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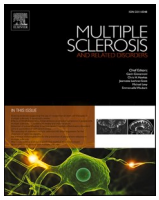

Editorial

Vaccine hesitancy in people with multiple sclerosis

While some of us are facing the prospect of a 4th or 5th COVID vaccination, others with neuro-immunological disorders have not even received their first shot. In an Irish study vaccine hesitancy amongst people with MS was estimated to be as high as 10–20% (Yap et al., 2021). The negative role of social media and even politically motivated disinformation was discussed recently in the *New England Journal of Medicine* (Larson et al., 2022). The initial wave of SARS-CoV-2 infections confronted us with patients being hospitalised for acute respiratory distress syndrome and multiorgan failure, often leading to death. An international effort to clarify the threat of severe infection in people with MS, outlined which disease modifying therapies (DMTs) amplify the known COVID-19 risk factors for severe infection in the general population (Tur et al., 2022). Currently we are seeing milder cases of COVID infection, likely due to a combination of evolving viral variants (currently Omicron B.A4 and B.A5) and rising population immunity. Even mild or asymptomatic acute infections can have long term sequelae such as fatigue and cognitive impairment, perhaps even cortical thinning (Zeng et al., 2022), with an estimated incidence of prolonged multisystem symptoms ("long COVID") of 7 to 10%. Furthermore, this risk is approximately halved in people who have been vaccinated prior to their COVID illness (Al-Aly et al., 2022). Despite rising numbers of infections, governments have moved on from scientifically-informed mandates, to leaving the individual to decide about their level of protection, including vaccination.

The international medical advice for people with multiple sclerosis or other neuro-immunological disorders recommends not only vaccinations for COVID but also for influenza, including booster shots (Sriwastava et al., 2022). In the UK and Australia, prior to starting immunosuppression, pwMS are encouraged to have vaccines against pneumococcus and varicella-zoster, particularly before any B-cell therapy, hepatitis B virus vaccination is recommended (if not already immune) .

In 2020, the first publications emerged about rare sporadic cases of transverse myelitis and Guillain Barre Syndrome (GBS) after vaccination against SARS-CoV-2 (Stuart and Krikorian, 1928). In the meantime, we have seen many cases of new onset neuro-immunological conditions like GBS or Neuromyelitis Optica, worsening of pre-existing conditions and MS relapses in those who have been recently vaccinated. The question of causality is yet to be resolved. The article from the Prague cohort in this issue is the first large-scale investigation to evaluate the risk of relapse of MS after vaccination compared to the likelihood of deterioration after Covid-19 infection (Stastna et al., 2022).

The debate about vaccine-related relapses existed long before COVID. Louis Pasteur described autoimmune encephalitis after vaccination for rabies that used neural tissue (Zrzavy et al., 2019). Although newer rabies vaccinations no longer contain any neuronal tissue, and their use is not associated with the development of autoimmune encephalitis, activation of autoimmune diseases is not surprising given the immunological action of vaccination. An effective inoculation can activate antigen presenting cells, mainly dendritic cells, which then stimulate CD4 and CD8 positive cells as well as B-cells, resulting in long lasting B-memory cells unless suppressed by DMTs (Kobiyama and Ishii, 2022). In the case of vaccines with adjuvants like hepatitis B (aluminium) it is often the adjuvants that are the most immunogenic. The benefit of mRNA vaccines is that they do not require adjuvants because the mRNA acts as its own adjuvant. Modified RNA-vaccines are recognized by toll-like receptors 7 and 8 and the NLRP3 inflammasome (a promoter of interleukins) in monocytes (Uraki et al., 2021). This triggers interleukin-1 and other cytokines as well as an interferon response. In the absence of an adequate regulatory T-cell response the immune activation could theoretically result in autoimmunity (Teijaro and Farber, 2021).

