Pharmacology in NMO & MS

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Rx Guideline in NMO

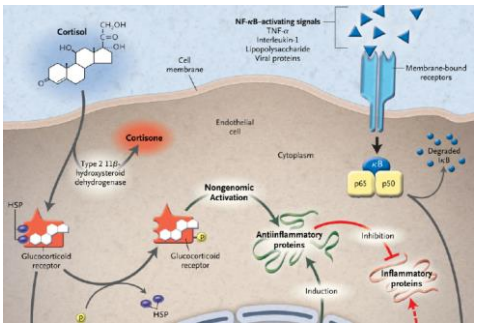
- No standard guideline
- Evidence-based in NMO treatment

Acute attack

High dose steroid

- Based on the experiences of other acute CNS immunological disease: MS
- Both non-genomic & genomic mechanism
- Results: anti-inflammation & leukocyte apoptosis
- Dosage: 500-1000 mg of methylprednisolone

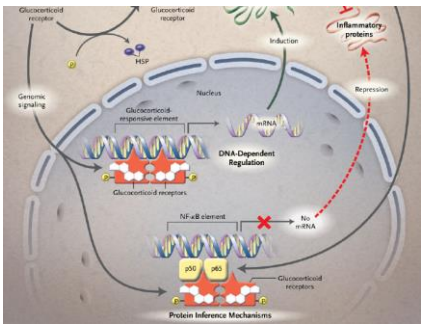
Non-genomic: anti-inflammation



Non-genomic: Anti-inflammation & immune cell apoptosis

- Fast action within week
- Only in high dose steroid
- Normally: lymphocytes activation needs ↑cytoplasmic Ca^{++}
- High dose steroid → ↓cytoplasmic Ca^{++}, inhibit mitochondrial function (↓cation cycling across plasma membrane)→ immune cell apoptosis

Genomic: anti-inflammation



Genomic effect

- Mediated by cytosolic receptor: *lower* steroid concentration
- Glucocorticoid + receptor → bind to glucocorticoid responsive element in nucleus → DNA-mRNA level →
  1. Induction anti-inflammatory protein
  2. Repression of inflammatory protein

Immunodepletion therapy

- Plasmapheresis & IVIg & immunoadsorption
- Deplete pathogenic antibody, inflammatory substance
- Varied in efficacy and response: depend on individual disease & time of treatment

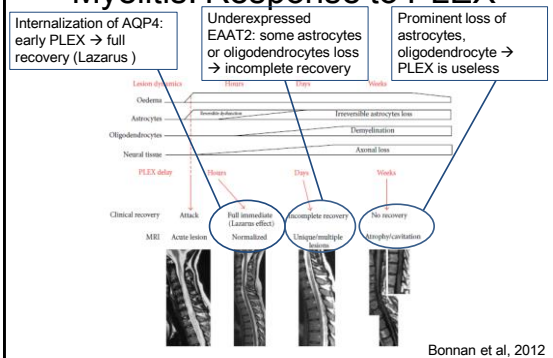
Evidence-base

Acute exacerbation

- Class II study: PLEX in acute, severe attacks who failed to improved after 5 days of IVMP

  PLEX showed 42.1% response rate vs 5.9% in controls
- Class IV study: IVIg in acute attack

Myelitis: Response to PLEX



Bonnan et al, 2012

Myelitis: Response to PLEX

	Basal EDSS (null)			Basal EDSS (1.0 to 5.5)			Basal EDSS (≥6.0)		
	St ($n = 17$)	St + PE ($n = 7$)	p	St ($n = 26$)	St + PE ($n = 13$)	p	St ($n = 24$)	St + PE ($n = 9$)	p
Basal EDSS	0 (0)	0 (0)	0.99	3.9 (0.8)	3.9 (1.6)	0.59	7.4 (1.0)	7.1 (0.8)	0.52
Acute EDSS	7.1 (1.5)	7.6 (1.2)	0.52	7.6 (1.3)	7.6 (1.1)	0.67	8.9 (0.9)	8.6 (0.6)	0.24
Residual EDSS	5.9 (1.9)	2.1 (1.9)	<0.01	5.8 (1.6)	5.1 (1.1)	0.21	8.5 (1.1)	7.6 (1.0)	0.05
ΔEDSS	5.9 (1.9)	2.1 (1.9)	<0.01	2.0 (1.5)	1.2 (1.6)	0.10	1.1 (0.8)	0.5 (0.8)	0.11

