Received: 12 May 2021 | Accepted: 12 May 2021

DOI: 10.1002/ajh.26263

COMMENTARY

Covid-19 vaccination in patients with multiple myeloma: Focus on immune response

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Funding information
Austrian Forum against Cancer

Patients with multiple myeloma (MM) are at increased risk for severe clinical symptoms and mortality due to SARS-CoV-2 infection. To protect against these complications, the International Myeloma Society recommends vaccinating all patients with monoclonal gammopathy of undetermined significance (MGUS), monoclonal gammopathies of clinical significance, smoldering MM (SMM), and MM.[1] Protective immunity against SARS-CoV2 in those patients is partially relevant given their increased risk for infections, which may cause significant morbidity and represent the second most frequent cause of mortality.[2] The extent of the immune impairment in MM largely depends on the disease-inherent immune suppression exerted by the malignant clone that can affect all immune effector mechanism including B cells, T cells, NK cell, and dendritic cells, and the complement system.[3,4] The myeloma-induced immune deficiency can resolve completely during periods of deep response, such as minimal residual disease negativity, but deep responses are achieved in a proportion of patients only, and several of those eventually relapse and become immune suppressed again and/or suffer from other causes of reduced immune competence. Many patients present at older age with comorbidities and immunosenescence[5] with an impaired defense against infections and compromised development of long-term immune memory, which is aimed at by vaccination. Myeloma therapy including proteasome inhibitors, dexamethasone, high dose melphalan, monoclonal antibodies, antibody-drug conjugates, BiTEs and cellular therapies, such as CAR-T cells, result in specific and cumulative immune suppression, and after extensive therapy in T cell exhaustion.[6] Hence, myeloma and myeloma treatment-induced immunosuppression and other above mentioned factors frequently impose critical hurdles for an effective vaccination response in many patients and emerging data seem to underpin these concerns.[7]

A recent study in 48 elderly patients with MM (median age 83 years) reported a significantly lower proportion of MM patients with a neutralizing antibody response on day 22 after the first dose of the BNT162b2 vaccine compared to controls of the same age category (20.6% versus 32.5%, respectively). Virus neutralizing antibody titers of ≥50% deemed to be clinically relevant, were noted in four (8.3%) of 48 patients and in 21 of 104 (20.2%) controls only; all these four patients were in remission without any therapy.[8] Only one of the nine patients with SMM had neutralizing antibody titers. This poor response did not improve substantially with the second dose. Part of the observed low response rate could be due to the high age of the study participants as specific antibody production in response to vaccination declines with older age.[9,10] Similar results were noted in 93 patients (median age 67 years) after one dose of the BNT162b2 or ChAdOx1-S vaccine.[11] After a median time from first dose to antibody testing of 33 days, SARS-CoV-2 IgG antibodies were noted in 55.9% of patients, with no difference between both vaccines.

