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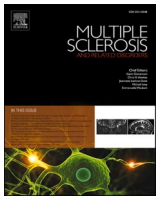

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Blunted vaccines responses after ocrelizumab highlight need for immunizations prior to treatment

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COVID-19 has reminded us that vaccines are lifesaving in high, middle and low-income countries. People with multiple sclerosis (pwMS), who are prone to inflammation-triggered disease exacerbation and treatment-induced opportunistic infections, might even be more at risk (Reyes et al., 2020). As the current treatment landscape directs a significant proportion of our patients towards ocrelizumab and other emerging anti-CD20 therapies, a study that helps us understand how this drug, as an example of CD20-monoclonal antibodies (mAb), affects the potential to mount antibody responses to vaccines and new antigens is much acclaimed.

From a mechanistic point of view, we know that CD20-mAb deplete all B cells apart from the long-lived plasma cells, most plasmablasts and lymphoid stem cells (Hauser et al., 2017) and that they ablate germinal centres (Ramwadhdoebe et al., 2019). This implies that crucial B cell functions such as antigen presentation (naïve and memory B cells), antibody formation, including class-switching, affinity maturation and production (naïve, memory and germinal centres B cells) are impaired. However, the extent of this dysfunction in the context of vaccine responses has remained poorly studied. Up until now, we had only indirect evidence available coming from mainly rituximab-treated subjects. Most informative were the results of a controlled trial including 103 people with rheumatoid arthritis comparing antibody responses in a methotrexate and methotrexate-rituximab arm (Bingham et al., 2010). Vaccine responses against tetanus vaccine were preserved among both immunosuppressed groups 24 weeks after treatment while responses to a neoantigen and pneumococcal vaccine were decreased. These findings were in line with the reduced seroprotection rate at 3–5 weeks following vaccination against influenza (H1N1) virus in rituximab (18.8%) vs. azathioprine (83.3%), IFN-β (87.5%) and healthy controls (100%) in 26 people with neuromyelitis spectrum disorder (Kim et al., 2013). Other studies also showed blunted post-rituximab responses following vaccination with *haemophilus influenzae* (Nazi et al., 2013) and hepatitis B (Richi et al., 2020) component vaccines. However, these studies are largely retrospective and heterogeneous in terms of the included age groups, autoimmune pathology and the extent of rituximab-induced B cell depletion.

In the VELOCE study, researchers evaluated if people on ocrelizumab who were fully B cell depleted were able to raise an antibody response to common vaccines and a neoantigen (Bar-Or et al., 2020). The study population (68 ocrelizumab, 34 controls) was exposed to four different vaccines/antigenic triggers: tetanus toxoid, pneumococcal and influenza vaccines as well as keyhole limpet haemocyanin (KLH). Response rates were evaluated at 4- and 8-weeks post-vaccination which corresponds to 16 and 20 weeks post-ocrelizumab dosing, respectively. Importantly, the antigenic triggers can be subdivided in two groups based on the likelihood of a previous exposure. First, it is very probable to have encountered some of the vaccine epitopes of the tetanus, pneumococcal and influenza vaccines. Tetanus vaccine requires boosters every ten years, and pneumococcal and influenza strains are ubiquitous pathogens. This implies that long-lived plasma cells can still exert their memory function and provide protection with well-targeted antibodies in the event of a recurrent infection. The VELOCE study showed that ocrelizumab-treated individuals are half as likely to mount an antibody response against tetanus toxoid vaccine (23.9% ocrelizumab vs. 54.5% controls) and two thirds less likely to mount an antibody response to 12 or more pneumococcal serotypes (37.3% ocrelizumab vs. 97.1% controls). On the other hand, the VELOCE study evaluated the response to the neoantigen KLH that requires recognition by naïve B cells (or other antigen-presenting cells) and subsequent transport to the germinal centres. The resulting antibody responses are worrisome as 12 weeks after KLH administration there was a 5-fold difference in IgM antibody levels and an 11-fold difference in IgG antibody levels between ocrelizumab-treated subjects and control subjects.