Bonnan et al, 2012

Factor associated with good outcome

1. Preserve reflex at acute phase
2. Shorter time from onset to treatment

Same response rate *irrespective* of AQP4-IgG status

ON: Response to PLEX

- Median time of PLEX given: 19 days vs 41 days (treatment success vs failure)
- Success rate 100% (first 11 days) → 57% (days 12-22) → 53% (days 23-73)

Time from disease onset to treatment is the most important factor!!!!

Dosage & duration

- In most pathologic conditions in which plasma exchange is used, 1 to 1.5 plasma volumes are exchanged per procedure per day.
- Routine treatment of 3 to 5 cycles (at least 24 hours in between); may be prolonged, depending on the individual patient's condition.

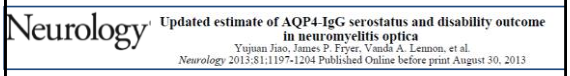
IVIG in NMO (Grade 1C)

- Retrospective study
- 10 (NMO 9, NMOSD 1)
- F:M 4:1
- 8 patients: AQP4-Ab positive
- Median duration of NMO at Rx: 3.3 years (0.5-16.6), start at median 0.5 months after attack (0-6)
- 10 events fail to 3-5 days of steroid and 5 events fail from PLEX

IVIG in NMO

- Improvement 5/11
- No further worsening in 6/11
- Time to Rx: response group = 1 week vs non response group = 14 weeks

Long term immunosuppression

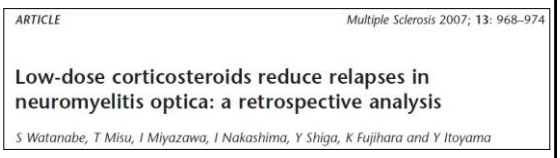

Neurology
Updated estimate of AQP4-IgG serostatus and disability outcome in neuromyelitis optica
Yujuan Jiao, James P. Fryer, Vanda A. Lennon, et al.
Neurology 2013;81:1197-1204 Published Online before print August 30, 2013

- Serostatus did not affect the interval to relapse or the relapse rate
- Serostatus does not affect attack severity or disability outcome
- Immunosuppressant therapy is associated with lower relapse rate (in both seropositive & negative)

Immunosuppression

- Prednisolone
- Azathioprine
- Mycophenolate mofetil
- Cyclophosphamide
- Mitoxantrone
- Rituximab
- Eculizumab
- Tocilizumab
- IVIG

Prednisolone

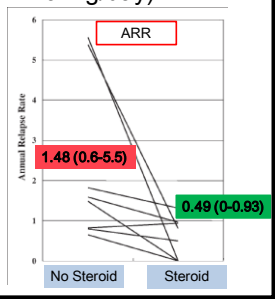

ARTICLE
Multiple Sclerosis 2007; **13**: 968–974

Low-dose corticosteroids reduce relapses in neuromyelitis optica: a retrospective analysis

S Watanabe, T Misu, I Miyazawa, I Nakashima, Y Shiga, K Fujihara and Y Itoyama

Prednisolone

- 1 retrospective study
- Low dose steroid (2.5 – 20 mg/day) showed less ARR



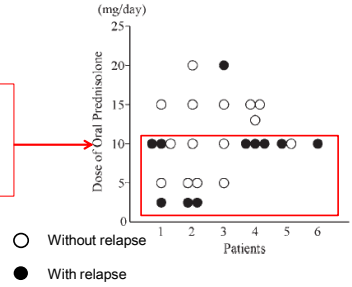
Watanabe S, et al 2007

Prednisolone

- Compared ARR steroid: ≤ 10 vs > 10 mg/day

Total 11 relapses:

