Practical long-term management in NMOSD & MS : What can we do in Thailand?

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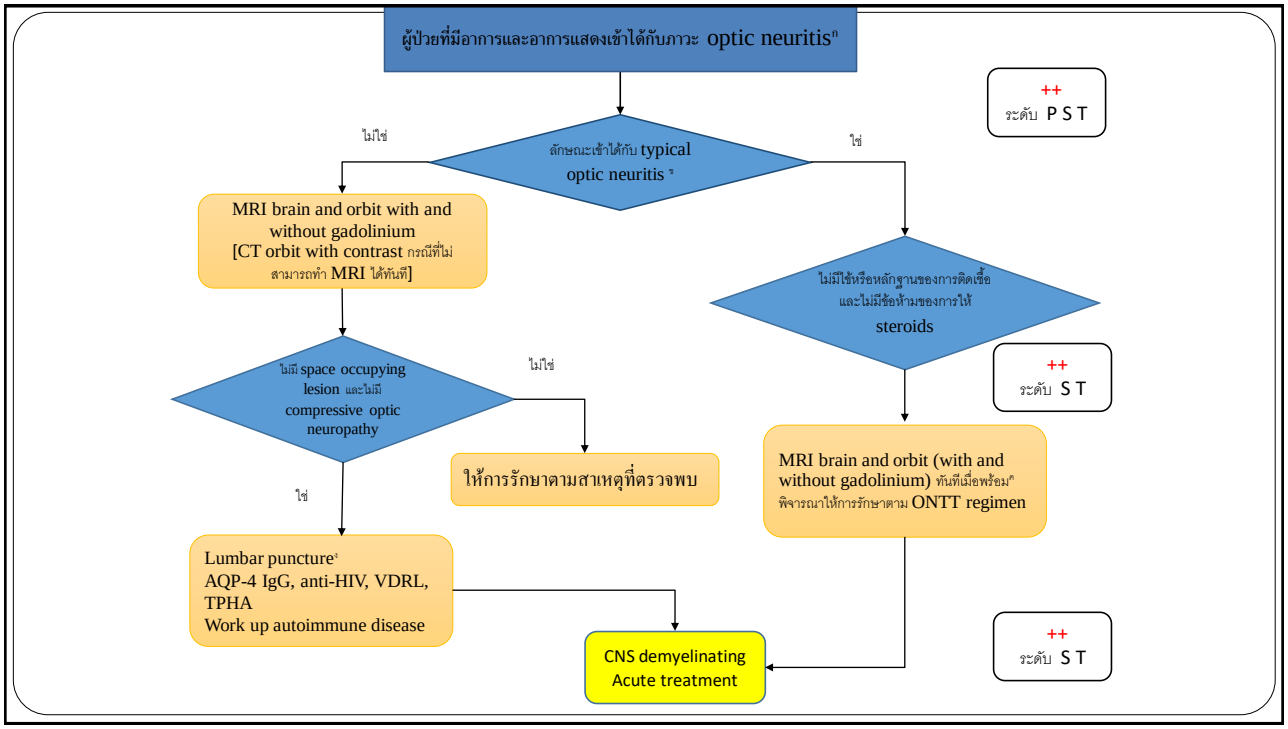
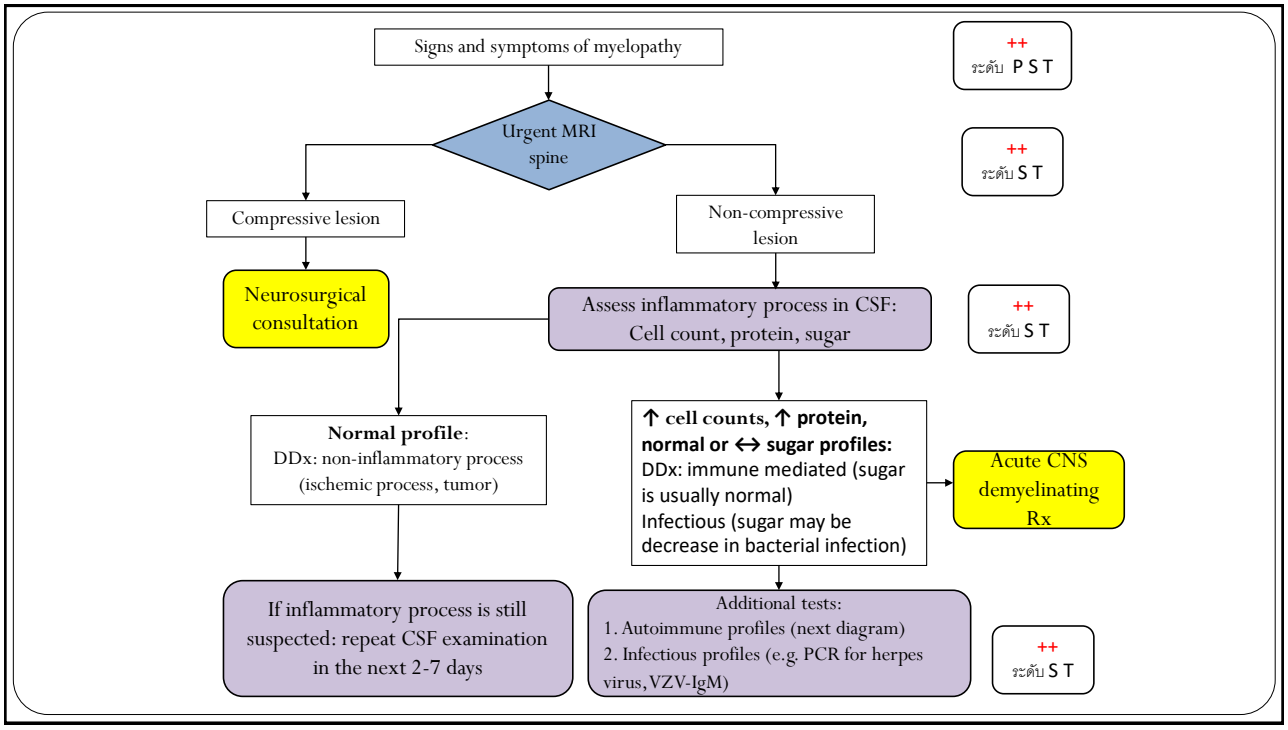
Outline

