THE EXPANDING ARMAMENTARIUM OF MULTIPLE SCLEROSIS DISEASE MODIFYING THERAPIES: MULTIPLE SCLEROSIS OVERVIEW II: CLINICAL ADVANCES

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Brief Overview

It is extremely important for clinicians treating multiple sclerosis (MS) to enhance their knowledge base about the changing landscape of the MS disease modifying therapies (DMTs). Making treatment decisions for an individual MS patient is a daunting task and the individualized patient benefit-risk assessment becomes increasingly difficult as new therapies emerge. Without the availability of direct comparative trials, clinicians are challenged with assessing emerging literature and asking whether new agents are more efficacious, offer more favorable safety profiles, and provide any additional practical advantages. Furthermore, if and when these therapies become available, clinicians need to have a full understanding of the risks/benefits and how they fit into their treatment armamentarium.

Why should we care about a new treatment paradigm in MS?

- Based on natural history studies, the majority of untreated MS patients develop disability[1]
- Treating early is extremely important for preventing future MS disease activity as demonstrated in multiple clinical isolated syndrome clinical trials
- Early clinical (relapses) and paraclinical (magnetic resonance imaging [MRI]) biomarkers are associated with future risk of disease activity and long-term risk of disability[2-4]
- Newer medications appear to be more effective
- Prevent epitope spreading
- Switching therapies after disability accrues is problematic[5]

There have been several clinical and paraclinical factors identified that are associated with a more aggressive phenotype of MS.[6] These include the following (below):

Clinical factors

- Male gender
- Older age at onset
- African American
- Motor involvement
- Cerebellar involvement
- Sphincter involvement
- Frequent relapses
- Poor recovery from relapses
- Multifocal involvement at onset

Paraclinical factors

- MRI high lesion burden at presentation
- Two gadolinium-enhancing/new T2 lesions or more than 2 T1-hypointense lesions
- Two spinal cord lesions
- Brain atrophy

- Low vitamin D

The Barcelona inception cohort study was designed to determine the factors that add value to clinical and brain MRI changes occurring during the first year, to predict conversion to clinically definite MS and disability accumulation (*N* = 1015 CIS patients [from 1995 until 2013]).[7]

Key Findings:

- First year clinical and brain MRI changes further improve the estimation of individual prognosis
- Independent predictors of further attacks:
  - Baseline lesions, new T2 lesions during the first year, DMT before second attack
- Independent predictors of accumulation of disability:
  - Oligoclonal bands, new T2 lesions, and incomplete recovery from relapse

Disease modifying therapies; good, bad, and ugly

There are a cascade of events that have to occur in order to lead to the MS lesions we see on MRI and the disability that we see at the bedside. It is extremely important for all of us to have a basic understanding of immunology as it relates to MS, because this will help us better understand how DMTs work and it will also help us understand the possible complications associated with these agents.

The current and emerging therapies target various regions of the MS immune attack. These different therapeutic strategies may help change or influence the way the immune system is behaving in MS. One way is using a broad immunosuppressant (AKA, non-biased approach). Another way is using a more selective approach as we see with monoclonal antibodies. Many of our current and emerging DMTs fall in the middle of the treatment spectrum. The landscape of MS therapeutics has changed significantly over the last two decades. At this time, there are more than 10 FDA approved therapies and over the next couple years there will likely be a couple more agents approved for use in MS.

Current DMTs efficacy profiles from initial pivitol clinical trials[8-18]

The various injectable therapies (interferon and glatiramer acetate) impact on reducing the annualized relapse rate (ARR) versus placebo ranged from 18% to 36%. Their impact on reducing gadolinium enhancing lesions compared to placebo ranged from 50% to 86%. Sustained disability progression (at 12 weeks) as measured by the expanded disability status scale (EDSS) was significantly decreased compared to placebo for most of the injectable therapies.

The oral therapies (fingolimod, dimethyl fumarate, teriflunomide 14mg) impact on reducing the ARR compared to placebo ranged from 32% to 54%. Their impact on reducing gadolinium enhancing lesions compared to placebo ranged from 80% to 90%. Disability progression was significantly decreased compared to placebo for these therapies (range 30% to 38%).