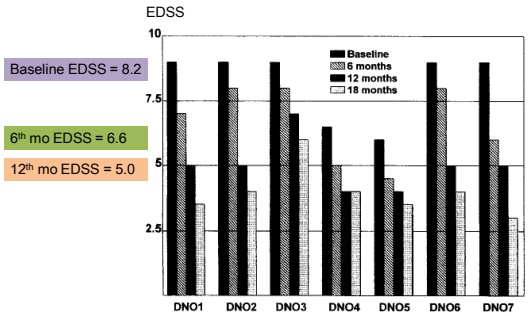
91% were in steroid **≤ 10 mg/day**



Azathioprine

Devic's neuromyelitis optica: A prospective study of seven patients treated with prednisone and azathioprine
Raul N. Mandler, Waseem Ahmed and John E. Dencoff
Neurology 1998;51;1219-1220

- All women (Hispanic, native American, Caucasian & AA)
- All received high-dose steroid then oral steroid for first 2 months → tapering + azathioprine 2 mg/kg/day in the 3rd week.

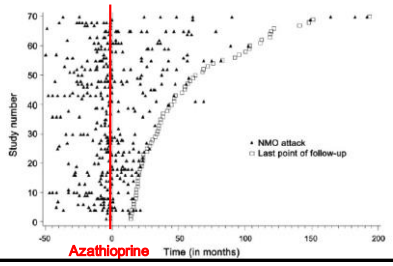


Azathioprine

Group	No.	Median ARR pre-azathioprine	Median ARR post-azathioprine initiation	p Value
All patients	70	2.18	0.64	<0.0001
≥2.0 mg/kg/d	48	2.20	0.52	<0.0001
<2.0 mg/kg/d	22	2.09	0.82	<0.0001
Concomitant prednisone	52	2.20	0.89	<0.0001
No concomitant prednisone	18	1.54	0.23	<0.0001
Immunosuppressant naive	60	2.2	0.57	<0.0001
Previous immunosuppressant therapy	10	2.1	1.1	0.016
Change in MCV <5	8	0.985	0.928	1.0000
Change in MCV >5	19	3	0.46	<0.0001

Azathioprine

Azathioprine: Tolerability, efficacy, and predictors of benefit in neuromyelitis optica
C. Costanzi, M. Matiello, C.F. Lucchinetti, et al.
Neurology 2011;77;659-666 Published Online before print August 3, 2011



Mycophenolate mofetil

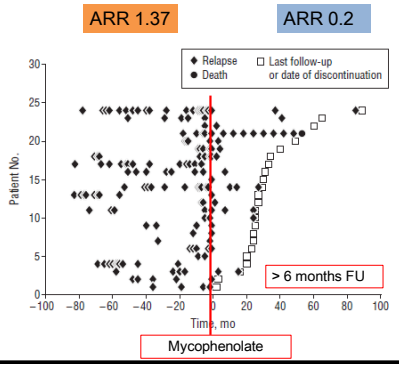
Treatment of Neuromyelitis Optica With Mycophenolate Mofetil

Retrospective Analysis of 24 Patients

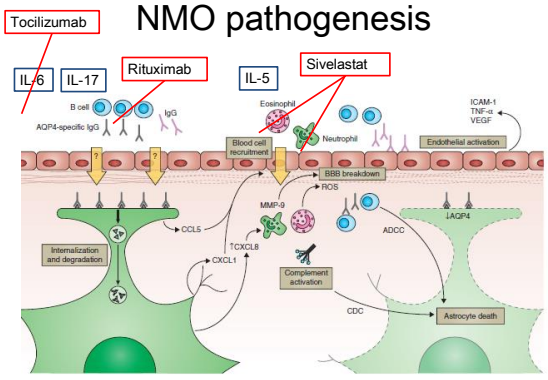
Anu Jacob, MD; Marcelo Matiello, MD; Brian G. Weinshenker, MD; Dean M. Wingerchuk, MD; Claudia Lucchinetti, MD; Elizabeth Shuster, MD; Jonathan Carter, MD; B. Mark Keegan, MD; Orhun H. Kantarci, MD; Sean J. Pittock, MD