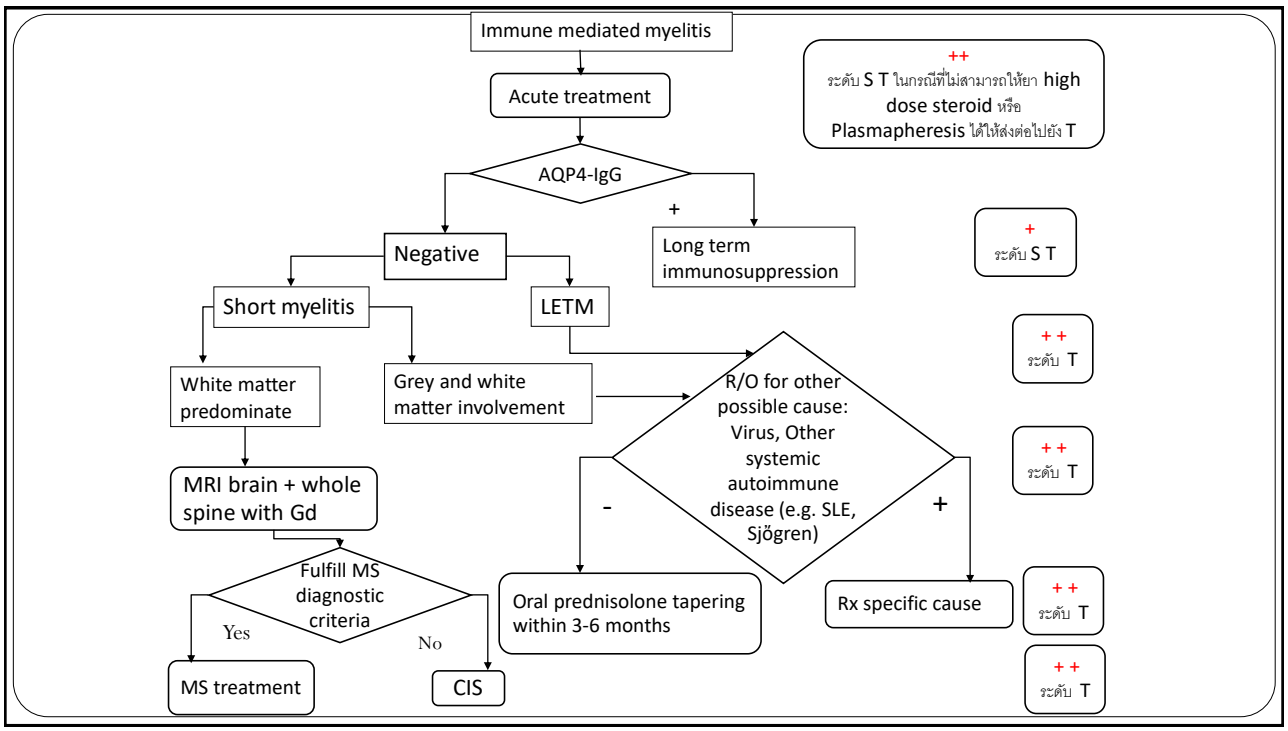
- Diagnosis of first CNS inflammatory disease
- Acute management
- Transitional care [NMOSD vs MS]
- Long-term treatment [NMOSD vs MS]

