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Can Natalizumab be Safely Used After Ocrelizumab in Treating Multiple Sclerosis?

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Introduction

Multiple Sclerosis (MS) treatment decisions are complex given the myriad options available. MS patients require long term therapy, thus sequencing of medications also becomes an important and complex issue. With high efficacy treatments, the decision is particularly difficult since serious safety issues may arise. Two of the most widely used high efficacy treatments are Ocrelizumab (OCR) and Natalizumab (NTZ). OCR is a monoclonal antibody directed against CD20+ cells, resulting in profound peripheral B-cell depletion. In some, this can be associated with hypogammaglobulinemia, increased infections, or both. NTZ is a monoclonal antibody against VLA4, an adhesion molecule on the surface of leukocytes, which inhibits the trafficking of lymphocytes into the CNS. This inhibition leads to a reduction of immune surveillance in the CNS and increases the risk of developing progressive multifocal leukoencephalopathy (PML).

The optimal strategy for sequencing high efficacy MS therapies remains unknown. The MS community has become increasingly comfortable in switching patients from NTZ to OCR with minimal wash out period (<12 weeks) and to continue MRI monitoring for carry over PML for at least 6 months post last NTZ dose [1].

Switching from OCR to NTZ has not been as clearly protocolized in clinical practice, but deserves consideration. As evidence emerges on the benefit of utilization of high efficacy therapy early in the disease [2], these DMTs will be used for longer periods of time and will lead to clinical situations where such a switch is necessary.

The aim of this correspondence is to describe the considerations by which 2 MS specialists make treatment decisions and to highlight the knowledge gap which exists in consideration of sequencing from OCR to NTZ.

Case Examples

Case 1

A 35-year-old woman was diagnosed with relapsing MS at age 25 after presenting with a mixed motor and sensory spinal cord attack. She improved with corticosteroids and CSF and imaging was diagnostic of MS. Her first disease modifying therapy was NTZ, Q4 week dosing, with breakthrough asymptomatic enhancing lesion at 6 months of therapy. Neutralizing antibodies to NTZ were negative. She had a new internuclear ophthalmoplegia after 12 months of NTZ, without MRI correlate. After 36 months of NTZ she transitioned to the newly available OCR. After 5 years on anti-CD20 she developed Crohn's Disease. Vedolizumab was added to control IBD with good effect. 12 months later she developed symptoms of inflammatory vaginitis. Return to NTZ was initiated due to multiple emergent autoinflammatory conditions on anti-CD20 therapy. JC virus antibody (JCV Ab) was negative prior to starting anti-CD20 therapy and remained negative. The patient will transition to NTZ 6 months after last anti-CD20 infusion, planned for early 2024.

Case 2

A 22-year-old man, with a family history of MS, was diagnosed with relapsing MS at age 18 after presenting with bilateral leg paresthesias with lesions noted on MRI brain and spine. CSF oligoclonal bands were present. He initiated fingolimod which he did not tolerate, and switched to OCR at age 19. In years 2 and 3 of treatment with OCR, he reported eight upper respiratory infections of extended duration, usually requiring an antibiotic course. Although JCV Ab sero-positive (Index 1.67), he transitioned to NTZ for a planned duration of two years to cover the period of high infectious exposure of congregant dwelling at a university. NTZ was started eight months after the last OCR dose. Close radiographic follow up of MRI Brain performed every 4 months was initiated to assess for potential radiographic findings of asymptomatic PML.

Discussion

Although the use of NTZ prior to anti-CD20 therapy is preferred by the authors, situations such as these do arise that prompt consideration of NTZ after OCR or other anti-CD20 agents. Reasons for switching from OCR to NTZ can include infections on OCR which may or may not be related to hypogammaglobulinemia, duration of therapy, immunosenescence observed with older age or increase number of comorbidities and concern for observation of higher risk of serious infections in patient with higher EDSS [3,4].

Furthermore, ongoing therapy with OCR may result in attenuated humoral response post vaccination which may play an important consideration in setting of worldwide pandemic

as we have recently experienced with COVID-19 or in setting of patient's need to travel to parts of the world that require new vaccinations [5].