- Retrospective case series with prospective telephone follow-up
- 24 NMOSD (7 Rx naïve), all AQP4-IgG positive
- Dosage median 2000 mg/day (750-3000 mg)

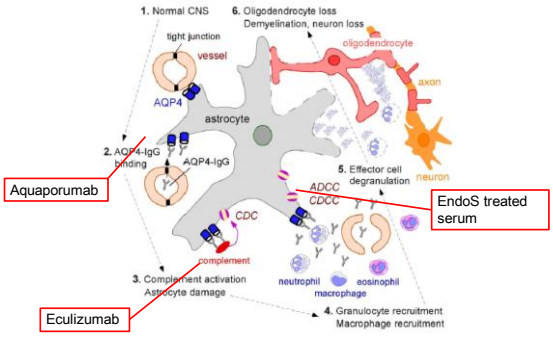
Mycophenolate mofetil



NMO pathogenesis



Obermeier et al 2013



Verkman, et al 2013

Conclusion: Acute attack

- High dose steroid:
  Methylprednisolone 1 g/day x 3-5 days
- If not response after Rx: plasmapheresis 5-7 cycles (at least 24 hrs apart or alternate days)
- Early plasmapheresis shows some benefits
- Early Rx ASAP associates with good outcome

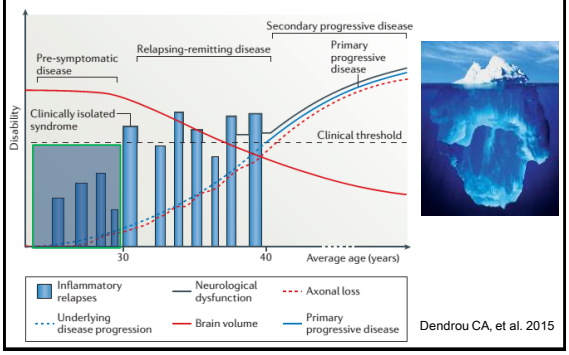
Conclusion: Maintenance

- Disability : attack related
- Prednisolone (low dose > 10mg/day → 20 mg/day)
- Azathioprine (2 mg/kg/day with MCV change > 5 fl)
- Prednisolone + Azathioprine
- Mycophenolate mofetil (2000 mg/day)
- Duration > 1 year (3-5 years or individual)

Rx consideration in MS

- **Acute attack**:
  - Reduce inflammation → shortening time to recovery
- **Relapsing phase (inflammatory phase)**:
  - Reduce relapse rate: ARR
  - Reduce accumulation of lesions
- **Progressive phase (degenerative phase)**:
  - Reduce disability progression