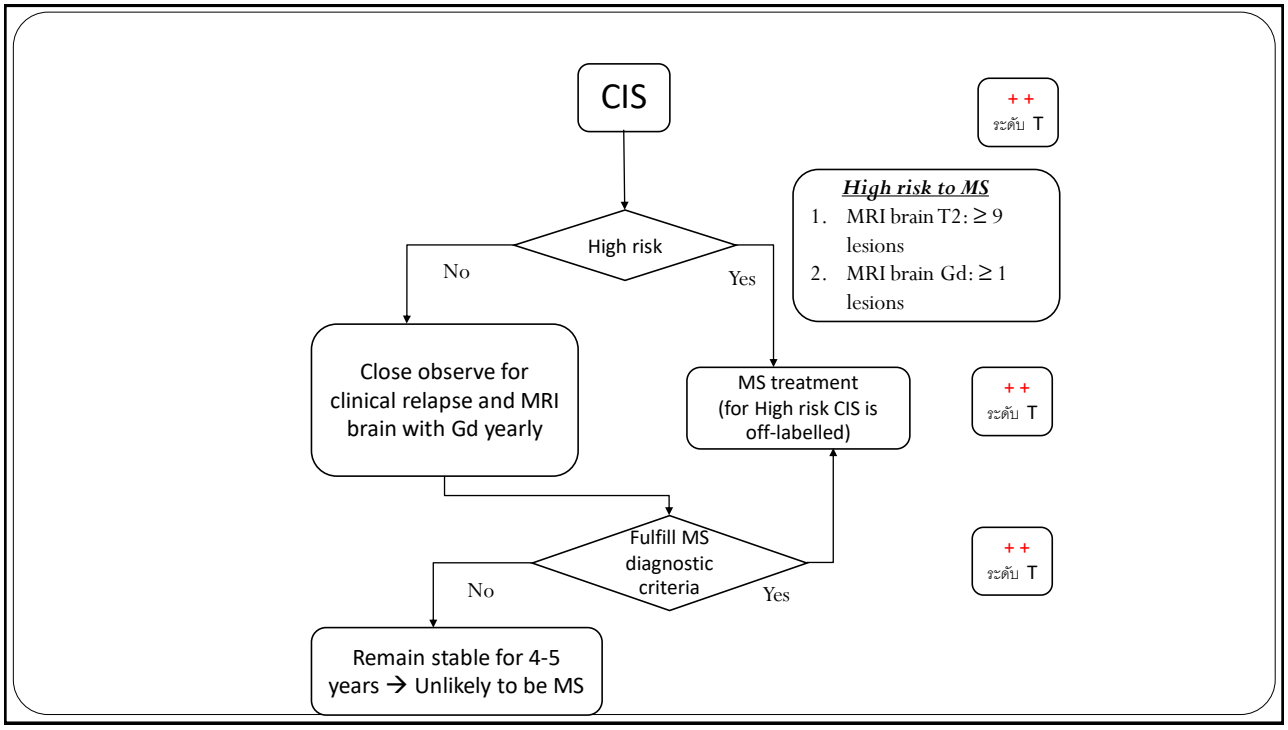
First CNS inflammatory disease

- Optic neuropathy
- Myelopathy
- Area postrema & dorsal BS syndrome
- Centrum semiovale & other cerebellar lesion




