Developing DMTs

Phase III trials:

Drug	Indication	Rout	MOA	Adverse React.	Trials
Ozanimod *NIH, licensed to Receptos*	RRMS	Oral	Selective sphingosine-1 Rc agonist modulator **(similar to fingolimod but specific to S-1P1 & S-1p5 and spares S-1p3 so spares the heart)** Better selectivity, penetration and clearance than fingolimod	No serious side effects. No macular edema Mainly headache and pharyngitis	**RADIANCE**: reduced number of Gd enhancing lesions to compared with 11 in placebo after 24w. ARR 0.15 after 72w. Thorough QT/QTc: **doesn't prolong QT Shorter half life (19h) compared with fingolimod (1w).**
Siponimod *Novartis*	SPMS	Oral	Selective sphingosine-1-P receptor modulator **(similar to fingolimod but specific to S-1P1 & S-1p5 and spares S-1p3 so spares the heart)**		**BOLD**
Ponesimod	RRMS	Oral	Selective sphingosine-1-P receptor modulator		
Ocrelizumab *Roche/Biogen*	PPMS	IV	**CD20 blocker (similar to Rituximab)** Depletes B cells via antibody-dependent cell-mediated toxicity (ADCC) and complement-dependent cytotoxicity (CDC). **Compared to rituximab, induces more ADCC and less CDC, which could reduce infusion-related toxicity**	Serious infections Thrombotic microangiopathy	**ORATARIO**: compared with placebo, reduced the risk of disability progression by 24% **OPERA I, II:** compared with IFN B1a, ocrelizumab reduced the ARR by ~50% and slowed disease progression by 40% **Kappos et al:** 89% reduction in the number of gadolinium-enhancing lesions as compared to placebo
Mastinib *AB science*	PPMS - SPMS	Oral	Blocks KIT Rc (stem cell factor Rc), platlet derived growth factor, inhibits mast cell degranulation, slowed cognitive decline in Alzheimer.	Nausea, abdominal pain, diarrhea, neutropenia	**Mastinib in PPMS, SPMS**: still pending
Laquinimod *Teva*	RRMS	Oral	Suppresses gene expression related to antigen presentation and inflammation	abdominal pain, elevated LFT	ARPEGGIO – CONCERTO: pending ALLEGRO: compared with placebo 23% reduction in the ARR (0.30 versus 0.39) and a reduction in disease progression (11.1% versus 15.7%). Marked improvement in EDSS which raise concerns about being neuroprotective.
Idebenone (Roxane) *Takeda*	PPMS	Oral	Works on reactive oxygen species, increase ATP synthesis, electron transport in cells with depressed mitochondrial functions → approved for Leber optic atrophy in EU.	Fatigue, headache, diarrhea	IPPOMS: pending

Dronabinol	SPMS for spasticity	Oral	Cannabinoid receptor agonist Decrease accumulation of cAMP, thought to be neuroprotective. Reduces signs of inflammation in animals.	Amnesia, ataxia, asthenia, euphoria, diarrhea, paranoid reactions	CUPID: not effective CAMS: didn't affect spasticity but increased patient's walking speed. Ungerleider et al: improved spasticity

Combination therapies:

Copaxone and IFn: didn't provide any additional benefit. (Randomized study combining interferon and glatiramer acetate in multiple sclerosis)

Sphingosine receptors:

- Required by lymphocytes in order to leave the lymph nodes. Suppression of S-1p receptors will lead to entrapement of memory and naiive lymphocytes in LNs.
- Alsot there has been evidence S-1P-5 modulators act on astrocytes in the brain. In animal models S-1p modulators didn't help animals with S-1p5 receptors knocked out from their astrocytes.
- There are 5 types of sphingosine-1 receptors that are present in different organs (including heart, causing bradycardia)
- Fingolimod is a non specific S-1-P Rc modulator, works on all S-1P receptors except type 2.
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Quiz of decreasing ARR in Placebo group

the annualized relapse rates (ARRs) among RRMS patients in the placebo arms of phase 3 trials have decreased substantially over the last two decades. In the 1990s ARRs tended to be above 1.0, but more recently ARRs have been 0.5 and below. It's unclear why people in the placebo groups of recent trials show a less active disease course but this fact brings new challenges in the design of upcoming RRMS trials. Lower event rates require larger trials, and this of course will increase costs.

Interesting topics in MS:

- **Celmastin (an old antihistaminic) improved VEP in patients with optic neuritis** (decreased VEP by > 1msec).
- **Phenytoin as a neuroprotective in optic neuritis**: phenytoin associated with increased retinal nerve fiber layer thickness (30%) and macular volume (34%) in patients with acute optic neuritis.
- **SLC9A9 gene is associated with resistance to IFN in patients with MS.**
- **Biogen report on PML**: total confirmed PML since 2004 was 588 making PML incidence in natalizumab treated patients 4/1000
- **There is ongoing efforts to develop JCV vaccine**