Clinical presentation of MS is the tip of iceberg

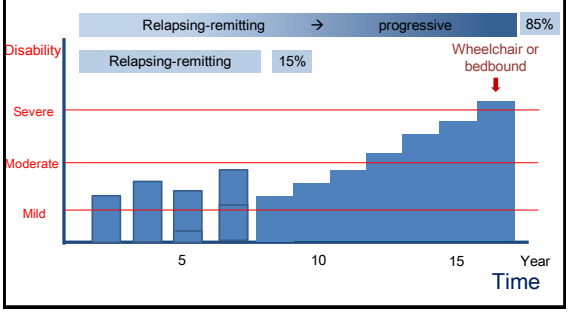


Dendrou CA, et al. 2015

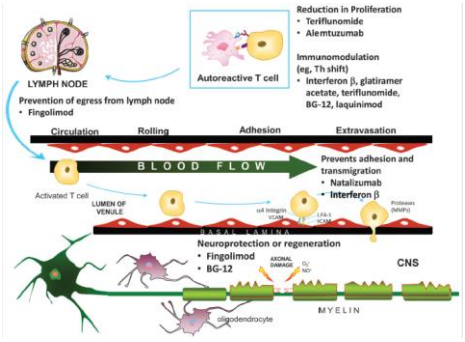
Feature	Stage 1 Initiation	Stage 2 Latency	Stage 3 Onset	Stage 4A Inflammation	Stage 4B-5A Transition	Stage 5B Neurodegeneration
DMT	None	None	Anti-inflammation Rx effective		Anti-inflammation less effective	None
Clinical event	None	None	Single event	Relapsing attack with satisfactory recovery, stable	Unstable, incomplete recovery	Steady progression, variable attacks without marked improvement
Pathogenesis	Autoreactive lymphocyte activation ??	Accumulation of inflammatory cells	Demyelination	Recurrent demyelination	Axonal injury threshold reached, failure to repair	Widespread glial activation, ongoing axonal degeneration
Typical age (yr)	13-15	15-30	30	30-45	45-55	45-75

MS disability progression

Disability α genetic?? + time



Mechanism of action of standard Rx



Continuum 2013

AIMS: NEDA

- Primary outcome:
  - Reduced ARR
- Secondary outcome:
  - Reduced confirmed disability progression
  - Reduced brain volume loss

NEDA-4

- No evidence of disease activity
- Outcome measurement: stringent standard of therapeutic efficacy → complete disease remission

Absence T1 Gd enhancing lesions

Absence of new or enlarging T2 lesions

Brain volume loss < 0.4%

NEDA-4

No confirmed EDSS progression

No clinical relapses

Factors determine Rx

Recent MS activity : attack frequency, severity & recovery

Concomitant medical illness

Lesions burden

DMT

Drug efficacy availability, cost, side effect, monitoring

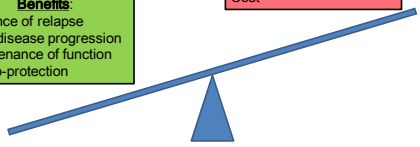
Degree of neurological impairment

Patient preferences

Benefit vs Risk of DMT

Risks:
Adverse events
Tolerability/side effects
Decreased quality of life
Loss of independence
Cost

Benefits:
Absence of relapse
Stop disease progression
Maintenance of function
Neuro-protection



MS-DMT failure

Patient factors

Clinical factors

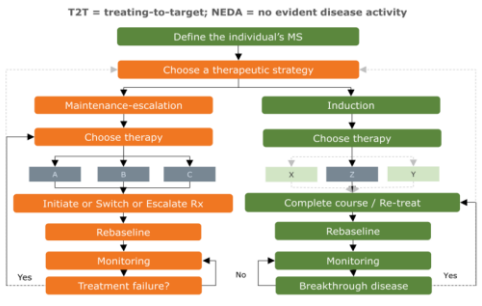
MRI factors

Therapeutic failure

Switching-escalation

Induction → maintenance

NEDA-algorithm



Giovannoni G et al 2015

Consideration for therapeutic failure

Patient factors:

1. Drug tolerability
2. Drug toxicity
3. Adherence to dose regimen
4. Adherence to monitoring requirement

Consideration for therapeutic failure

Clinical factors:

1. Comparison of pre-Rx & on-Rx relapse rates
2. On-Rx relapse rate ≥ 1 per year, severity & degree of recovery
3. Increased neurological impairment (EDSS increase by 1 point in 1 yr)
4. Increased cognitive dysfunction
5. Presence of neutralizing Abs (IFN & natalizumab)

Consideration for therapeutic failure

MRI factors:

1. Increase in brain lesion number
2. Occurrence of on-Rx active (Gd-enhancing lesions)
3. Increase in brainstem or spinal cord lesions
4. Increase in brain MRI T1 "black holes"
5. Development or worsening of cerebral atrophy

