Management challenges in MS: immunology Q&As

Dr Angela Vidal-Jordana

Q. A lymphocyte count of 0.3 x 10^9/L would be expected in patients with fingolimod – is this a concern to you?
A. Because of its mechanism of action, lymphopenia is a common and expected adverse reaction in fingolimod-treated patients and although it may put patients at a higher risk of opportunistic infections, fingolimod treatment should only be withdrawn if a lymphocyte count below 0.2 x 10^9/L, confirmed in a second blood test, is detected.

Q. Is there any role for checking vaccination status for MMR etc. at the beginning of the disease course so that we don't need to worry about it later when trying to transition to a higher-efficacy agent?
A. Yes, of course, you are absolutely right! Live attenuated vaccines are contraindicated when taking most multiple sclerosis (MS) treatments, and if vaccination is needed then treatment onset should be at least 4 weeks after vaccination. Therefore, checking for VVZ as well as MMR if there are flare-ups in your country (as is the case in Spain) should be performed as soon as the diagnosis is made, so that vaccines can be administered before any treatment onset.

Q. Great talk, it is very relevant. I would like specifics per drug – what do you screen for and what do you use as prophylaxis, for example cladribine, acyclovir?
A. Thank you very much for your encouraging comment and your interesting question. We screen for almost all preventable infections before any treatment onset (in fact, we try to screen as soon as the diagnosis is made). This includes: VHB, VHA, VVZ, MMR and tetanus. In case the patient is not protected, we recommend that they get vaccinated (being aware of the need for waiting for treatment onset after the live attenuated vaccines are administered). We also check for HIV and tuberculosis (by QuantiFERON testing) before starting alemtuzumab or cladribine. We recommend acyclovir for both alemtuzumab- and cladribine-treated patients, following the European Medicines Agency (EMA) product information sheet. And, according to our infectious team recommendations, in both cases,

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we also prescribe trimethoprim and sulfamethoxazole (three times per week) as part of the prophylactic treatment until the leukocyte counts are higher than 1000/µL. Lastly, considering HPV issues, including both adhering to cancer screening as well as discussing vaccination against HPV with the gynaecologist, is also recommended.

Q. Do you think that there is a higher risk for infections with therapies that change or narrow the TCR repertoire?

A. I think that the risk of infections with MS treatments can vary depending on the effects that the drug has on the immune system and the specific immune cell types affected. Therefore, patients receiving treatments targeting mainly T cells are more prone to almost all type of infections, such as bacterial (i.e. listeria, nocardia), fungi (i.e. cryptococcus), virus reactivations (i.e. herpes and John Cunningham virus) as well as parasite infection (i.e. toxoplasmosis), and almost all of these infections have been described with MS treatments. Although there are limited data regarding treatments targeting B cells in patients with MS, the experience with these treatments in other areas suggests that the risk of infections is low.

Prof Jan Lünemann

Q. How about the hepatitis B vaccination, do you think it's useful or should be mandatory?
A. All patients receiving immunoregulatory treatments (IRTs) should be vaccinated for hepatitis B before treatment initiation.

Q. Regarding routine testing before starting a disease-modifying therapy (DMT; e.g. CMV, HIV), what do you routinely screen for before treatment with, for example, alemtuzumab and ocrelizumab?
A. All patients receiving IRTs should be checked for/seronegative for HIV before treatment initiation. There is no need for CMV serology.

Q. Now that we are vaccinating against meningitis in our patients with neuromyelitis optica, I have wondered whether there is any role for this in patients with MS?
A. All patients receiving IRTs should be vaccinated against pneumococcal infections.

Q. Is there a role for antibiotic and acyclovir prophylaxis?
A. Patients receiving IRTs do not routinely require antibiotic and/or acyclovir prophylaxis.

Dr Saúl Reyes

Q. When asked whether you would vaccinate for shingles and pneumovax in patients with MS, you said that you would follow recommendations, but in this case the patient is 44 years old – are you recommending that we do use Shingrix in 40-year-olds? 30-year-old? How do you decide?

A. Because there is no evidence to support the use of herpes zoster vaccination in people younger than 50 years, we would recommend following the standard guideline and only to use herpes zoster vaccination in patients with MS aged 50 years or older. However, clinicians may choose to administer the vaccine off-label in patients younger than 50 years if, in their clinical judgement, they think that the vaccine is indicated (e.g. history of recurrent zoster episodes, such as the patient discussed in the debate). The patient should be informed that the use is off-label and that efficacy and safety of the vaccine have not been tested in people younger than 50.

