Demyelinating Disease

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Therapy of two specific inflammatory demyelinating CNS diseases will be discussed in this course: multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD).

I. Multiple Sclerosis

Treatment of MS may be divided into four general areas: disease-modifying therapies (DMTs) for prevention of disease worsening; treatment of attacks; symptomatic therapy; and reparative/remyelinating therapies.

Disease-modifying therapies. There are no proven lifestyle, dietary, or other nonpharmacologic treatments to alter the long-term natural history of MS. There are 13 drug therapies approved for relapsing MS, including self-injectable drugs (5 beta-interferons; 2 glatiramer acetate preparations), 3 oral drugs (fingolimod, dimethyl fumarate, teriflunomide), and 3 intravenous drugs (natalizumab, alemtuzumab, and mitoxantrone).[1] These DMTs favorably influence relapse rate and MRI measures, and some also show benefit on disability assessments over the duration of 1-3 year controlled trials. None of the approved DMTs has significant benefit on progressive forms of MS with the exception of mitoxantrone (approved for secondary progressive MS (SPMS) but rarely used for safety reasons). The anti-CD20 monoclonal antibody ocrelizumab slows disease progression in primary progressive MS, a form for which there is as yet no other effective or approved treatment.[2] Ocrelizumab has been shown to be superior to interferon beta-1a in 2 large trials and US regulatory assessment is nearly complete.

Although there are few head-to-head trials and challenges comparing between studies, available evidence suggests that natalizumab, alemtuzumab and probably fingolimod may be categorized as “highly efficacious” DMTs. These are generally approved as second or third-line agents although in the US, fingolimod is considered a reasonable first-line option. The remaining self-injectable and oral therapies are considered “moderate or standard efficacy” first-line agents by both the FDA and the European Medicines Agency (EMA).[3]

Cumulative results from controlled trials suggest that there is a window of opportunity during the relapsing phase of MS to optimize DMT use in hopes of achieving long-term benefits such as delay or prevention of SPMS or need to gait aids. This window extends from first presentation (clinically isolated syndrome; CIS) to a currently unknown time during the relapsing phase when the mechanisms that will ultimately dictate conversion to SPMS are established.

There is much ongoing debate and research about optimal treatments strategies for relapsing disease. Should one use a traditional “escalation” strategy, beginning with a so-called first-line therapy and switching to riskier but highly efficacious drugs only if the first drug is deemed a failure? Or should most (or all) patients use highly effective drugs up front, perhaps with an “induction” strategy (e.g., with alemtuzumab) aimed at inducing longer term immunological modifications before there is evidence of advancing disease?

We do not yet have predictive biomarkers that allow treatment selection based on pharmacogenomics or other biological data. In practice, selection of an initial DMT is therefore influenced by disease course to date (relapse frequency, severity, and recovery; neurological exam status), MRI data (lesion burden, contrast-enhancing lesions; presence of markers associated with irreversible axonal loss such as T1-black holes and cerebral atrophy), and patient-specific factors (comorbidities, patient preferences). Most patients with “average” or “mild” disease activity and absence of markers that suggest a high risk of severe disease typically, but not always, select a first-line drug using the “escalation” approach. A particularly aggressive disease course may warrant use of a highly efficacious drug as first therapy. Choosing between the highly efficacious drugs usually hinges upon JC virus antibody status. Seropositive patients are at risk for progressive multifocal leukoencephalopathy (PML) with natalizumab and so that drug is typically avoided.

Regardless of treatment selection, a plan for clinical and MRI disease surveillance is needed for all DMT-treated patients. Treatment changes are considered if the treatment is not tolerated, causes serious adverse effects, or is not controlling the disease. Recent revisions to MS phenotype descriptors (CIS, relapsing MS, progressive MS) also include modifiers of "active/not active" or "worsening/without worsening". Regular clinical and annual MRI assessments of treated patients to detect clinical relapses and MRI activity (new/enlarging/enhancing lesions) are recommended in order to help determine whether relapsing MS is "active" and thus not fully controlled by the current DMT. Declaration of treatment failure is not always straightforward but some guides such as the modified Rio score, which takes into account relapses and MRI measures, can be used to assist decision-making.[4] Recently, the concept of "no evidence for disease activity" (NEDA) has gained popularity. The most advanced measure, NEDA-4, is achieved when a patient proves to have no clinical relapses, change in disability status, new/enlarging MRI lesions, or excessive cerebral atrophy over a specific period of time.[5] It is not yet clear whether short-term NEDA achievement is predictive of the desired long-term outcomes of prevention of SPMS and serious irreversible disability.

Initial treatment selection, specific drug risks, overall treatment strategies, and emerging DMTs will be discussed in greater detail at the course. Treatment of acute attacks, updates on symptom management, and an overview of novel reparative or remyelinating therapies in development will also be covered.

II. Neuromyelitis Optica Spectrum Disorder (NMOSD)

NMOSD is an inflammatory CNS disease that commonly causes transverse myelitis and optic neuritis but has a broader clinical and neuroimaging spectrum.[6] About 70% of cases are associated with antibodies to aquaporin-4 (AQP4).[7] It is particularly important to distinguish NMOSD from MS because of the fundamental differences in their treatment approach. Some MS therapies actually aggravate NMOSD.

Diagnosis of NMOSD

The International Panel for Neuromyelitis Optica Diagnosis (IPND) proposed revised consensus diagnostic criteria in 2015.[8] The new criteria use a single term, NMOSD. Patients are diagnosed with NMOSD with AQP4-IgG or NMOSD without AQP4-IgG.