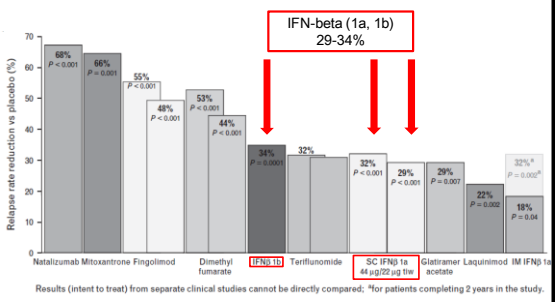
Disease-modifying therapy in MS

- Injectable drugs (First line therapy)
  - Interferon-beta
    - 1a (Rebif, Avonex)
    - 1b (Betaseron)
  - Glatiramer acetate (Copaxone)
- Oral medication (Escalating therapy)
  - Fingolimod (approved as first line Rx in US)
  - Teriflunomide
  - BG12

Disease-modifying therapy in MS

- Intravenous infusion (Escalating therapy)
  - Alemtuzumab
  - Natalizumab
- Immunosuppressive therapy
  - Mitoxantrone

Efficacy of DMT for MS

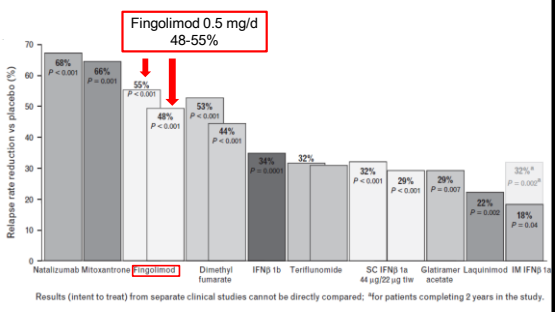


Curr Opin Neurol 2014

Interferon beta

Preg	Neu-Ab	Routine monitoring	Adverse events	Evaluation & management
C	Yes	Baseline & regular CBC, LFT	Injection site reaction,	Dose titration, ice, self-limited
			Flu-like symptom	Dose titration, NSAIDS, self-limited
			LFT elevate	Review other potential med, temporary IFN suspension, rechallenge lower dose
			Leukopenia	Lower dose or suspension then rechallenge
			Depression	Psychiatric evaluation, anti-depressant, if severe discontinue drug

FREEDOMS: primary endpoint

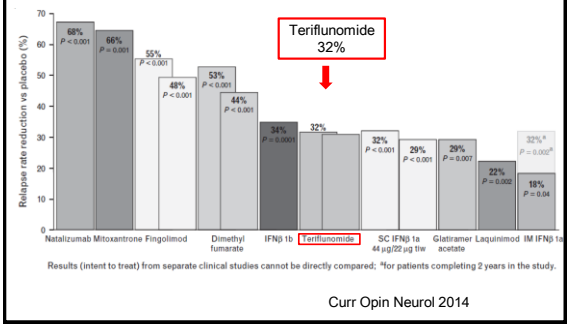


Curr Opin Neurol 2014

Fingolimod

Preg	Neu-Ab	Routine monitoring	Adverse events	Evaluation & management
C	No	Baseline & regular CBC, LFT (q 6 months)	Bradyarrhythmia	**First-dose observation** protocol (6-h monitoring of heart rate & blood pressure), Prolong monitoring if risks factors or events during first-dose
		Baseline ECG & VZV serology		Cardiology consultation if risk factors or abnormal baseline ECG results
		Baseline & 3-mo ophthalmological examination (minimum)	Macular edema	Ophthalmological monitoring consider indefinitely in patients with DM or hx of uveitis
			Herpes infection (VZV)	Prompt antiviral therapy; consider prophylaxis in patients with recurrence