Q. Do you routinely use amantadine in your patients with MS to prevent flu?

A. At present, vaccination is the mainstay of influenza prevention. We therefore recommend annual influenza vaccination with the inactivated vaccine for all patients with MS, their relatives and their carers. We do not recommend amantadine for protecting our patients with MS from flu, although some antiviral drugs (e.g. oseltamivir or zanamivir) may be effective in preventing influenza in seasonal prophylaxis. Evidence for amantadine is much more limited, which may be related to the fact that many strains of influenza are now resistant to this drug.

Q. I am confused. We are using varicella zoster vaccine in patients who are not chicken pox immune to present a primary infection, aren't we? And the shingles vaccine in people who have been previously infected to prevent shingles, no? This would be Shingrix, which is not live. Could you please clarify?

A. You are right. However, the live vaccine in the table is not the one used to prevent the primary infection but the one used to prevent herpes zoster (shingles) and related complications in older people.

Q. Should every patient with MS (or every patient with MS receiving Ocrevus) of any age get a) Pneumovax b) Shingrix? Or should these be given to only those over 50 years of age?

A. (a) The pneumococcal vaccine should be offered to patients with MS at high risk of pneumococcal disease: all patients ≥ 65 years of age and, regardless of age, patients who anticipate long-term immunosuppression (including ocrelizumab) and those with compromised pulmonary function or high levels of disability (with a risk of aspiration). (b) Because the risk and severity of shingles is considerably higher among immunosuppressed individuals, eligible individuals anticipating immunosuppressive therapy should ideally be assessed for vaccine eligibility before starting treatment that may contraindicate future vaccination. However, there is no evidence to support the use of herpes zoster vaccination in people younger than 50 years. We would recommend following the standard guideline and use herpes zoster vaccination only in patients with MS aged 50 years or older, but clinicians may choose to administer a herpes zoster vaccine off-label in patients younger than 50 years if, in their clinical judgement, they think that the vaccine is indicated (e.g. history of recurrent zoster episodes). The patient should be informed that the use is off-label and that efficacy and safety of the vaccine have not been tested in people younger than 50. We do not have specific recommendations regarding the use of herpes zoster vaccination in immunocompromised people aged 50 years or older because they were excluded from the original efficacy studies. However, more recent data suggest that herpes zoster vaccination and other non-live VZV vaccines are likely to also benefit this population (Mullane KM, Morrison VA, Camacho LH *et al. Lancet Infect Dis* 2019; http://dx.doi. org/10.1016/S1473-3099(19)30310-X; Dagnew AF, Ilhan O, Lee W-S *et al. Lancet Infect Dis* 2019; http://dx.doi.org/10.1016/S1473-3099(19)30163-X).

Q. For Shingrix what do you recommend for younger patients who are expected to be on DMT beyond 50 years of age?

A. Because the risk and severity of shingles is considerably higher among immunosuppressed individuals, eligible individuals anticipating immunosuppressive therapy should ideally be assessed for vaccine eligibility before starting treatment that may contraindicate future vaccination. However, there is no evidence to support the use of herpes zoster vaccination in people younger than 50 years. We would recommend following the standard guideline and use herpes zoster vaccination only in patients with MS aged 50 years or older, but clinicians may choose to administer a herpes zoster vaccine off-label in patients younger than 50 years if, in their clinical judgement, they think that the vaccine is indicated (e.g. history of recurrent zoster episodes). The patient should be informed that the use is off-label and that efficacy and safety of the vaccine have not been tested in people younger than 50. We do not have specific recommendations regarding the use of herpes zoster vaccination in immunocompromised people aged 50 years or older because they were excluded from the original efficacy studies. However, more recent data suggest that herpes zoster vaccination and other non-live VZV vaccines are likely to also benefit this population (Mullane KM, Morrison VA, Camacho LH *et al. Lancet Infect Dis* 2019; http://dx.doi. org/10.1016/S1473-3099(19)30310-X; Dagnew AF, Ilhan O, Lee W-S *et al. Lancet Infect Dis* 2019; http://dx.doi.org/10.1016/S1473-3099(19)30163-X).

Q. How long do you expect to wait before initiating ocrelizumab in order to check for active infections and vaccinations of a patient?
A. The vaccination schedule should be verified and updated as soon as possible after the diagnosis of MS is established. In patients who are due to start treatment with ocrelizumab: (a) inactivated vaccines should ideally be administered at least 2 weeks before the initiation of treatment; and (b) live vaccines are not recommended within 4 weeks before treatment initiation. We recommend vaccination against influenza and pneumococcal disease before starting treatment with ocrelizumab. Because both vaccines are inactivated, patients would be able to start treatment at 2 weeks after vaccination.

