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SARS-CoV-2 vaccination in the immunocompromised host

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Immunocompromised patients, such as individuals with inborn errors of immunity (IEI), individuals with immunodeficiency secondary to immunosuppressive therapies (such as in solid organ transplant recipients [SOTRs] and patients with autoimmune diseases or hematologic malignancy), and persons with poorly controlled HIV are at increased risk of infections due to impaired host defenses. Vaccination is a critical measure to reduce preventable infections among this vulnerable patient population. Immunocompromised patients were largely excluded from the original severe acute respiratory distress syndrome–coronavirus 2 (SARS-CoV-2) vaccine trials, and although international efforts have attempted to address the resultant data deficit, many questions remain. Herein, we review currently available data on the safety and efficacy of SARS-CoV-2 vaccination, as well potential strategies to optimize protection in the immunocompromised host.

SAFETY OF SARS-CoV-2 VACCINES IN IMMUNOCOMPROMISED PERSONS

SARS-CoV-2 vaccination has additional safety considerations for immunocompromised patients, namely, the impact on underlying disease state. Indeed, despite the significant morbidity and mortality associated with coronavirus disease 2019 (COVID-19) infection, the paucity of SARS-CoV-2 vaccine safety data has contributed to vaccine hesitancy. To date, the findings have been very encouraging. Among 1377 immunosuppressed patients with autoimmune disease, there were no reports of severe reaction or flare of underlying disease requiring hospital admission following vaccination.[1] Additionally, postvaccination reactions among SOTRs, persons with HIV, and patients with IEI have been similar to those in the general population.[1-3] Data on the safety of additional vaccine doses are more limited. Although sequential antigenic exposures and subsequent immune recall could theoretically elicit a more potent immune response, the early reports are thus far reassuring.[4]

ANTIBODY RESPONSE IN IMMUNOCOMPROMISED PERSONS

Circulating antispike antibodies represent an important source of immunity against COVID-19 infection. Antispike binding titers have been shown to correlate well with titers of neutralizing antibodies, which have been identified as the best proxy for protection after vaccination in the general population.[5] As new variants of concern (VOCs) emerge, antibody quality, as well as quantity, has become an important factor.

Although SARS-CoV-2 vaccination induces seroconversion and robust antibody responses among most immunocompetent patients, the rates of seroconversion are lower in many immunocompromised patients, particularly in those with IEI and in SOTRs.[3,4,6] Notably, persons with HIV with well-controlled disease appear to respond similarly to the general population.[2] Lymphocyte-depleting agents, such as anti-CD20 therapies (eg, rituximab), anti–T-cell stimulators (eg, belatacept), and certain antimetabolites (eg, mycophenolate mofetil), with resultant B-cell incompetence, are the primary immunosuppressive therapies associated with an attenuated antibody response following vaccination[3,6] (Fig 1). There is also accumulating evidence that intensity, as well as mechanism, of the immunosuppressive regimen is important in blunting the vaccine response. These findings prompted widespread recommendations for an additional vaccine dose or "additional primary dose" for immunocompromised patients. Although additional doses can induce *de novo* antibody response in some patients and augment antispike titers in others, some patients fail to seroconvert despite multiple antigenic encounters.[4]

PROTECTIVE ANTIBODIES IN IMMUNOCOMPROMISED PATIENTS

The definition of immune correlates of clinical protection among immunocompromised patients remains elusive; this is further challenged by the advent of VOCs. VOCs are characterized by mutations in the SARS-CoV-2 spike protein that enable immune evasion. In fact, the large number of mutations in the Omicron variant compared with the wild-type virus have resulted in a significant reduction in neutralization capacity, requiring much higher antibody titers to effectively prevent infection. Breakthrough infections are more common among immunocompromised persons, and an association between seronegative status and breakthrough infections in immunosuppressed patients with autoimmune diseases has been reported.[7] Although seronegative status is a helpful marker to identify those at greatest risk of infection, the definition of a protective threshold of immunity is urgently required to inform risk and the need for additional protective strategies.

