q1m, TSH q3m
Ocrelizumab	CBC, HCG, HBV	HCG, HBV, CD19 Q6 months

Tysabri:

Factors that increase risk of PML with natalizumab (Tysabri)

1- **Treatment duration, if duration > 2 years and:**
   a. JCV Ab negative → risk is < 1/1000
   b. JCV Ab positive:
      i. 1-24 months → risk is <1/1000
      ii. 25-48 months → risk is 3/1000
      iii. 49-72 months → risk is 6/1000
   c. Seroconversion rate is 3-6% annually
2- **Prior treatment with immunosuppressants (MTX, cyclophosphamide)**
3- **JCV antibody index:**

Antibody index	1-24 months	25-48 months	49-72 months
<= 0.9	1/10,000	3/10,000	4/10,000
<= 1.1	1/10,000	7/10,000	7/10,000
<= 1.3	1/10,000	1/1,000	1.2/1,000
<= 1.5	1/10,000	1.2/1,000	1.3/1,000
> 1.5	1/1,000	8.1/1,000	8.5/1,000

Fingolimod:

A non-specific sphingosine-1 phosphate modulator that works on both subtypes 1 & 3. Subtype 1 reduces lymphocyte recirculation from the lymph nodes. Subtype 3 reduces heart rate and prolongs the PR interval. Cardiac effects of fingolimod are maximal after the first dose but persist for about 14 days after initiation of treatment.

Siponimod (FDA approved), Ozanimod and Ponesimod (phase II trials) are SP-1p specific subtype 1 modulator that lack the cardiac side effects.

Tecfidera:

- Dimethyl fumarate has long been used for psoriasis and when psoriasis patients who had MS reported improvement of their MS symptoms, a clinical study was done and did reveal efficacy for RRMS.
- Diroximel fumarate and dimethyl fumarate are both prodrugs with active molecule of monomethyl fumarate (MMF). Diroximel did show better GI tolerability the the dimethyl salt.