Another potential reason to trigger a switch from OCR is the risk of developing secondary autoimmunity, including colitis, which may trigger a switch of DMT. Although the exact pathophysiology of anti-CD20-induced colitis remains unknown, immunological dysregulation through treatment-mediated B-cell depletion has been proposed as a possible mechanism. A significant reduction in B cells and IL-10 caused by anti-CD20 therapies can therefore lead to CD4+ T cell proliferation and increased production of proinflammatory cytokines, disrupting gut homeostasis and causing colitis [6]. In fact, the US Food and Drug Administration (FDA) recently issued a warning regarding OCR due to reports of colitis among patients taking this medication. Patients may also experience infusion reactions (although more likely to occur during initial infusion) [7] or develop an intolerance to preinfusion medications use. Finally, patients may request a return to NTZ having seen a decline in a sense of "the feel-good effect" described with the drug [8], which has previously been described as a main reason for switching back to NTZ [9].

The ideal time of starting NTZ after OCR exposure has not been identified. We would argue that initiating NTZ within 3-6 months post last OCR exposure is good practice. We would suggest a shorter time between therapies (~3mo) for those patients with presumed aggressive disease which would allow NTZ to be near steady state at the time of B cell repletion is expected to occur. If infections are of a concern, clinicians may consider awaiting B cell repletion to start NTZ, weighing this risk against a potential exacerbation.

JCV index has become a standard in assessing PML risk in patients on NTZ. One concern that arises in patients transitioning from OCR to NTZ is the reliability of the anti-JCV index. Some studies have shown a decrease in JCV antibody index [10]. One study demonstrated a 14% decrease in the index with the authors suggesting that a decline in JCV antibody index likely represents the effect of anti-CD20 therapies on circulating antibodies and is not reflective of PML risk [11]. Therefore, it is prudent that clinicians do not rely on JCV index in assessing PML risk for the patient with OCR exposure and instead implement a high-risk MRI Brain surveillance protocol to assess for PML every 3-4 months. To our knowledge there are no studies available that can help determine when JCV index reliability can be restored, although one can hypothesize that resolution of hypogammaglobulinemia may result in restabilization of JCV index. Further studies should be done to evaluate this important clinical question.

In consideration of the ramifications of PML risk using NTZ after B cell depletion, especially in individuals with known sero-positive JCV index, there is currently limited evidence to guide treatment decisions. A recent paper by Mathias et al, demonstrated a depletion in memory CD8+CD20+ T cells post OCR. Although JCV specific cell immune responses were not studied, one can extrapolate a similar response [12].

Further PML risk stratification with NTZ depends on prior use of immunosuppressants. Patients with prior chronic immunosuppression have been shown to have significantly increased risk in PML [13]. A question arises whether patients treated with OCR should be considered to be in the same risk stratification. The data on original PML risk stratification looked at patients with older immunosuppressants that have a wide immunosuppression effect - unlike ocrelizumab [14]. Therefore, at this current time, we do not have evidence to suggest this similar risk applies to the patients at hand. However, close monitoring of these patients should be instituted, perhaps via the existing United States risk evaluation and mitigation strategy (REMS) program, TOUCH, so we can accurately assess if prior OCR exposure increases PML risk.

Although this manuscript considered switching patients from OCR to NTZ, the authors conjecture similar conclusions can be made with other anti-CD20 therapies available for MS, such as ofatumumab, ublituximab and the off label use of rituximab.

Conclusion

Although no guidelines exist on the sequencing of DMT, the use of NTZ, especially in those individuals who are seronegative for the JC Virus, should be considered prior to the start of the B cell depleting agents. However, in cases where NTZ has to be used after B cell depleting agents, implementing a high risk PML surveillance protocol with frequent MRIs is recommended even in those that are showing to be seronegative for the JC virus, given the lack of consensus on the reliability of this test after B cell depleting agents exposure. Further consideration should include the implementation of patient specific wash out that minimizes risk for relapse yet may reduce the risk of immunosuppression. Future studies are required to better understand the safety of NTZ after B cell depleting agents which should include a better understanding of cellular immunity to the JC virus after B cell depletion and inclusion of anti-CD20 agents use in the REMS TOUCH program so more comprehensive data of PML risk can be obtained.

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