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

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

### MRI brain and orbit (with and without gadolinium)

MRI brain and orbit with and without gadolinium [CT orbit with contrast accompany MRI for better]

- No space occupying lesion and no compressive optic neuropathy
- For further assessment of the cause of symptoms

#### Lumbar puncture

- AQP-4 IgG, anti-HIV, VDRL, TPHA
- Work up autoimmune disease

#### CNS demyelinating Acute treatment

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++ ระดับ S T

++ ระดับ P ST
Signs and symptoms of myelopathy

Urgent MRI spine

- Compressive lesion
- Non-compressive lesion

Neurosurgical consultation

Assess inflammatory process in CSF:
- Cell count, protein, sugar

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)

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)

Acute CNS demyelinating
Rx

Immune mediated myelitis

Acute treatment

AQP4-IgG

- Negative
  - Short myelitis
    - White matter predominate
    - MRI brain + whole spine with Gd
      - LETM
      - Fulfill MS diagnostic criteria
        - Yes
          - Oral prednisolone tapering within 3-6 months
          - R/O for other possible cause: Virus, Other systemic autoimmune disease (e.g. SLE, Sjögren)
        - No
          - CIS
          - Rx specific cause
- Positive
  - Long term immunosuppression
  - R/O for other possible cause: Virus, Other systemic autoimmune disease (e.g. SLE, Sjögren)

Additional tests:
- Oral prednisolone tapering within 3-6 months
- Fulfill MS diagnostic criteria
- Rx specific cause
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 \(\rightarrow\) 30 days)
- Plasmapheresis outcome is independent of serostatus \(\rightarrow\) 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 within 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 months
  - 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

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

- 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)

Third line Rx:
- Rituximab 1000 mg x2 (2 weeks apart) then q 6 months or 375 mg/m²/week x 4 then maintenance 375 mg/m²/week monitor CD19⁺27⁺ keep < 0.05% PBMC 0-2 years, then < 0.1%
- Cyclophosphamide (pulse 500-1000 mg/m² monthly 3-6 months)
- Plasma exchange in cycles
- New drugs: Eculizumab, Inebilizumab, Tocilizumab, Satralizumab

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

Free of drugs,
If relapse: Rx as usual (IVMP, PLEX)

Rituximab 1000 mg
Rituximab 1000 mg
Rituximab 1000 mg

← 2 weeks →
← 1 month → Conception
Partum
←1 week→
Unplanned pregnancy or could not use rituximab

Mycophenolate, metrotraxate or cyclophosphamide **must be OFF** during pregnancy and lactating

<table>
<thead>
<tr>
<th>Prednisolone 10 mg/day</th>
<th>Prednisolone 15-20 mg/day</th>
<th>Prednisolone and AZA as usual but postpone lactating 4 hrs after drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine continue as usual dose: Keep WBC &gt; 4000</td>
<td>Keep WBC &gt; 8600 to avoid fetal hematopoiesis suppression</td>
<td></td>
</tr>
</tbody>
</table>

1. Advice of risk of minor congenital defect that may be found: facial cleft, IUGR
2. Monitor gestational DM

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1. In the relapsing phase
2. Clinical relapses $\geq 2$ in the past 2 years
3. EDSS from the last relapse (at least 3 months apart) $\leq 5.5$
4. Non-pregnant
5. Not in the progressive phase
**Diagram 1: Disease Modifying Therapies for MS**

<table>
<thead>
<tr>
<th>Level of Therapy</th>
<th>Level of Pharmacological Agent</th>
<th>Relapsing Remitting Active MS*</th>
<th>Aggressive Relapsing Remitting MS*</th>
<th>Secondary Progressive MS with Relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Therapy</td>
<td>First-line</td>
<td>Interferon beta/Glatiramer acetate*/Teriflunomide/Dimethyl fumarate*</td>
<td>Fingolimod/Natalizumab/Cladribine*</td>
<td>Interferon beta/Siponimod FDA US 2018</td>
</tr>
<tr>
<td>Escalation Therapy</td>
<td>Second-line</td>
<td>Fingolimod/Natalizumab/Cladribine*</td>
<td>Fingolimod/Natalizumab/Cladribine*</td>
<td>Ocrelizumab/Cyclophosphamide/Mitoantrone</td>
</tr>
<tr>
<td>Third-line</td>
<td>Alectuzumab/Ocrelizumab*/Cyclophosphamide/Rituximab/Mitoantrone</td>
<td>Alectuzumab/Ocrelizumab*/Cyclophosphamide/Rituximab/Mitoantrone</td>
<td></td>
<td></td>
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</table>

Relapse Therapy
- First-line: Methylprednisolone
- Second-line: Plasma Exchange

*Please note: Certain medications are not available in Thailand (Richtly 2561)
Aggressive MS by Thai guideline

- Disabling MS attacks at least 2 relapses in 1 year
- MRI
  - MRI brain with $\geq 2$ Gd lesions or high MRI brain T2 lesions ($\geq 9$ lesions)
  - MRI spine lesion $\geq 2$ 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/m² 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/m² /week x 4 then maintenance 375 mg/m² 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