Signs and symptoms of myelopathy
++ ระดับ P S T
Urgent MRI spine
++ ระดับ S T
Compressive lesion
Non-compressive lesion
Neurosurgical consultation
Assess inflammatory process in CSF: Cell count, protein, sugar
++ ระดับ S T
Normal profile: DDx: non-inflammatory process (ischemic process, tumor)
↑ cell counts, ↑ protein, normal or ↔ sugar profiles: DDx: immune mediated (sugar is usually normal) Infectious (sugar may be decrease in bacterial infection)
Acute CNS demyelinating Rx
If inflammatory process is still suspected: repeat CSF examination in the next 2-7 days
Additional tests: 1. Autoimmune profiles (next diagram) 2. Infectious profiles (e.g. PCR for herpes virus, VZV-IgM)
++ ระดับ S T


Immune mediated myelitis
Acute treatment
++ ระดับ S T ในกรณีที่ไม่สามารถให้ยา high dose steroid หรือ Plasmapheresis ได้ให้ส่งต่อไปยัง T
AQP4-IgG
+
Long term immunosuppression
+ ระดับ S T
Negative
Short myelitis
LETM
White matter predominate
Grey and white matter involvement
R/O for other possible cause: Virus, Other systemic autoimmune disease (e.g. SLE, Sjögren)
++ ระดับ T
++ ระดับ T
MRI brain + whole spine with Gd
-
+
Fulfill MS diagnostic criteria
Yes
No
Oral prednisolone tapering within 3-6 months
Rx specific cause
++ ระดับ T
++ ระดับ T
MS treatment
CIS

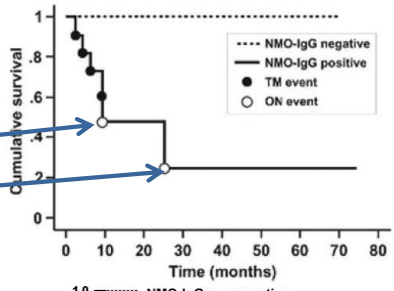


Acute attack management

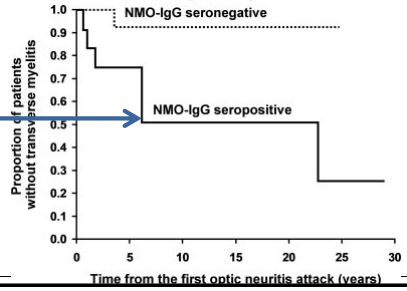
- High dose steroid:
  Methylprednisolone 1 g/day x 5 days
- If not response after Rx: plasmapheresis 5-7 cycles (at least 24 hrs apart or alternate days)
- *Early* plasmapheresis associates with good outcome (best benefit within 5 days after onset → 30 days)
- **Plasmapheresis outcome is independent of serostatus → should not delay plasmapheresis due to waiting for serology**

The serology predicts outcome: AQP4-IgG

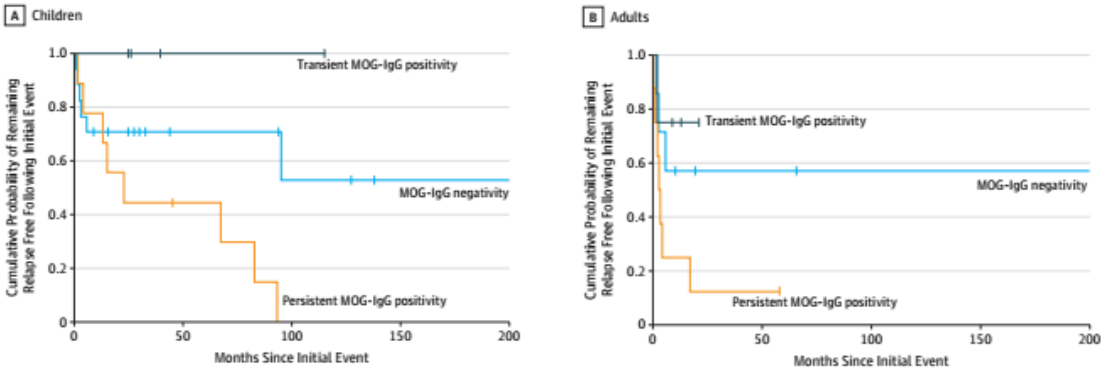
- AQP4-IgG predict outcome
- sLETM + AQP4-IgG → rLETM
  - >50 % in 1st year
  - >70 % in 3rd year