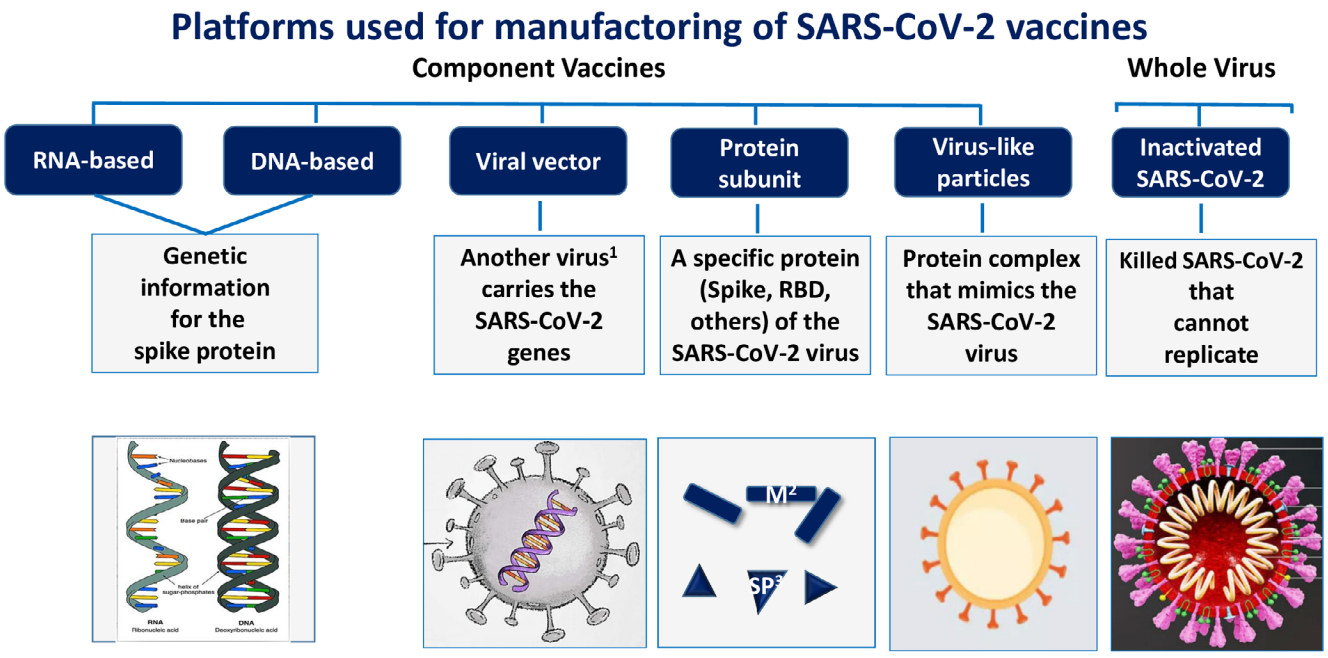

FIGURE 1 Platforms used for development of anti-SARS-CoV2 vaccines

These results compare with a positivity rate of 98.8% observed in hospital staff. When testing was expanded for IgA and IgM antibodies in 40 of the IgG antibody negative patients, a positive result was obtained in further 13 patients, adding up to a total antibody response in 65/93 patients (69.9%). Factors associated with antibody response were depth of response (CR-PR), absence of immunoparesis, and fewer lines of therapy, while being on therapy was associated with poor antibody response. Another presently unpublished study included seven patients with MM within a group of 38 patients with hematological cancers, which showed an IgG antibody response to the SARS-CoV-2 spike protein in only 13% of them, compared to 97% in healthy controls after one dose of the BNT162b2 vaccine.[12] Furthermore, half of the patients with haematologic malignancies tested had an impaired T cell response, and eight of the nine who showed a cellular immune response were serological non-responders. Similarly, a discordance between cellular and IgG antibody response was noted in previously Covid-19 infected health care workers; during follow up a T cell response, but no antibody formation was observed in seven out of 70 individuals, while in two subjects weak antibody titers, but no cellular responses were detected.[13]

These findings raise the question about the kind of humoral and cellular immune response which is required for protection against infection with SARS-CoV-2 virus, and which test systems provide most relevant information. Neutralizing antibodies have been shown to correlate with protection in rhesus macaques,[14] and may be more informative than assessing levels of antibodies against spike proteins, but data comparing their clinical relevance are not available as yet. For evaluation of cellular immunity, spike peptides are used for T-cell stimulation, but Covid-infected patients show reactivity against other peptides as well.[15] This shows that available evidence is insufficient for clear guidance, therefore more laboratory data need to be generated and linked with clinical outcome including asymptomatic and symptomatic infection rate, hospitalization and mortality. Another issue of importance is the duration of the protection in patients with a documented immune response. Will antibodies and T-cell reactivity wane with time, even in patients in complete remission, and how fast will protection be lost in patients with progressive or recurrent disease? Will it be worthwhile to add additional doses of the same vaccine to non-responders or low-responders, or will a change of one vaccine to another elicit the desired immune response? For the latter strategy, several options are available, for instance mixing an RNA vaccine with an adenovirus vector, peptide, protein, inactivated virus, or adjuvanted vaccine, or a vaccine designed by a new molecular technology called NDV-HXP-S, which facilitates the manufacturing process. Figure 1 shows a schematic overview the various platforms used for anti-SARS-CoV2 vaccine production. More specifically new developments of interest are self-amplifying mRNA vaccines that produce more antigens, the design of vaccines for intranasal administration for induction of an additional secretory IgA response, or the production of bi- or trivalent vaccines, or of pan-respiratory virus vaccines including SARS-CoV-2, influenza, and other respiratory viruses.

The present vaccination program is endangered by the high mutation rate of SARS-CoV-2 virus leading to new mutants with relevant

TABLE 1 List of recent SARS-CoV-2 variants of concern, their clinical attributes and coverage by selected common vaccines