The two vaccine formulations — mRNA encoding the SARS-CoV-2 spike (S) protein encapsulated in lipid nanoparticles or adenovirus (AdV) vectors encoding the S protein — gain entry into dendritic cells (DCs) at the injection site or within lymph nodes, resulting in production of high levels of S protein. In addition, innate sensors are triggered by the intrinsic adjuvant activity of the vaccines, resulting in production of type I interferon and multiple pro-inflammatory cytokines and chemokines. RNA sensors such as Toll-like receptor 7 (TLR7) and MDA5 are triggered by the mRNA vaccines, and TLR9 is the major double-stranded DNA sensor for the AdV vaccine. The resultant activated DCs present antigen and co-stimulatory molecules to S protein-specific naive T cells, which become activated and differentiated into effector cells to form cytotoxic T lymphocytes or helper T cells. T follicular helper (T_{FH}) cells help S protein-specific B cells to differentiate into antibody-secreting plasma cells and promote the production of high affinity anti-S protein antibodies. Following vaccination, S protein-specific memory T cells and B cells develop and circulate along with high affinity SARS-CoV-2 antibodies, which together help prevent subsequent infection with SARS-CoV-2. Fig. 1 from: COVID-19 vaccines: modes of immune activation and future challenges.

This risk of vaccine-related activation of MS is particularly evident in people not effectively treated with MS DMTs. Epitope spreading or mimicry has been a speculated mechanism of MS relapse not only after COVID-19 vaccination but also after influenza, mumps, measles and rubella as well as hepatitis B and HPV vaccination (Kobiyama and Ishii, 2022). Most case-control studies do not reveal any increased risk of central nervous autoimmunity post inoculation but one large insurance claims-based study uncovered an HR of 2.23 in younger individuals

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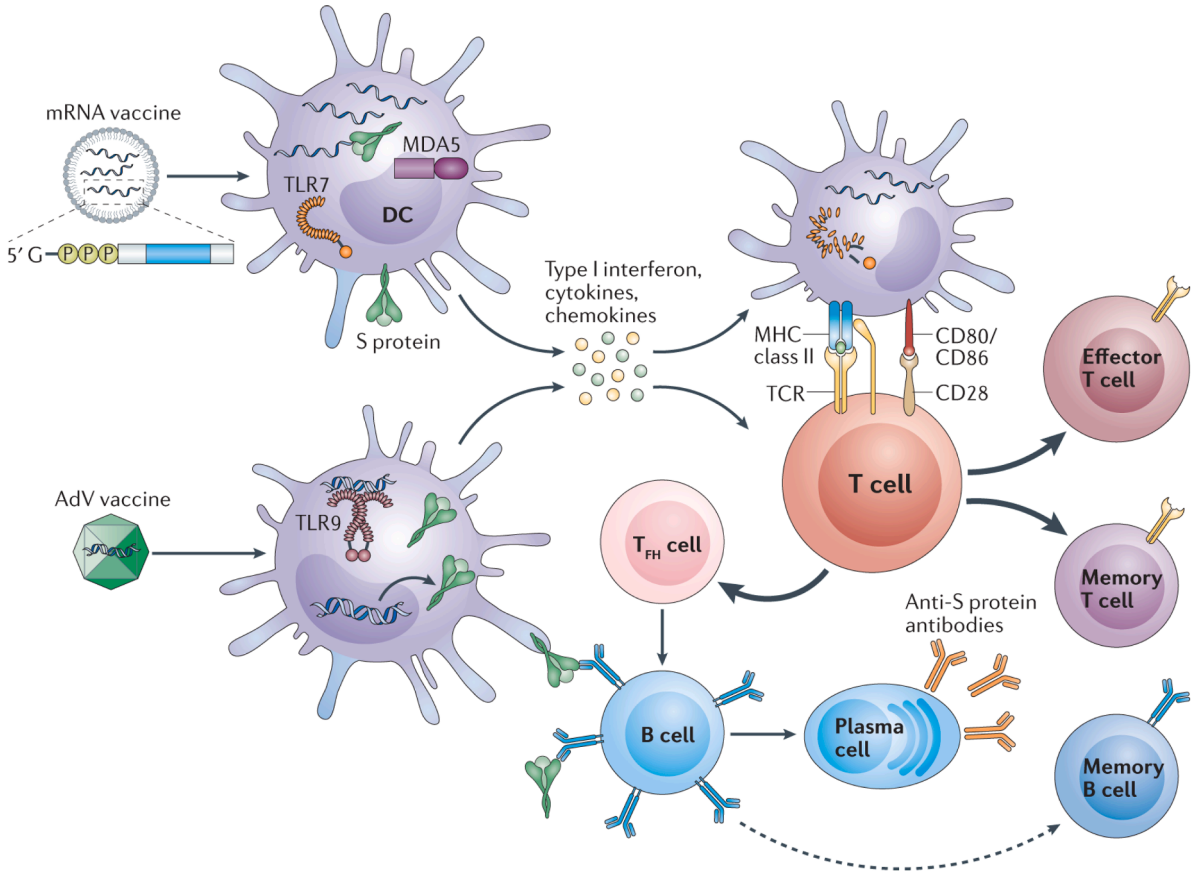