Q. Would you still revaccinate for VZV in a patient who tested VZV seronegative but with documented prior VZV vaccination?
A. You should first confirm whether the patient received the second dose of varicella vaccine (Advisory Committee on Immunization Practices (ACIP), 2007: 'Only doses of varicella vaccines for which written documentation of the date of administration is presented should be considered valid. A self-reported dose is not considered adequate evidence of immunity'). The rate of seroconversion after one dose of the vaccine may be suboptimal. The two-dose vaccination schedule provides about 98% protection in children (Shapiro ED, Vazquez M, Esposito D *et al. J Infect Dis* 2011; https://doi.org/10.1093/infdis/jiq052) and about 75% protection in adolescents and adults (Annunziato PW, Gershon AA. 2000. In: Arvin AM, Gershon AA. Varicella-zoster virus. Cambridge: Cambridge University Press). If the patient's medical record shows that he/she received two doses of varicella vaccine, serological testing is not indicated. If the patient was tested and the results come back negative, please bear in mind that commercially available assays may lack sensitivity for detecting vaccine-induced immunity: 10–15% false-negative and 8–11% false-positive results often occur (Sauerbrei A, Wutzler P. *J Clin Microbiol* 2006; https://dx.doi.org/10.1128%2FJCM.00719-06; Schmid DS, Jumaan AO. *Clin Microbiol Rev* 2010; https://doi.org/10.1128/cmr.00031-09). If, after considering all of the above, you believe that the patient is susceptible to primary VZV infection, varicella vaccination should be given. Vaccination of individuals who may be in the false-negative serological group is not detrimental.

Q. How can we tell whether the relapse is because of therapeutic failure of the DMT or the varicella zoster vaccine?
A. Studies over the past two decades have failed to show any causal link between vaccination and the exacerbation of MS. The available evidence suggests that hepatitis B, tetanus, tick-borne encephalitis or influenza vaccinations do not increase disease activity in patients with MS. Although there are limited data related to other specific vaccinations (e.g. VZV), vaccinations are generally considered safe from a 'disease activity' standpoint.

Q. What do you think routine seasonal influenza vaccination for patients with MS?
A. All adults with chronic neurological conditions (including MS) and/or those who are immunosuppressed because of disease or treatment should receive the influenza vaccine every year (we recommend vaccination with inactivated non-live vaccines, in

immunocompromised patients with MS). Influenza immunization should also be recommended for household members and carers of patients with MS.

Q. There are some data suggesting a link between HPV vaccination and demyelinating diseases. Do you still recommend it? For whom?
A. Yes, definitely. Although there are some few case reports suggesting a link between HPV and the onset of MS, we don't have evidence at a population level. On the contrary, we have the huge Scandinavian study of almost 4 million people confirming that HPV vaccination is not associated with an increase risk of MS or any other demyelinating conditions (Scheller NM, Svanström H, Pasternak B *et al. JAMA* 2015; https://doi.org/10.1001/jama.2014.16946). Younger patients would benefit the most, especially if they receive the vaccine before they get the natural HPV infection. I would also particularly consider HPV vaccination in patients who are about to start treatment with fingolimod. This medication may potentially impair cancer immunosurveillance, and some reports have suggested an association between fingolimod and HPV-driven conditions including malignancies.

Q. Do you recommend hepatitis B vaccination before therapy or just hepatitis B screening?
A. Just screening (ocrelizumab is contraindicated in patients with active hepatitis B). We recommend vaccination against influenza and pneumococcal disease in all patients who are due to start treatment with ocrelizumab. Patients who require any other vaccination (e.g. VZV) should complete their immunizations at least 2 weeks before treatment for inactivated vaccines and 4 weeks before treatment for live vaccines.

Q. Can children in contact with immunocompromised patients with MS receive the live influenza vaccine?
A. There is a theoretical potential for transmission of the live attenuated influenza virus in the vaccine from recipients to their close contacts. However, this is mainly relevant to patients who are severely immunocompromised (i.e. patients receiving haematopoietic stem cell transplant [HSCT], especially during the first month after transplantation). So the answer is yes, but there is always the option to consider the alternative inactivated influenza vaccine; otherwise, close contacts who need the live influenza vaccine should be temporarily separated from the HSCT recipient (this is also true for other live vaccines such as the varicella vaccine or the rotavirus vaccines).

Q. How about hepatitis B vaccination – is it mandatory for ocrelizumab?
A. We do not routinely recommend hepatitis vaccination before initiating treatment with ocrelizumab. Because ocrelizumab is contraindicated in patients with active HBV, we do recommend HBV screening before initiating treatment with this DMT. In terms of vaccines before starting treatment, we recommend vaccination against influenza and pneumococcal disease. Patients who require any other vaccination (e.g. VZV) should complete their immunizations at least 2 weeks before treatment for inactivated vaccines and 4 weeks before treatment for live vaccines.

Note

Please note that due to the current global circumstances, not all the questions asked during the recent *triMS.online* event have been answered. If there is a specific topic that you would like further information on, please contact Info@trimsonlineconference.com.