Efficacy of DMT for MS

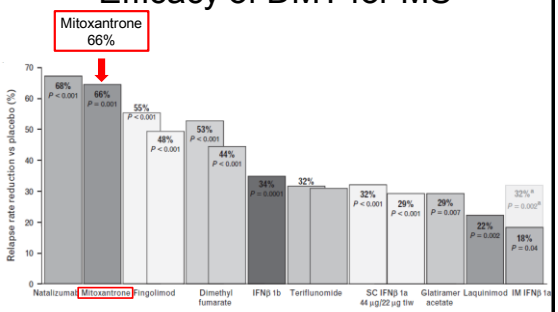


Curr Opin Neurol 2014

Terifunomide

Preg	Neu-Ab	Routine monitoring	Adverse events	Evaluation & management
X	No	Baseline & regular CBC, LFT (q 6 months)	Hepatotoxicity	Discontinue drug & use accelerated washout protocol for moderate or severe toxicity
		Baseline Pregnancy test, TB test		Emphasize need for reliable contraception; discontinue drug & use accelerated washout protocol if pregnancy occurs or is planned after discontinuation
		Baseline & regular BP	Teratogenic risk	

Efficacy of DMT for MS



Curr Opin Neurol 2014

Mitoxantrone

Preg	Neu-Ab	Routine monitoring	Adverse events	Evaluation & management
D	No	Baseline & regular CBC, LFT Baseline echocardiography; repeat before each dose	Cardiac toxicity	Predose echocardiogram; annual F/U scans even after course completion to detected delayed cardiac toxicity
			Leukemia	Regular CBC; F/U recommended for years after course completion

Alemtuzumab

- Anti-CD52 → prolonged lymphocytes depletion, including autoreactive T cell
- Reduced ARR by 50% (compared to high dose IFN-b1a)
- 12 mg/day IV infusion for two treatment course:
  - Baseline: 5 consecutive days
  - 12 months later: 3 consecutive days
- Patients should be pre-treated with corticosteroid immediately prior to administration + oral prophylaxis for herpes infection
- Regular monitoring for secondary autoimmune disease (autoimmune thyroid (1/3), ITP) for 2 years or more after last treatment

Alemtuzumab

Preg	Neu-Ab	Routine monitoring	Adverse events	Evaluation & management
C	No	Baseline & regular CBC, Thyroid function test (q 6 months)	Secondary autoimmunity (Thyroiditis, ITP, Goodpasture syndrome)	Laboratory monitoring
			Infusion reaction	High dose steroid infusion before drug infusion
			Herpes infection	Anti-herpes prophylaxis (acyclovir on the first day of drug administration & continue until 2 months after treatment or the CD4 > 200 ul whichever come later

Drugs for RRMS summary

Medication	Route	Efficacy	Major side effects	Safety	Convenience
IFN	SC t.i.w or q.d or IM weekly	32%	Flulike, LFT, site reaction	+++++	+
Glatiramer	SC daily	29%	Site reaction	+++++	+
Fingolimod	p.o. daily	54%	Cardiac conduction, macular edema, infection, malignancy	+++	+++++
Teriflunomide	p.o. daily	30%	Hepatotoxic, HT, PN	+++	+++++
Natalizumab	IV q 4 wks	68%	PML	++	++
Mitoxantrone	IV q 3 mos.	63%	Cardiac toxicity, AML	+	++
Alemtuzumab	IV 12 mg/d X 5 days, then after 12 months 12 mg/d X 3 days	53% (compare to IFN-b)	Secondary autoimmunity	++	++++

Lindsey JW 2014

Immune directed therapy in MS

- B cell depletion therapy
  - Rituximab
  - Ocrelizumab
- Hematopoietic stem cell transplantation

B cell depletion therapy

B-Cell Depletion with Rituximab in Relapsing–Remitting Multiple Sclerosis

Stephen L. Hauser, M.D., Emmanuelle Waubant, M.D., Ph.D., Douglas L. Arnold, M.D., Timothy Vollmer, M.D., Jack Antel, M.D., Robert J. Fox, M.D., Amit Bar-Or, M.D., Michael Panzara, M.D., Neena Sarkar, Ph.D., Sunil Agarwal, M.D., Annette Langer-Gould, M.D., Ph.D., and Craig H. Smith, M.D., for the HERMES Trial Group*

NEJM 2008

RCT, double-blind, 48 weeks phase II trial:

Rapid significant reduction of disease activity (MRI measurement and clinical disease activity)

