Andiamo! Moving forward with autologous hematopoietic transplantation for highly active MS

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The cause and exact processes underlying the pathophysiology of multiple sclerosis (MS) development and progression have eluded clinicians and scientists for almost 150 years, since Jean-Martin Charcot recognized it as a distinct disease. Based on current understanding, an inflammatory immune response, potentially elicited by a common pathogen or unidentified microbial or environmental agent, is inappropriately targeted against CNS components, possibly a myelin protein, and not properly tempered by immune regulatory circuits. Blood-derived T and B cells are critical components of the adaptive immune response that initiates the inflammatory attack, although innate immunity is also implicated, with macrophages and microglia operating as antigen presenting cells, as demyelinating effector cells, and possibly as mediators of a diffuse chronic CNS inflammatory state.

Various components of the inflammatory process have been targeted with immune-modifying therapeutics with increasing degree of success. The majority of these agents require frequent self-administration or periodic infusion to maintain their disease-modifying effect. Although some recently approved disease-modifying treatments (DMTs), such as natalizumab and alemtuzumab, appear more effective than first-generation DMTs, such as interferon-β and glatiramer acetate, breakthrough of disease activity can occur and some patients continue to develop inflammatory lesions and accumulate disability, either from incomplete recovery of relapses or from progressive disease. No treatment prevents the onset or arrests the course of progressive MS.

Hematopoietic stem cell transplantation, a procedure routinely utilized for hematologic malignancies, such as leukemia and lymphoma, has been investigated as a therapy for severe autoimmune disease, including MS.[1] Although allogeneic transplantation is required to cure the majority of lymphoid cancers and would be theoretically preferable to autologous hematopoietic stem cell transplantation (AHSCT) to eradicate autoimmune diseases, AHSCT can be performed with greater safety and without the threat of graft vs host disease and its attendant risks. Increasing mechanistic evidence suggests that the mode of action of AHSCT does not solely rely on an initial profound immunosuppression, but is related to the reconstitution of a qualitatively different immune system, with a renewed T-cell repertoire,[2,3] from enhanced thymic output[2] harboring reduced number of proinflammatory effector T cells,[4,5] enhanced frequency of regulatory cells,[5] and relative normalization of global gene expression profiles.[6] The clinical effects of this one-off procedure are highly promising, and spectacular responses have been documented in patients with highly aggressive, malignant forms of MS, when AHSCT was performed during the early course of disease.[7] Remission of relapses and suppression of subclinical inflammation without maintenance therapy following AHSCT can occur in a majority of patients with MS, who previously exhibited moderately to highly inflammatory active disease during conventional treatment.[1] Confirmed improvement in disability after AHSCT was reported in patients with relapsing-remitting MS.[8] None of these studies, however, included a control arm, and it remains unknown how the safety and efficacy of AHSCT would compare to an approved treatment.

In this issue of *Neurology*®, Mancardi et al.[9] report the first randomized controlled multicenter trial of intense AHSCT vs approved therapy for treatment of highly active MS not responding to conventional therapy. Mitoxantrone, an immunosuppressant and immunomodulatory agent exerting a strong suppressive effect on the development of gadolinium-enhancing lesions and approved in several countries as second- or further-line treatment for MS, was chosen as control arm. The main findings were that in the 4 years following randomization, AHSCT exhibited a 79% suppression of new T2 MRI lesions compared to mitoxantrone, a large and significant reduction. Differential treatment effects in favor of AHSCT were also observed for gadolinium-enhancing lesions. Strikingly, none of the patients treated with AHSCT had a gadolinium-enhancing lesion during the follow-up, whereas 56% of patients in the mitoxantrone arm had at least 1 gadolinium-enhancing lesion. On the other hand, it was not surprising that there were no

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differences in the experimental vs control treatment arms on progression of disability and Expanded Disability Status Scale scores, since the study was clearly underpowered for detecting such differences. Safety and tolerability were in line with data from the more recent (post 2000) transplantation activity for MS reported to the European Blood and Marrow Transplant database[1]: there was no mortality in the trial and all serious adverse events, expected in the AHSCT arm by the nature of the procedure, resolved without permanent consequences.

Along with its merits, some limitations of this study should be highlighted. As acknowledged by the authors, the number of patients in the study was small (21 patients enrolled, with completed MRI assessments available in only 17). Furthermore, mitoxantrone would not be a contemporary choice as comparator treatment, having lost traction because of its cardiac toxicity and risk of lymphoma. It was, however, the most appropriate control treatment at the time the trial was initiated, and it remains an adequate efficacy comparator because mitoxantrone is highly active on the main trial endpoints (new MRI lesions development), possibly to a degree similar to newer DMTs such as natalizumab, notwithstanding its higher toxicity. Although comparisons among protocols are difficult, in the pivotal trials mitoxantrone combined with methylprednisolone showed an 84% reduction in the number of gadolinium-enhancing lesions compared to the methylprednisolone-only control arm over 6-month monthly MRI[10] and natalizumab showed a 92% reduction compared to placebo at 2 years.[11] The proportion of patients who did not develop new gadolinium-enhancing lesions (90% of mitoxantrone-treated vs 31% of methylprednisolone-only-treated patients over 6 months)[10] was also comparable (97% of natalizumab-treated vs 72% of placebo-treated patients on the year 2 MRI scan).[11]

What are the implications of this study for clinical practice? For MS, AHSCT remains an unlicensed therapy, and more work is needed to define its clinical indication. A phase 3 trial randomizing patients to AHSCT employing a lower intensity (nonmyeloablative) immunosuppressive regimen or Food and Drug Administration–approved standard of care is under way (clinicaltrials.gov identifier: NCT00273364). More recently, consensus was reached on the design of a phase 3 trial comparing the efficacy of AHSCT utilizing an intermediate-intensity regimen against best available approved highly active therapy (including, but not limited to natalizumab, fingolimod, and alemtuzumab).[12] I anticipate that the article by Mancardi et al.[9] will raise interest and catalyze activities to move forward with the new trial. *Andiamo!*

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DISCLOSURE

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