- rON + AQP4-IgG → TM
  - > 50% in 5th year
  - (6.7% in seronegative)



MOG-IgG status predicts long-term Rx



- Persistent of MOG-IgG (> 3 months) is the risk for relapse and justify for long term immunosuppression
- In transient MOG-IgG positive → more likely to be monophasic and may not benefit for long term immunosuppression

Lopez Chiriboga S, 2018

NMOSD Long-term immunosuppressive drugs

- If AQP4-IgG & MOG-IgG negative may consider discontinue steroid with in 6-9 months
- If AQP4-IgG positive: recommend added steroid sparing agents (e.g. azathioprine 2-3 mg/kg/day keep MCV ↑ 5% from baseline) from the beginning
  - ***Disability : attack related***
  - ***Duration may be life-long***
- If MOG-IgG positive: recommended *recheck* MOG-IgG status in the next 3 month
  - If still MOG-IgG positive: consider long term Rx [may be up to 3-5 months or longer]
  - If MOG-IgG convert to seronegative: tapering and off steroid in 6-9 months

NMOSD Long-term immunosuppressive drugs

- Transition from high-dose to low dose steroid:
  - Start with prednisolone 1 mg/kg/day → tapering 10 mg q 4 weeks until 30 mg/day then 5 mg q 4 weeks until 15-20 mg/day
  - Alternatively use steroid as alternate days

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)

Goal of Rx for NMOSD: Prevent relapse

First line Rx:
Low dose prednisolone (10-20 mg/day) +
Azathioprine (keep MCV ↑5% from baseline)

Second line Rx:
Methotrexate (15-25 mg/week) or
Mycophenolate mofetil (2000 mg/day)

- **Avoid MS drugs**:
  IFN-beta, Glatiramer, Teriflunomide, Fingolimod, Natalizumab, Alemtuzumab

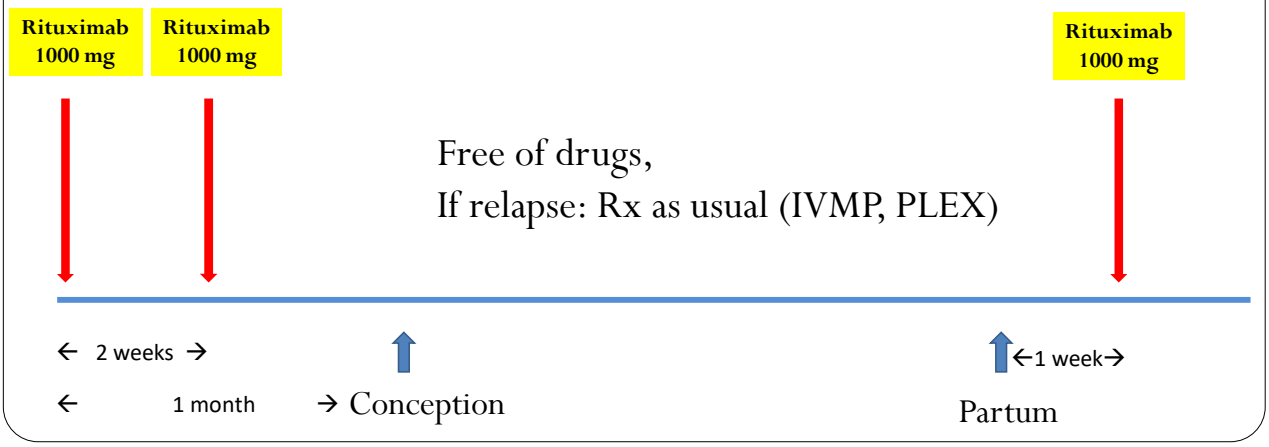
Third line Rx:
- **Rituximab 1000 mg x2 (2 weeks apart) then q 6 months or 375 mg/m^2 /week x 4 then maintenance 375 mg/m^2 monitor CD19$^+$27$^+$ keep < 0.05% PBMC 0-2 years, then < 0.1%**
- Cyclophosphamide (pulse 500-1000 mg/m^2 monthly 3-6 months)
- Plasma exchange in cycles
- New drugs: Eculizumab, Inebilizumab, Tocilizumab, Satralizumab

