Moving Towards a Cure for MS: Increased Immunosuppression and Striving for No Evidence of Disease Activity (NEDA)

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ABSTRACT

Multiple sclerosis (MS) is a chronic central nervous system demyelinating disease. The cause is unknown, but likely results from a combination of genetic predisposition and environmental exposures leading to autoimmune destruction of the brain and spinal cord. The most common phenotype of MS is relapsing-remitting (RRMS), characterized by episodes of neurological symptoms, typically lasting days to weeks, followed by symptom remission. After years of disease, the majority of RRMS cases transform into secondary progressive MS (SPMS), characterized by slowly worsening symptoms and progressive neurological disability, which may or may not be also accompanied by superimposed relapses. A third distinct phenotype, primary progressive MS (PPMS) is characterized by slowly worsening neurological symptoms and disability from disease onset, without clinical relapses.

The first disease-modifying agent was approved by the FDA in 1993. There are now 14 FDA-approved disease-modifying therapies (DMTs) with almost all agents indicated for relapsing forms of MS. The medical management of multiple sclerosis has changed dramatically over the past decade as the number of available DMTs has increased [See Table 1].

Most of the newer agents have been shown to decrease clinical relapse rates to a greater degree than the older agents. These DMTs frequently also decrease the rate of disability progression in MS. With the increased immunosuppression of the newer therapies comes the potential for more serious side effects. Balancing efficacy with potential adverse events is a primary consideration of patients and clinicians treating MS today. The potential for near complete control of the disease is becoming a reality in select cases, and a new goal of “no evidence of disease activity” (NEDA) may be supplanting the previous aim of relapse rate reduction.

KEYWORDS: multiple sclerosis, NEDA, disease-modifying therapy, PML

ESCALATION VS. INDUCTION THERAPY

Early in the disease course, multiple sclerosis is characterized by periods of inflammation associated with demyelination and axonal injury. However, as the disease reaches a later progressive phase, inflammation and relapses become less prominent and neurodegeneration becomes the more defining feature of the illness. It has been proposed that aggressive treatment early in the disease course may have a greater effect on morbidity in multiple sclerosis because it is during this period that DMTs have the greatest opportunity to reduce inflammation. Two strategies used in selecting the best DMT to treat an individual MS patient are “escalation” and “induction” therapy. An escalation approach has been widely utilized in the treatment of multiple sclerosis since the 1990s. This entails starting a patient on a first-line agent (typically glatiramer acetate or interferon-beta) and transitioning to a second-line agent only in the event of disease progression while on therapy. This is a reasonable strategy, as a patient may be well controlled on an agent with a long safety profile history. However, this approach does not take into consideration how early or late a patient is in their disease course or the degree of initial clinical or radiographic activity. Ultimately, the majority of patients starting treatment with glatiramer acetate or interferon-beta will continue to show evidence of disease activity. If there truly is a critical period early in the disease course where DMTs can provide the greatest impact, an aggressive approach may instead be warranted. This practice is analogous to induction chemotherapy for some cancers. Induction therapy is the alternative strategy where drugs with the highest efficacy are used for a defined period of time as an initial treatment despite their increased risk of serious side effects. Using an induction strategy to control inflammatory disease activity early in the course of MS, may ultimately decrease long-term disability.

FIRST-LINE AGENTS

Glatiramer acetate and several interferon-beta preparations [See Table 1] are frequently considered first-line agents. Each of these self-injectable agents reduces relapse rates in relapsing MS by modest amounts (approximately 30–35% relapse rate reduction), but their effectiveness in preventing long-term disability progression is limited.

The three oral agents approved for relapsing MS represent an advance in the treatment of the disease by reducing relapse
rates to a greater degree when compared to the self-injectable agents, and in some cases showing decreased rates of disability progression.\(^5\) Fingolimod and dimethyl fumarate both reduce relapse rates vs. placebo by approximately 50%.\(^5,6\) Fingolimod also reduces relapse rates compared to an active comparator, intramuscular interferon beta-1a.\(^6\) Teriflunomide reduces relapse rates by approximately 30% in relapsing MS and decreases the risk of sustained disability progression compared to placebo by ~26% over a two year period.\(^7\)

Despite the improvements in efficacy with the oral agents, there are still many patients who experience clinical relapses, new MRI disease activity, and disability progression on these medications. Unfortunately, clinicians’ ability to predict from disease onset which patients will fail to respond to the first-line injectable or oral agents is limited.