B cell depletion therapy

Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis

S.L. Hauser, A. Bar-Or, G. Comi, G. Giovannoni, H.-P. Hartung, B. Hemmer, F. Lublin, X. Montalban, K.W. Rammohan, K. Selmaj, A. Traboulsee, J.S. Wolinsky, D.L. Arnold, G. Klingelschmitt, D. Masterman, P. Fontoura, S. Belachew, P. Chin, N. Mairon, H. Garren, and L. Kappos, for the OPERA I and OPERA II Clinical Investigators*

NEJM 2017

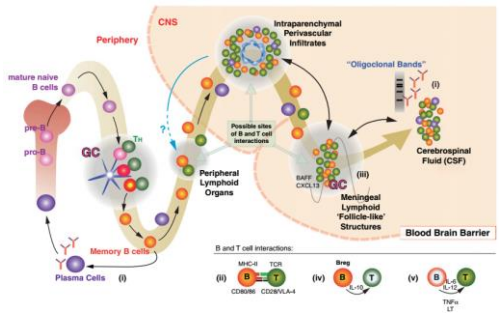
Compare: ocrelizumab 600 mg q 24 weeks vs IFN-beta 1a 44 ug sc trice weekly:

Primary outcome: ARR

Result:
1. Ocrelizumab reduced relapse rates by 46% & reduced confirmed disability progression by 40%.
2. Ocrelizumab reduced Gd-enhancing lesions by 94%.

Side effects were comparable.

B cell in MS



HSCT in MS

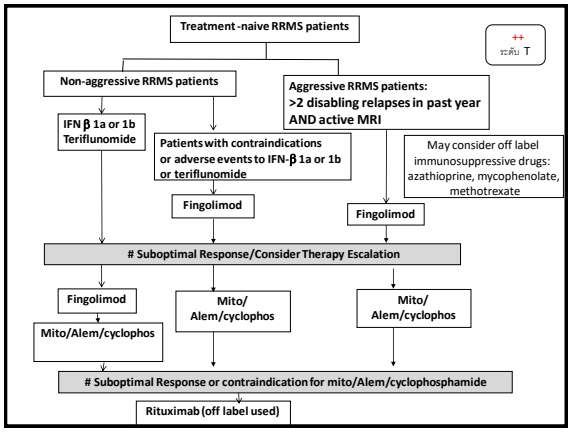
Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial

Harold L Atkins, Marjorie Bowman, David Allan, Grizel Anstee, Douglas L Arnold, Amit Bar-Or, Isabelle Bence-Bruckler, Paul Birch, Christopher Bredeson, Jacqueline Chen, Dean Fergusson, Mike Halpenny, Linda Hamelin, Lothar Huebsch, Brian Hutton, Pierre Laneuville, Yves Lapierre, Hyunwoo Lee, Lisa Martin, Sheryl McDiarmid, Paul O'Connor, Timothy Ramsay, Mitchell Sabloff, Lisa Walker, Mark S Freedman

Lancet 2016

Ablation of the adaptive immune system and maturation of the new immune repertoire that lacks autoreactive immune cells

24 highly active MS patients: 1 died of transplant-related complication,
70% of the rest → no disease activity during 3 years followed up.
30% → early & sustained disability progression, but without relapses and MRI activity
23 patients: none experienced relapse or developed new Gd-lesions upto 12 yrs



Duration of RRMS immunomodulating therapy

- First start *at least 2-3* years
  - Drug effect usually begin after 6-9 months
  - Monitor disease activity (ARR, MRI activity, EDSS)
- Stop Rx when patients turn to ***progressive phase*** (~ 8-15 years)

Progressive MS

Two Preclinical phase of PPMS

1. ***Fingolimod***
   - INFORMS trial: did not influence 3-month confirmed disability progression vs placebo
2. ***Ocrelizumab***
   - ORATORIO trial: reduced confirmed disability progression over 3 months by 24% and over 6 months by 25%; reduced the T2-volume change by 90%
   - Increased risk of neoplasm (breast cancer 2.3% vs 0.8%)

One phase III SPMS

Natalizumab → did not showed any effect on disease progression