Overall, immune responses against pathogens encountered before ocrelizumab administration are significantly reduced but not absent. However, responses to entirely new pathogens (and thus realistically speaking also SARS-CoV-2 or COVID-19-related virus) (Doshi, 2020) cannot rely on an efficient antibody response and will be largely dependent on possible cellular immunity. Of note, patients included in the VELOCE study had only received a single course of ocrelizumab. As repeated 6-monthly infusions with ocrelizumab induce hypogammaglobulinemia and prohibit replenishment off the long-lived plasma cell pool, a reduction or greater blunting in the vaccine responses over time is to be expected, unless shown otherwise. Although the VELOCE study

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focuses on ocrelizumab, diminished responses after vaccination have also been reported for several other MS disease-modifying treatments rendering the topic of general relevance to derisk treatments (Reyes et al., 2020).

First and foremost, this study highlights the importance of immunizations prior to the initiation of ocrelizumab treatment. Although pneumococcal and influenza vaccines prior to ocrelizumab treatment are currently recommended and not obligatory (EMA, 2020), the potential gain in terms of meaningful humoral immunity is apparent. In this context, we recommend to vaccinate against *varicella zoste*r virus with the component vaccine (Shingrex™) to boost immunity to lower the risk of herpes zoster reactivation (Reyes et al., 2020). In people older than 50 years old, vaccine efficacy was 91.3% against herpes zoster infection and 88.8% against the development of postherpetic neuralgia compared to placebo (Cunningham et al., 2016). Moreover, an efficacy of 63.6% was shown in adults with solid tumor malignancies receiving chemotherapy compared to placebo (Mullane et al., 2019). Based on these recent data, the component vaccine has now officially been licensed by the European Medicine Agency for use in immunocompromised people. As approximately 2.1% of people treated with ocrelizumab are affected with zoster in the first year and a half of their treatment compared to 1.0% of individuals on interferon-beta (Hauser et al., 2017), the component zoster vaccine offers an opportunity to reduce the opportunistic burden associated with this treatment.

Moreover, the repopulation kinetics of a low-dose/high-frequency CD20-mAb regimen with ofatumumab vs. a high-dose/low-frequency ocrelizumab regimen might reflect on vaccine readiness. Also, the differences between both mAb when it comes to complement- vs. antibody-dependent lysis might be of relevance in this context (Hauser et al., 2020). After four intravenous infusions with 600 mg ocrelizumab, it takes a median time of 72 weeks for the total B cell counts to reach the lower level of normal (Baker et al., 2020). Based on the repopulation kinetics of other similar doses of ofatumumab, it is expected to take approximately 40 weeks for B cells to recover after 20 mg subcutaneous injections (Bar-Or et al., 2018). Although still far from ideal, the shorter time to repopulate B cells expedites vaccine readiness after treatment with ofatumumab. Nonetheless, the exposure-response profile of high- vs. low-dose CD20-mAb regimens also needs to be addressed in future studies. Higher doses of ocrelizumab have namely been associated with a greater risk reduction in terms of confirmed disability progression (Kletzl et al., 2019). Studies are needed to determine T cell responses to vaccine epitopes and titres of neutralizing antibodies to confer protection and whether dosing within the treatment cycle can achieve these.

Declaration of Competung Interest

I.S. and S.R. report no conflict of interests. In the last 5 years, G.G. has received compensation for serving as a consultant or speaker for or has received research support from AbbVie, Actelion, Atara Bio, Biogen, Canbex, Celgene, EMD Serono, Japanese Tobacco, Sanofi-Genzyme, Genentech, GlaxoSmithKline, GW Pharma, Merck, Novartis, Roche, Synthon BV and Teva. D.B. has received compensation for consultancy activities related to: Canbex therapeutics, InMune Bio, Lundbeck, Merck, Novartis and Roche.

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