The diagnosis of NMOSD with AQP4-IgG requires a positive serological test together with a clinical syndrome indicating involvement of at least one of 6 neuroanatomically-based CNS regions: optic nerve, spinal cord, area postrema of the dorsal medulla, brain stem, diencephalon, and cerebrum (Table 1). The 3 most common presentations (spinal cord, optic nerve, and area postrema) do not require MRI confirmation of any specific lesion pattern. Transverse myelitis associated with a non-LETM lesion (i.e., <3 contiguous vertebral segments long) can qualify an AQP4-IgG seropositive patient. A single brain stem attack is also sufficient for seropositive patients. Involvement of the diencephalon or cerebrum, both of which are less common and less specific symptomatically, require additional neuroimaging support, specifically findings of "NMOSD-typical" lesions.

NMOSD without AQP4-IgG diagnosis has more stringent criteria (Table 1). Involvement of 2 of 6 neuroanatomic regions is required. Although this could occur with one attack (e.g., classic Devic's syndrome of simultaneous LETM and optic neuritis), in practice it is most likely to be accomplished through multiple attacks. Spinal cord lesions must be meet LETM criteria (unlike AQP4-IgG seropositive patients).

Care is required to exclude competing disorders, especially in AQP4-IgG seronegative cases. "Red flags" can alert the clinician to alternative diagnoses; see the IPND paper for complete details. A final diagnostic requirement is that there is no better explanation for the clinical syndrome than NMOSD.

Table 1. NMOSD Diagnostic Criteria for Adult Patients

Diagnostic Criteria for NMOSD with AQP4-IgG

1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses

Diagnostic Criteria for NMOSD without AQP4-IgG or NMOSD with Unknown AQP4-IgG Status

1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
    a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
    b. Dissemination in space (2 or more different core clinical characteristics)
    c. Fulfillment of additional MRI requirements, as applicable
2. Negative test(s) for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses

Core Clinical Characteristics

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brain stem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

Additional MRI Requirements for NMOSD without AQP4-IgG and NMOSD with Unknown AQP4-IgG Status

1. Acute optic neuritis: requires brain MRI showing a) normal findings or only nonspecific white matter lesions; or b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm
2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) or ≥3 contiguous segments of focal spinal cord atrophy in patients with prior history compatible with acute myelitis
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions
4. Acute brain stem syndrome: requires associated peri-ependymal brain stem lesions

Treatment of NMOSD

The natural history of NMOSD is worse than that of MS. Individual attacks are more severe, recover less well, and disability milestones are met earlier. Within 5 years, more than 50% of NMOSD patients are functionally blind (visual acuity worse than 20/200) or have lost the ability to ambulate without assistance. All AQP4-IgG seropositive patients and AQP4-IgG seronegative patients with relapsing disease require preventive therapy.

Acute attacks:
First line: Intravenous corticosteroids
Rescue: plasma exchange
Other considerations: intravenous immune globulin (IVIG), cell-depleting therapies

Relapse Prevention
Drugs to avoid. Current approved immunomodulatory MS therapies such as beta-interferon or glatiramer acetate appear to be ineffective for NMOSD. Moreover, NMOSD exacerbation has been reported with beta-interferon drugs, natalizumab, fingolimod, and alemtuzumab; these drugs should be avoided.

Available treatments. There are no completed randomized controlled trials of preventive therapies in NMOSD. Case series suggest that immunosuppressive therapies reduce relapse rate and are associated with preserved neurological function.[9] General immunosuppressants such as oral corticosteroids, azathioprine, mycophenolate mofetil, mitoxantrone, and methotrexate have been reported to be helpful. Available therapies with greater immunological target specificity include the monoclonal antibodies rituximab (anti-CD20; B cell depleter) and tocilizumab (anti-interleukin-6 receptor). Miscellaneous maintenance therapies with broad immunological effects include intravenous immunoglobulin and plasma exchange but evidence is very limited for each.

*Treatment strategies***.** There are no validated treatment algorithms for attack prevention. Most patients are treated with one of the following 3 therapies: rituximab, mycophenolate mofetil, or azathioprine. In some world regions, oral corticosteroids or mitoxantrone are used as first-line treatments. If there is breakthrough disease on

a first drug, switching to one of the other available agents is often successful at inducing remission, at least for 1-2 years as reported in several case series. Drug combinations can be tried for those with breakthrough disease (e.g., adding mycophenolate to rituximab). There is less experience to date with tocilizumab but it has been reported to be beneficial in case series of patients with active disease despite use of rituximab.

Emerging Therapies. Identification of AQP4-IgG as the likely cause of seropositive NMOSD has facilitated dozens of potential opportunities for treatment. A prospective study demonstrated good safety, tolerability, and preliminary efficacy of the monoclonal antibody eculizumab, which targets the terminal component of complement [10]. Only 2 possible attacks occurred amongst 14 AQP4-IgG seropositive individuals during one year of therapy and several relapses occurred after eculizumab was discontinued and the subjects transitioned to other immunotherapies. A phase 3 RCT is underway. Other RCTs currently in progress include studies of the anti-CD19 monoclonal antibody MEDI-551 (causes B cell depletion; affects more cell subtypes than rituximab) and the interleukin-6 receptor monoclonal antibody SA237.

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