The intravenous therapy, natalizumab, impact on reducing the ARR compared to placebo was 68%. This agent's impact on reducing gadolinium enhancing lesions compared to placebo was 92%. Disability progression was significantly decreased compared to placebo by 42%.

The intravenous therapy, alemtuzumab, impact on reducing the ARR compared to interferon beta-1a in CARE-MS 1 and CARE-MS 2 ranged from 49% to 55%. There was a modest impact on MRI measures and disability progression was significantly decreased in only CARE-MS 2.

Current disease modifying therapies (DMTs) safety profiles; minor and major side effects[19-30]

Interferon therapies minor side effects may include injection site reactions, flu-like symptoms, headache, mild transaminitis, and depression. This class of therapies major side effects may include suicidal ideation, anaphylaxis, severe transaminitis, provoke rheumatic conditions, congestive heart failure, blood dyscrasias, seizures, and autoimmune hepatitis.

Glatiramer acetate's minor side effects may include injection site reactions and a post-injection vasodilatory reaction. This therapies major side effects may include lipoatrophy, skin necrosis, and anaphylaxis.

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Fingolimod's minor side effects may include lymphopenia (absolute lymphocyte count >200) and mild transaminitis. This therapies major side effects may include symptomatic bradycardia, heart block, hypertension, herpetic infections, lymphopenia (absolute lymphocyte count <200), severe transaminitis, macular edema, skin cancer, reactive airway, PRES, and PML.

Teriflunomide's minor side effects may include diarrhea, nausea, and hair thinning. This therapies major side effects may include transaminitis, lymphopenia, teratogenic (men and women), latent tuberculosis, neuropathy, and hypertension.

Dimethyl fumurate's minor side effects may include flushing and gastrointestinal distress. This therapies major side effects may include transaminitis, leukopenia, and PML.

Natalizumab's minor side effects may include headaches, joint pain, fatigue, and wearing off phenomenon. This therapies major side effects may include progressive multifocal leukoencephalopathy, infusion reaction, herpes zoster, other infections, and liver failure.

Alemtuzumab's minor side effects may include infusion reactions. This therapies major side effects may include autoimmune thyroid disease, ITP, Goodpasture syndrome, and infections (HSV, VZV).

Important safety monitoring can be found in the prescribing information for each medication.

Recently Approved and Late Stage Emerging Therapies

Daclizumab HYP is a humanized monoclonal antibody against CD25, the high-affinity α-subunit of the IL-2 receptor.[31-32] It is administered subcutaneously once a month. Two proposed main mechanisms of action; activate/expand $CD56^{bright}$ NK cells; inhibit antigen-specific T-cell activation. DECIDE trial (Phase III): Daclizumab HYP vs IFN β-1a (N = 1841) for 96 weeks.[33]

- Annualized relapse rate: ↓ 45%
- Disability progression: 3-month 16% reduction (p = .16) and 6-month 27% reduction (p = .033)
- MRI: 65% reduction in new gadolinium-enhancing lesions vs IFNβ-1a

Potential main side effects[34-36]

- Cutaneous events, including severe skin reactions
- Elevated liver enzymes

- Infections
- Secondary autoimmune disorders
- Diffuse lymphadenopathy

Ocrelizumab is a fully humanized monoclonal antibody targeted against CD20 B cells which is infused every 6 months. Ocrelizumab's impact on reducing the ARR compared to interferon beta-1a in OPERA I and II ranged from 46% to 47%. The impact on reducing gadolinium enhancing lesions compared to interferon ranged from 94% to 95%. Disability progression was significantly decreased compared to interferon (range 37% to 43%).[37-38]

In the Oratorio primary progressive MS clinical trial, Ocrelizumab demonstrated a significant impact of decreasing both 12 week and 24 week disability progression (24-25%) compared to placebo.[39]

Side effects of Ocrelizumab infusion reactions and opportunistic infections.[40-41]

Switching a patient with MS with breakthrough disease to another therapy is associated with reduced relapse risk and starting with a higher efficacy therapy appears to be more beneficial than starting off on a lower efficacy therapy.[42-47]