Fig. 1. How mRNA and adenovirus vector vaccines elicit immunity to SARS-CoV-2 (Teijaro and Farber, 2021).

(Frederiksen and Mailand, 2017). The same investigation did not find any increased risk of central nervous autoimmunity post inoculation in the overall population most such surveys are underpowered (Di Filippo et al., 2022).

The current study (Stastna et al., 2022) is novel as it describes the probability of MS relapse after mRNA- vaccines. It is strengthened by the fact that the nationwide immunisation programme in Czech Republic took place at the same time and the cohort was closely monitored before and after vaccination. (Stasna et al., 2022). Over an 18-month period, the authors observed 1661 MS patients who were vaccinated and 495 patients who were not. Excluding a change of treatment as a potential confounder, there was a significantly higher risk of relapse within 90 days after vaccination compared to a 90 day period prior to vaccination ($p < 0.001$). One could argue that 90 days is too short to establish causality although the average time to relapse was 41 days after COVID inoculation. In similar fashion, they observed a significantly increased risk of relapse after COVID infection compared to the 180 days period prior to vaccination but not 90 days after it ($p = 0.01$). The possibility of relapse is small and less after vaccination than the infection itself. Thus 5% of patients had a relapse after vaccination and 7% after the infection itself (not clinically significant). Considering other sequelae of COVID infection, the recommendation for vaccination is justified as long as the risk of infection remains high. These are only the results of a single centre and contradict a smaller Italian multicentre study with 324 pwMS, that did not identify an increased relapse risk after vaccination (Larson et al., 2022). An international effort against COVID in MS, would accumulate large numbers and afford greater statistical power that might highlight other factors relevant to exacerbation after vaccination, such as younger age, disease duration, and maybe type or lack of DMT.

The issue of vaccine hesitancy has wider implications for the management of MS. One study demonstrated that 40% of people with MS on Ocrelizumab who were instructed to have pneumococcal vaccine ignored this advice (Bedford and Donovan, 2022). Furthermore, the number of children receiving the MMR vaccine worldwide is falling (Gaddis, 2019) and will clearly lead to multiple measles epidemics across the world (Teijaro and Farber, 2021). This is a problem for patients with MS on long term immunosuppression who could acquire preventable infections such as measles. Of note, live vaccines for pwMS are not recommended while taking DMT, but inactivated vaccines are believed to be safe (Langer-Gould et al., 2014).

We recommend that a detailed vaccination history is taken from all MS patients prior to initiation of DMT, and that catch-up vaccines should be administered prior to initiation of such treatment if needed. One cannot combat current vaccine hesitancy without addressing the underlying causes of such reluctance. An urgent and important area for future large scale investigation.

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