	First detection			Evidence of clinical changes			
SARS-CoV-2 Variant	Location	Date	Notable mutations	Transmissibility	Virulence	Antigenicity	Protected by
B.1.1.7	UK	Sep 2020	N501Y, 69-70del, P681H	Increased ~ 74% (NERVTAG)	32%–104% (~64%) more lethal (BMJ)	Reduced antigenic activity (ECDC)	BNT162b2 (Pfizer/BioNTech) mRNA-1273 (Moderna) AZD1222 (Oxford/AstraZeneca)
B.1.351	South Africa	Dec 2020	N501Y, K417N, E484K	Increased 50% (ECDC)	-	Reduced neutralization by antibodies (ECDC)	BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) may be 2/3 less effective (serum neutralizing antibodies), AZD1222 (Oxford/AstraZeneca) effective only in 10%
P.1	Brazil, Japan	Jan 2021	N501Y, E484K, K417T	Likely increased (CDC)	10%–80% (~45%) more lethal (CADDE)	Overall reduction in effective neutralization (ECDC)	Possible reduction of vaccine efficacy (ECDC)
B.1.525	Nigeria, UK	Dec 2020	E484K, F888L	Likely increased (CDC)	Likely increased (CDC)	„Modestly "reduced neutralization (COG-UK)	No data available as yet
B.1.427/B.1.429*	US	May 2020 July	L452R, D614G *plus S131, W152C	~20% increased (CDC)	Increased (CDC)	4.0–6.7 and two-fold decrease in neutralization titers, from convalescent patients and vaccine recipients, respectively (CDC)	No data available as yet
B.1.617	India	Oct 2020	E484Q, L452R, P681R	Increased (WHO)	Under investigation	Slight reduction in effective neutralization	No data available as yet

Abbreviations: CDC, Center for Disease Control; COG-UK, Covid-19 Genomics UK Consortium; ECDC, European Center for Disease Prevention and Control; NERVTAG, New and Emerging Respiratory Virus Threats Advisory Group; WHO, World health organization.

changes in the ACE-2 receptor-binding domain of the spike protein, which is one of the 26 virus proteins, and of other epitopes[16] some of which resulting in higher transmissibility, virulence and lower antigenicity for all or some of the existing vaccines[17–19] (Table 1). The neutralizing activity of the immune response elicited by the available mRNA vaccines was found to be significantly lower for the B.1.315 variant compared to the USA-WA1/2020 virus (identical to the original Wuhan SARS-CoV-2 virus).[20] Although neutralization titers usually are high in the normal population,[10] lower neutralization efficacy can be critical in immunosuppressed patients like those with MM. Recent research indicates that certain mutations can also alter T-cell epitopes hiding mutated virus from recognition by T killer cells. Hence, adaptation of vaccines to the corresponding epitopes is necessary. A clinical trial has already been activated evaluating whether a vaccine targeting the B.1.315 variant (mRNA-1273.351) will provide better protection when given after a dose of the original mRNA-1273, or when administered concomitantly with the original vaccine.[21]

The above-mentioned considerations mandate close surveillance of the humoral and cellular vaccination response obtained in individual patients with MM to correlate findings with their level of protection. If improvement with further doses, other vaccines or vaccination strategies is unlikely in non-responders, new strategies such as employing monoclonal antibody cocktails against SARS-CoV-2 for protection against Covid-19 infection may be considered. These treatments are presently not approved for prophylactic use, but may turn out to protect all those with insufficient immune response to Covid-19 vaccines, particularly when preparations with extended half-life will be introduced. But until this option will become available for clinical practice, creation of" herd immunity" using a strategy of" ring vaccination" around affected patients will be required. Those patients will also be obliged to strictly follow general recommendations for infection risk reduction. They will desperately hope for new effective anti-COVID treatments, and finally for an end of the pandemic.

CONFLICT OF INTEREST

H.L.: Research Funding: Amgen, Takeda, Speaker's Bureau/Advisory Boards: Amgen, Takeda, Janssen, Celgene-BMS, Sanofi, Seattle Genetics; J.S.M.: Honoraria/Consultancy: Amgen, Celgene-BMS, GlaxoSmithKline, Janssen, Karyopharm, Novartis, MSD, Takeda, Sanofi, Roche; NM: Advisory Boards: Takeda, Celgene, Novartis; PS: Research Funding: Karyopharm, Amgen, Celgene, Janssen, Member BOD or advisory committee: SkylineDx, Honoraria: Amgen, Celgene, Janssen; M.V.M.: Honoraria: Janssen-Cilag, Celgene, Amgen, Takeda, GlaxoSmithKline, Abbvie/Genentech, Adaptive Biotechnologies, Consulting or Advisory Role: Takeda, Janssen-Cilag, Celgene, Amgen, Abbvie, GlaxoSmithKline, Pharmamar; P.M.: Honoraria/Advisory Boards: Abbvie, Janssen, Celgene-BMS, Amgen; ET: Research Funding: Amgen, Janssen, Celgene, Genesis Pharma, GlaxoSmithKline, Sanofi, Consultancy/Honoraria: Amgen, Celgene-BMS, Janssen, Takeda, Genesis Pharma, GlaxoSmithKline, Sanofi.

AUTHOR CONTRIBUTIONS

All authors contributed equally to concept and writing of the manuscript. All authors approved the final version.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Ludwig H, San-Miguel J, Munshi N, et al. Covid-19 vaccination in patients with multiple myeloma: Focus on immune response. *Am J Hematol*. 2021;96:896–900. https://doi.org/10.1002/ajh.26263