**MONOClonAL ANTIbodies: MORE EFFICACIOUS, BUT GREATER RISK**

To justify the use of agents with increased serious side effects, the disease severity may be considered. Some patients with multiple sclerosis have a rapidly progressive course and respond poorly to first-line agents. In this population, the risk of serious side effects from a second-line agent may be acceptable. Using a Canadian database containing 5891 patients with adult-onset MS, an attempt was made to define aggressive multiple sclerosis |AMS. The three definitions proposed were: (1) Expanded Disability Status Scale (EDSS) 6 or greater within 5 years of symptom onset, (2) EDSS 6 or greater by age 40, or (3) secondary progressive course within 3 years of relapsing-onset course. Depending on the definition, between 4–14% of patients were characterized as having aggressive multiple sclerosis. There was a higher likelihood of aggressive MS in patients who were male, older at symptom onset, or presented with PPMS.\(^8\)

An aggressive treatment approach could also be considered to achieve a disease activity free status in multiple sclerosis. The term “no evidence of disease activity” [NEDA] has emerged to describe this disease activity-free state.\(^9\) More specifically, NEDA-3 has been defined as: [1] absence of relapses, [2] absence of focal MRI activity, and [3] absence of confirmed disability progression. While NEDA-3 captures inflammatory disease activity well, it may not fully account for the neurodegenerative component of MS. Thus another more stringent definition was developed. NEDA-4 includes the criteria included in NEDA-3, but also requires an annualized rate of brain volume loss of less than 0.4%.\(^10\) Since brain volume loss has been shown to correlate with disability progression and cognitive decline, this definition may more accurately reflect a complete absence of disease activity. However, other researchers have noted that NEDA criteria do not fully capture disability related to MS, neglecting some cognitive measures, visual function, fatigue, and pain.\(^11,12\)

Natalizumab was first approved by the FDA for the treatment of relapsing forms of MS in 2004. The medication is a humanized monoclonal antibody which binds to the \(\alpha_4\) subunit of \(\alpha_4\beta_1\) and \(\alpha_4\beta_7\) integrins on the surface of lymphocytes. Binding to these integrins blocks lymphocytes’ ability to interact with endothelial cell receptors (VCAM-1 and mucosal addressin-cell adhesion molecule 1) and prevents lymphocyte migration into the central nervous system. In clinical trials, natalizumab reduced clinical relapses (67% relapse-free at two years), new MRI disease activity (97% free of gadolinium enhancing lesions at two years), and disability progression (no EDSS disability progression in 29% compared to 17% of placebo).\(^13\) The number of patients who met all the criteria satisfying NEDA-3 was not included in the final analysis of the study; however, a smaller Italian study of 152 patients with RRMS treated with natalizumab demonstrated that 34% of patients were able to maintain NEDA-3 status after 7 years of follow-up.\(^14\)
Alemtuzumab, another intravenous infusion agent, was approved for use in the treatment of relapsing forms of MS in November 2014. Alemtuzumab is a humanized anti-CD52 monoclonal antibody which binds to the CD52 receptor on B and T lymphocytes causing a long-lasting depletion of lymphocytes. Alemtuzumab is given as an infusion over 5 days initially, repeated once for a cycle of three more days after one year. Most patients do not require further treatment for a period of five or more years. Alemtuzumab is perhaps the only true induction agent for the treatment of relapsing forms of MS. Following depletion, there is a subsequent slow repopulation of these cells. In clinical trials compared to subcutaneous interferon-beta 1a, alemtuzumab was superior in achieving an endpoint equivalent to NEDA-3 [referred to as “freedom from disease activity” in the study]. 39% [139/360] of patients in the alemtuzumab arm maintained freedom from clinical or radiographic disease at 24 months compared to 27% of patients in the interferon beta 1a group. Furthermore, patients treated with alemtuzumab had less brain atrophy on MRI.15

The newest disease modifying agent, Ocrelizumab, was approved by the FDA in March, 2017 for both relapsing and primary progressive forms of MS. Ocrelizumab is a humanized monoclonal antibody that targets the CD20+ receptor found on pre-B cells, mature B cells, and memory B cells. This receptor is not present on stem cells or plasma cells. Thus the medication should preserve existing humoral immunity and potential for B cell reconstitution. The mechanism is identical to rituximab and only differs in that ocrelizumab is a humanized antibody rather than a chimeric antibody. In clinical trials of relapsing MS, ocrelizumab patients achieved NEDA-3 approximately 47% of the time, compared to approximately 27% in subcutaneous interferon-beta 1a.16 The rate of brain volume loss in the ocrelizumab group compared with the subcutaneous interferon-beta 1a group was also decreased to a statistically significant degree in one study.