Conclusion: Maintenance

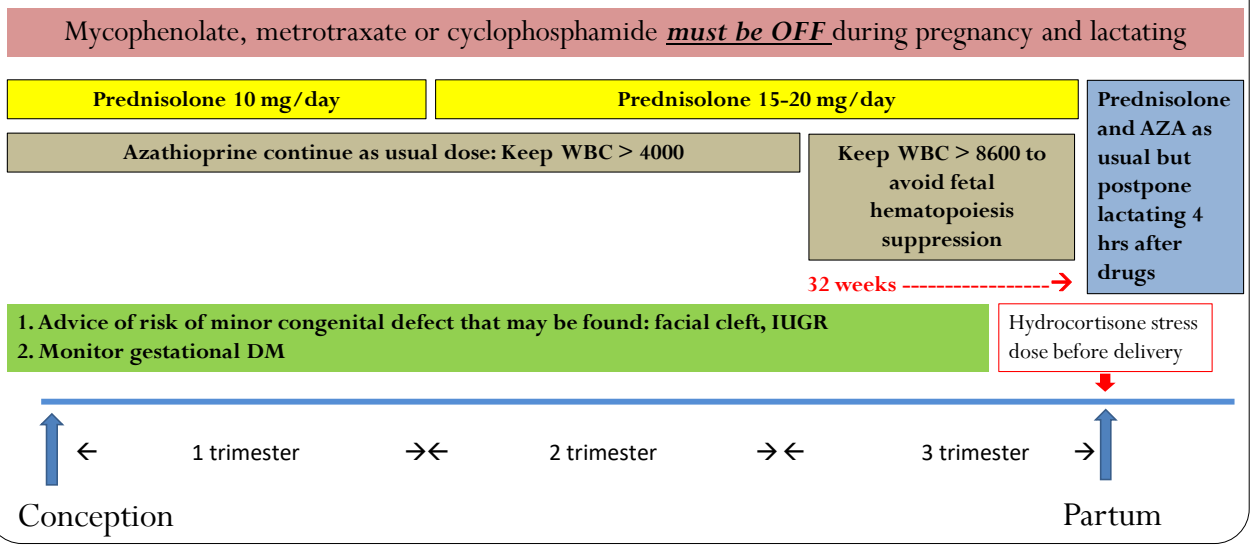
- Disability : attack related
- Prednisolone (low dose > 10mg/day → 20 mg/day)
- Azathioprine (2 mg/kg/day with MCV change > 5 fl)
- Prednisolone + Azathioprine
- Methotrexate (15-25 mg/week)
- Mycophenolate mofetil (2000 mg/day)
- Duration if AQP4-IgG positive → may be life long

Planned pregnancy

Mycophenolate must be off 6 weeks before pregnancy
Methotrexate & cyclophosphamide must be off 12 weeks before pregnancy



