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Editorial

B-Cell Depleting Monoclonal Antibodies for Multiple Sclerosis-A Paradigm Shift

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Introduction

Multiple Sclerosis (MS) is an autoimmune disease of the Central Nervous System (CNS) that often leads to a high level of disability for those affected [1]. Clinical attacks and typical CNS lesions that are disseminated in time and space are necessary to fulfill the current diagnostic criteria for MS [2]. The general consensus is there are 3 subtypes of MS which include the most common type, relapsing-remitting MS, with the majority of these patients eventually transitioning into the second subtype known as secondary progressive MS, and the third subtype being primary progressive MS. The hallmark of relapsing-remitting MS is that patients have clinical attacks where they partially or fully recover but then subsequently have more attacks which contrasts with primary progressive MS which is defined as patients experiencing gradual disease progression from the onset [2]. Further attempts have been proposed to refine these phenotypes of MS to more adequately reflect identifiable aspects that show ongoing disease activity, including active disease both clinically and radiologically [3]. The immune cells in MS target specific CNS antigens which leads to demyelination, glial activation, failure of myelin repair mechanisms, and the eventual loss of axons and neurons [4]. We are in the midst of a therapeutic revolution in the field of neurology and there is no better example of that than the progress that has been made over the last two decades in treating the disease of MS. The caveat to this is that the majority of treatments in MS have been developed exclusively for relapsing-remitting MS and have shown impressive reductions in the rates of relapse, slowing of new lesions seen on Magnetic Resonance Imaging (MRI), and some having an effect on slowing disability progression [5].

The mechanisms of action of the MS therapies vary quite significantly; for example, some attempt to block the trafficking of immune cells into the CNS, some target T-cell activation, and others target effector functions of the lymphocytes. Many current MS disease-modifying therapies have some effect on B cells. The importance of B cells in MS pathogenesis has been intensely researched over the last decade and it has become quite clear that at least a subset of B cells contributes significantly to disease progression. Since B cells also migrate into the CNS from the periphery, selective B-cell depleting therapies have been studied in MS. The first of these studies was conducted with rituximab, a chimeric anti-CD20 monoclonal antibody, and it was able to slow relapse rates and MRI lesions in relapsing-remitting MS however it was not able to show benefit in slowing down disability progression of those with primary progressive MS [6-8]. The exception to this being rituximab did show an ability to slow disability progression in the primary progressive study in a post hoc analysis of patients less than 51 years of age with MRI gadolinium enhancing lesions.

The most recent evidence to support B cell involvement in MS pathogenesis is the success of ocrelizumab, a fully humanized anti-CD20 monoclonal antibody tested in three separate phases 3 clinical trials; two identically-designed relapsing MS studies (OPERA I/II) and a primary progressive MS study (ORATORIO) [9,10]. In OPERA I/II, 1656 relapsing MS patients were randomized in a 1:1 fashion to receive either ocrelizumab 600mg intravenously every 24 weeks or interferon beta-1a 44µg subcutaneously three times a week in a double-blind, double-dummy design. Cumulative results showed a significant reduction in annualized relapse rate (47%) in ocrelizumab-treated patients over interferon beta-1a. Additionally, there was a significant reduction in confirmed disability progression along with decreases in new MRI lesions in the ocrelizumab-treated arms. ORATORIO became the first ever primary progressive MS clinical trial to have a positive primary outcome. Those treated with ocrelizumab showed a significant reduction in time to confirmed disability progression at both 12 and 24 weeks compared to placebo. Also, results showed MRI T2 total brain volume lesion burden decreased with ocreli-

zumab and increased with placebo. Based on the above data from the phase 3 relapsing MS and primary progressive MS studies, the FDA approved ocrelizumab for both relapsing and primary progressive MS on March 28, 2017, making it the first MS therapy to be approved for both forms of the disease.

All of this data combined clearly shows how B-cell depletion can have a positive impact on MS however the mechanism by which this occurs is still not fully elucidated. We know that B cells have multiple levels of impact on the immune system, including antigen presentation, antibody secretion, and releasing inflammatory cytokines [11]. Impacting these mechanisms by decreasing circulating B cells would likely have a positive impact on MS. For decades, the Epstein-Barr virus has been consistently associated with MS pathogenesis, in part due to its ability to react with myelin basic protein, and interestingly, B cells serve as a reservoir for this virus. Therefore, with B-cell depletion it can be postulated that this would decrease the reservoir and along with it the potential trigger of autoreactivity from the Epstein-Barr virus [12,13]. One potential explanation for the positive results of the ORATORIO trial is the average age of the cohort was lower than the general population of primary progressive MS patients, with a mean age of 45, and entry data showed patients with active disease o n MRI (>25% had gadolinium enhancing lesions). Generally, primary progressive MS is considered more neurodegenerative and less inflammatory than relapsing-remitting MS however this MRI activity on baseline scans for ORATORIO patients shows that at least a subset of patients entering the study were having acute inflammatory disease activity. This potentially would have afforded ocrelizumab the ability to have an anti-inflammatory effect on these patients thus contributing positively to the primary outcome. Beyond the anti-inflammatory effect, another possibility is that B cells through their abilities to secrete cytokines and their effect on immunoglobulin deposition after they enter the CNS, may have the ability to mediate some of the axonal neurodegeneration that occurs over time with primary progressive MS [14].

Therapies that suppress the immune system, even in a limited and targeted fashion such as seen with ocrelizumab, increase the risk for infections and potentially impair immune surveillance of new cancer cells, thus increasing the risk of neoplasms. Additional monitoring post-FDA approval, including the ongoing data collected from the extension studies of the core phase 3 trials, will be helpful to further define the long-term risk of chronic B-cell depletion. The balancing act of weighing the possibility of clinical stabilization or perhaps even improvement in those with either relapsing MS or primary progressive MS versus the very real and possibly even serious side effects associated with long-term ocrelizumab use will be challenging. This responsibility underscores the importance of clinicians to be able to relay the pros and cons of this therapy in a way that shared decision making with patients can occur. For example, patients that were primarily wheelchair bound were excluded from enrolling in the relapsing and primary progressive MS trials. Should clinicians not use this therapy in those types of patients? What if it is a patient with primary progressive MS who is non-ambulatory but has preserved upper extremity function and wants to be on a therapy that might prevent disease progression in their arms and hands? More studies are needed to more accurately assess the effect of disease-modifying therapies, including ocrelizumab, on preservation of upper extremity function. Furthermore, strong consideration should be made to fundamentally change clinical trial design to not exclude this type of patient from future clinical studies.

The importance of finally slowing primary progressive MS with a therapeutic intervention cannot be overstated. It truly represents a pivotal moment in clinical research in MS. Building on this momentum will be key to improving clinical outcomes for those afflicted with MS.

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