Ocrelizumab has also been shown to be effective in primary progressive MS. Although NEDA does not apply to PPMS and was not a secondary end point in this trial, the ocrelizumab patients had statistically significant better outcomes in disability progression (~25% relative risk reduction), volume of T2 lesions, and mean percentage change in brain volume when compared to placebo.17 Based on this clinical trial, ocrelizumab became the first FDA-approved agent for the treatment of PPMS.

The mainstay of relapse treatment continues to be intravenous high-dose methylprednisolone. Acthar Gel (repository corticotropin injection) is used in rare cases where IVSM is not tolerated.

**Autoologous Hematopoietic stem cell transplantation**

While modern disease modifying agents have demonstrated improved efficacy in minimizing disease progression in RRMS, autologous hematopoietic stem cell transplantation (AHSCT) for the treatment of MS, which can be considered the ultimate in induction therapies for MS, has also shown encouraging results. AHSCT for MS patients began in 1995 and by 2008 approximately 400 cases had been performed worldwide.18 Although protocols from early transplantations varied greatly, even initial data showed a slowing of disease progression in a majority of patients following treatment. However, the procedure carries significant risk and transplant-related mortality was initially as high as 7.3%.

The protocol for AHSCT varies at each institution, but in general involves four main steps. First, hematopoietic stem cells are mobilized, typically using granulocyte colony stimulating factor. Then hematopoietic stem cells are collected in the patient’s circulating blood. The patient’s remaining immune cells are then eradicated via a “conditioning” regimen using one or several chemotherapeutic agents, and lastly the previously harvested stem cells are reintroduced to the patient.18

AHSCT has demonstrated NEDA status rates of 78–83% at 2 years and 60–68% after 5 years.19

**ADVERSE EFFECTS AND MINIMIZING RISK**

Because NEDA is a new concept in the MS treatment field, specific NEDA rates of the older agents are not readily available. In longitudinal follow-up studies for the older agents, and in the clinical trials for the newer agents, NEDA status rates between 13–46% have been reported after two years of treatment. Direct comparison of NEDA status rates is impossible due to variations in the study populations.

Decisions about disease-modifying therapy must be made with consideration given to risks and side effects as well as efficacy. There are few serious side effects from the older self-injectable agents, but with newer oral and infusible agents, treating neurologists must monitor for specific side effects (See Table 2) including hepatic dysfunction, cardiac arrhythmia, and ocular disorders.

With the increased immunosuppression of the newer highly effective agents, there is increased risk of possible serious infections, secondary autoimmunity, and malignancy. One such serious infection is progressive multifocal leukoencephalopathy (PML), which is a rare brain infection that can be fatal. PML is associated with several of the DMTs used for MS, and in the highest risk patients may occur at a rate of 13/1000 individuals. Therefore, carefully selecting the appropriate DMT for each patient is critical.

Despite the increasing number of medications, the cost of each of these drugs remains prohibitively high for many patients. On average, treatment with one of these agents costs $55,000/year and decision-making often requires consideration of insurance coverage limitations.

**CONCLUSIONS**

As newer therapies are used more frequently as the initial treatment in MS, and therapies are modified and refined to minimize side effects, there will likely be improved long-term outcomes and increasing rates of NEDA. The goals for
an individual patient starting treatment for MS today are shifting from reducing relapses to completely controlling the disease clinically and radiographically. Reducing disability in the long-term and decreasing morbidity of the disease over many years is becoming a reality. Although none of the treatments discussed here is a cure for MS, the field is increasingly moving toward that goal as patients and providers become less accepting of new symptoms, signs, or MRI changes.

References

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Table 2. Common and serious potential side effects of the disease-modifying agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common side effects</th>
<th>Serious potential side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon-beta</td>
<td>Post-injection flu-like symptoms</td>
<td>Rare</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>Injection site reaction (skin irritation)</td>
<td>None</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Few</td>
<td>Heart failure (0.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hematological malignancy (0.8%)</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Few</td>
<td>PML JCV + patients (1/1000 patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JCV – patients (extremely rare)</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Few</td>
<td>Macular edema (0.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heart block (0.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PML (extremely rare)</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>Mild alopecia</td>
<td>Hepatic dysfunction (uncommon)</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>Gastrointestinal upset, Abdominal cramping</td>
<td>PML (extremely rare)</td>
</tr>
<tr>
<td>Peginterferon-beta 1a</td>
<td>Post-injection flu-like symptoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Injection site reaction</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver function abnormalities</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Infusion reaction</td>
<td>Immune thrombocytopenic purpura (ITP) (1%) Autoimmune thyroid disease (30%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serious infections (uncommon)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glomerular disease (0.3%)</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>Skin rash</td>
<td>Hepatic dysfunction (rare)</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>Infusion reaction</td>
<td>Breast cancer? (unclear evidence)</td>
</tr>
</tbody>
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