Unplanned pregnancy or could not use rituximab



Thai MS guideline

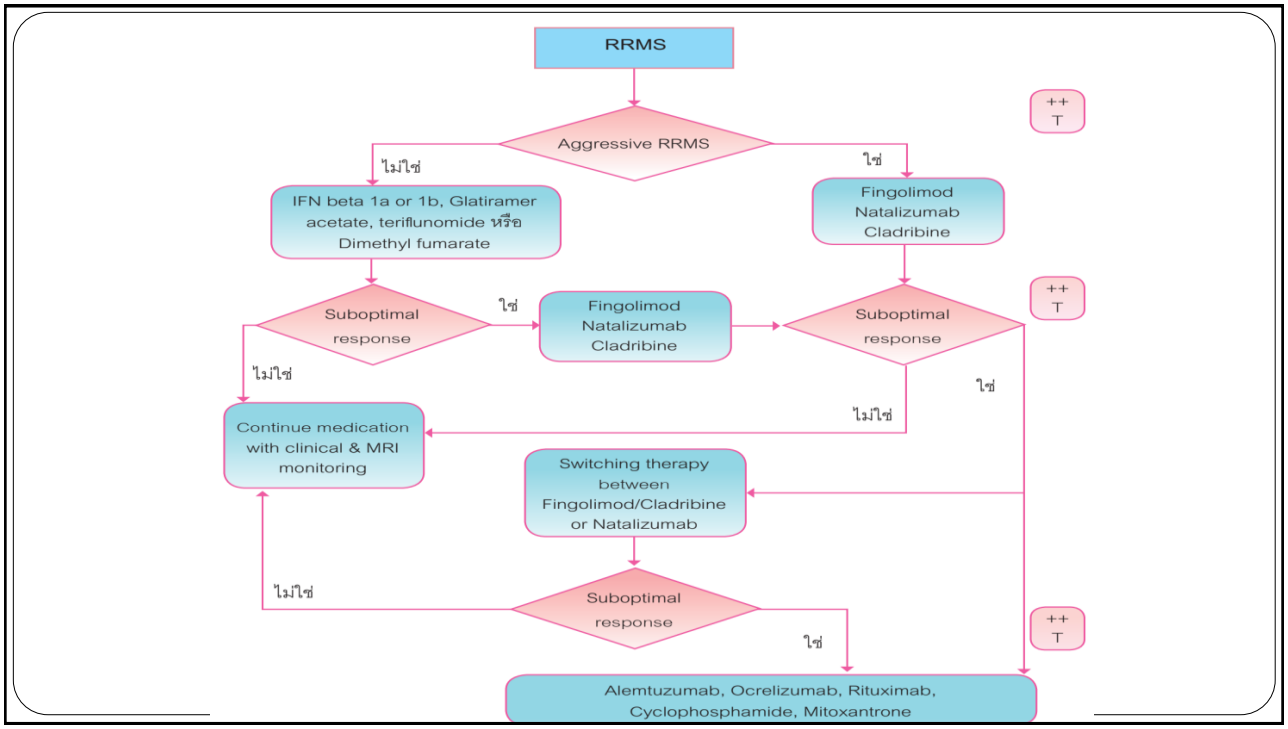
Indication for using DMT in MS patients: 1st line Rx

1. In the relapsing phase
2. Clinical relapses ≥ 2 in the past 2 years
3. EDSS from the last relapse (at least 3 months apart) ≤ 5.5
4. Non-pregnant
5. Not in the progressive phase

ภาคผนวก 1 DISEASE MODIFYING THERAPIES FOR MS

Level of therapy	Level of pharmacological agent	Relapsing remitting active MS*	Aggressive relapsing remitting MS*	Secondary progressive MS with relapses
Initial Therapy	First-line	Interferon beta/ Glatiramer acetate*/ Teriflunomide/ Dimethyl fumarate*	Fingolimod/ Natalizumab/ Cladribine*	Interferon beta Siponimod FDA US 2018
Escalation Therapy	Second-line	Fingolimod/ Natalizumab/ Cladribine*	Fingolimod/ Natalizumab/ Cladribine*	Ocrelizumab* Cyclophosphamide/ Mitoxantrone
	Third-line	Alemtuzumab/ Ocrelizumab*/ Cyclophosphamide/ Rituximab/ Mitoxantrone	Alemtuzumab/ Ocrelizumab*/ Cyclophosphamide/ Rituximab/ Mitoxantrone	
Relapse Therapy	First-line	Methylprednisolone		
	Second-line	Plasma Exchange		

*ยังไม่มีจำหน่ายในประเทศไทย (สิงหาคม 2561)



Aggressive MS by Thai guideline

- Disabling MS attacks at least 2 relapses in 1 year
- MRI
  - MRI brain with ≥ 2 Gd lesions or high MRI brain T2 lesions (≥ 9 lesions)
  - MRI spine lesion ≥ 2 lesions

FU of MS patient

- **Monitor acute side effect**
  - IFN-beta : flu-like symptoms, injection reaction
  - Teriflunomide : leukopenia, hepatitis, hair loss, peripheral neuropathy
  - Fingolimod : First dose observation for bradycardia, hypotension, leukopenia, hepatitis, macula edema
- **Monitor long term side effect**
  - Infection (zoster, PML)
  - Secondary malignancy

FU of MS patient

- **Re-baseline clinical status & MRI activity**
  - Time from start to effective period → around 3-9 months
- **Monitor disease activity**:
  - Clinical relapse
  - EDSS change
  - MRI brain w Gd if no symptoms at least once per year