One study demonstrated the impact on annualized relapse rate before and during the first treatment as well as after switch (see below):
Switching from interferon beta to glatiramer acetate: 0.50, 0.55, and 0.25
Switching from glatiramer acetate to interferon beta: 0.90, 0.50, and 0
Switching from one interferon to another interferon: 0.50, 0.68, and 0

In another study, switching from a first-line to a second-line therapy demonstrated reduction in relapse rate (see below):
Switching from first-line therapy to natalizumab: 70% reduction in relapse rate (95% CI 50, 82%; $p<0.001$)
Switching from first-line therapy to immunosuppressant: 77% reduction in relapse rate (95% CI 59, 87%; $p<0.001$)

Large, observational studies have also demonstrated a robust positive impact on MS disease activity after switching from first-line therapies (injectables) to second-line therapies (natalizumab and fingolimod). Moreover, another study demonstrated that first-line natalizumab treatment was associated with a greater, sustained reduction in relapse rate, including in the higher disease activity subgroups, than injectable therapies.

Lastly, higher efficacy disease-modifying therapies may differentially impact neurodegenerative measures that are associated with long-term disability as shown in a recent study using a non-invasive retinal imaging (optical coherence tomography [OCT]).[48]

Novel treatments in MS; Remyelination

There are two main strategies for remyelination; endogenous and exogenous. Endogenous stem cells are present within the central nervous system including neural progenitor cells. This approach allows natural remyelintion and repair to occur. Exogenous stem cells are from another human source and requires purification, culture, transplantation, and immunosuppression.[49]

Anti-LINGO is a fully humanized monoclonal antibody that targets the cell surface glycoprotein LINGO-1; negatively regulates myelination/regeneration of CNS axons.[50] Anti-LINGO has shown to promote remyelination in vitro and in EAE. It is administered via infusion every 4 weeks. Two phase II studies have been conducted with this agent. The RENEW study included 82 patients with first episode of optic neuritis; standard of care and 100 mg/kg anti-LINGO-1 or inactive placebo every 4 weeks for 20 weeks. This study was successful as the primary outcome was met; VEP conduction velocity (34% percent improvement, week 24; 41% improvement, week 32.[51] The second Phase II study, SYNERGY, did not meet the primary outcome of the study; however, there was a subgroup of patients that did seem to benefit which will be reviewed.[52]

The exogenous stem cell study, High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT-MS), was a phase II clinical trial for aggressive relapsing-remitting MS. This study included 24 patients with a primary endpoint as event-free survival (EFS) which was defined as no death or disease activity (i.e., no disability progression, relapse, or new lesions on MRI). Participants were evaluated through 5 years and the overall EFS was 69.2%.[53]

Key Considerations in Treatment

- Disease severity and burden
  - Recovery from relapses, MRI lesion burden, location of lesions
- Clinical and radiological disease activity (No Evidence of Disease Activity-NEDA)
  - Relapse frequency, MRI activity
- Prior treatment(s)
- JCV antibody status
- Risk tolerance
- Desire to pursue pregnancy

Reasons to Consider Switching Treatments

- Breakthrough disease activity (*Zero tolerance policy?*)
  - Definite relapses
  - Examination changes suspicious for disability progression
  - MRI activity (new/enlarging T2 lesions, Gd lesions): Even when asymptomatic
- Neutralizing antibodies
- JCV antibody seroconversion
- Poor adherence
- Intolerable medication side-effects
- Switching therapies is not without risks; Breakthrough/rebound disease activity, washout concerns and risk for PML vs leaving patient untreated, timing of treatments with potential for long-lasting lymphopenia will become increasingly important

Conclusions

- The world of MS therapeutics is evolving and becoming more complicated (↑ efficacy = ↑ risks).
- Treating early and having a low threshold to escalate therapy are key.
- Current clinical and paraclinical biomarkers can be helpful for assessing treatment success or failure, although combining outcomes may be more informative (NEDA/NADA).

- No more “one size fits all” dogma; ongoing need to balance efficacy, safety, and tolerability of therapeutic interventions for each patient.
- Putative re-myelinating/neuro-repair trials are underway.
- Additional research needed to examine the potential disconnect between neuro-inflammation and neurodegeneration.

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