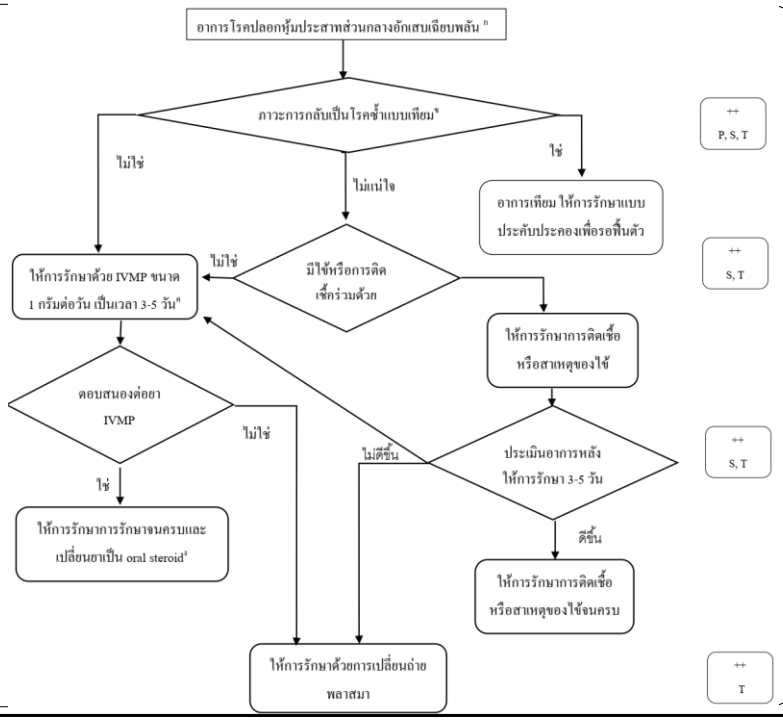
Suboptimal response (2 of 3 following)

- **Relapse with disabling symptoms**
- **Disease progression** (EDSS after 3 months of relapse)
  - EDSS ↑ 1.5 if EDSS baseline = 0
  - EDSS ↑ 1.0 if EDSS baseline = 1-5
  - EDSS ↑ 0.5 if EDSS baseline = 5.5
- **New MRI lesion**
  - ≥ 2 T2W lesions or
  - ≥ 1 Gd lesion

Pseudorelapse

- Precipitating by heat, fever, infection
- Presentation symptoms: on the previous lesions
  - *Visual symptoms*: Uhthoff's phenomenon
  - *Worsening of motor symptoms*: usually not more than 1-2 MRC grading
- Last less than 24 hours if precipitating cause is corrected

How to deal with true acute or pseudorelapse



Drug compliance

- Injection site reaction: M/C cause of inadherence
- Alopecia & hair loss: teriflunomide

Duration of RRMS DMT

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

Off label protocol

- Azathioprine: as NMOSD
- Cyclophosphamide:
  - Pulse protocol 800-1000 mg/m^2 IV monthly for 12-24 (3-6) months [limit lifetime maximum 80-100 g]
- Rituximab:
  - 1000 mg x 2 (2 weeks apart) then q 6 months
  - 1000 mg x 2 (2 weeks apart) or single dose then q 6 months with 500-1000 mg
  - 375 mg/m^2 /week x 4 then maintenance 375 mg/m^2 monitor CD19+27+ keep < 0.05% in PBMC.

When to stop medication

- Intolerable to side effect
- Progressive phase (those medication approved for RRMS)
- Inactive disease ???
  - By the age of 50, annual risk of relapses & new Gd lesions are below 10%
  - Increasing age: comorbid with DM, HT, cancer
  - No relapse for minimum 5 years + no new MRI lesion for minimum 3 years → on going trial

Symptomatic Rx is also important

- Spasticity especially in progressive phase
  - Stretching exercise
  - Baclofen, cannabis oil (THC:CBD 1:1)
- Central neuropathic pain
  - Biofeedback
  - Anticonvulsant (carbamazepine is the drug of choice in painful tonic spasm), antidepressant, cannabis oil
- Fatigue
  - Antidepressant, stimulant drugs, amantadine

Symptomatic Rx is also important

- Bowel & bladder dysfunction
  - Bowel or bladder training
  - High fiber diet & adequate fluid intake
- Tremor
  - Poor response
- Balance, ataxia
  - Balance exercise

Avoid precipitating

- Avoid hot temperature
- Avoid infection
- Immunization
  - No evidence of immunization induce relapse
  - Avoid live-attenuated vaccine if on DMT

Most important: Other disease modifying strategy

- Maintain healthy weight: obese patient → risk for MS
- Sun exposure: lower vitamin D → risk of autoimmune disease
- Smoking cessation
- Exercise