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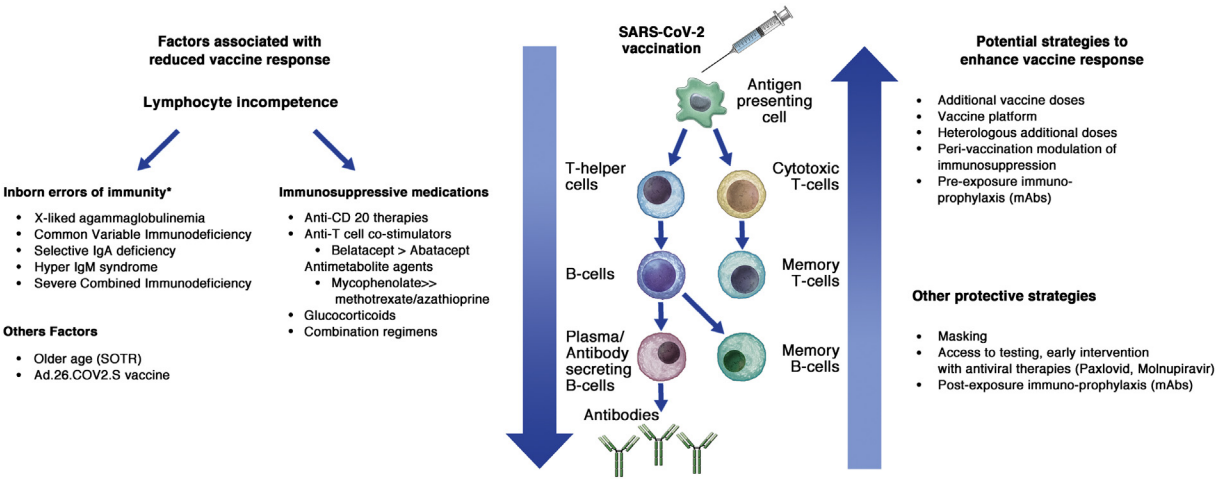

FIG 1. SARS-CoV-2 vaccine response. Factors associated with reduced vaccine response and strategies to enhance response and protection. Vaccine response is elicited by sequential activation of T cells and B cells, which results in generation of antibody response and memory cellular response. mRNA or adenovirus vector encoding the SARS-CoV-2 spike (S) protein enters antigen-presenting cells that present antigen and costimulatory molecules to naive T cells, which differentiate into cytotoxic or T_H cells. T_H cells promote B-cell differentiation into antibody-secreting plasma cells that produce anti-S protein antibodies. Thereafter, S protein–specific memory T cells and B cells develop and circulate along with anti-S antibodies. *IEI include more than 400 different diseases; the most common disorders of humoral immunity, T-cell defects, and combined B-cell and T-cell defects are listed. Glucocorticoids include prednisone and prednisone equivalents; dose affects response. Combination therapies include regimens consisting of 2 or more immunosuppressive therapies.

STRATEGIES TO ENHANCE PROTECTION AGAINST COVID-19

Several potential strategies exist to augment the immune response to SARS-CoV-2 vaccination. First, antibody decay with associated waning immunity can be addressed with additional vaccine doses. Although short-interval redosing is not a viable long-term global strategy, further insights into the immune correlates of immunity and dynamics of the immune response following additional doses are needed to inform the optimal timing of redosing. The benefit of additional doses appears to be greatest among individuals with poor antibody response, and serologic testing may represent a potential personalized approach to inform risk and maximize the benefit and equity of additional vaccine doses.

Second, choice of vaccine platform is important. Two-dose vaccination has elicited greater antibody response than that elicited by the single-dose Ad.26.COV2.S vaccine in immunocompromised patients.[8] Furthermore, among immunocompetent persons, 2-dose mRNA-1273 vaccination results in lower rates of breakthrough infections than with BNT162b2 vaccination,[9] whereas heterologous boosting is associated with lower COVID-19 incidence rates than homologous boosting. These findings raise the questions of whether the data could be extrapolated to immunocompromised persons and whether use of the mRNA-1273 platform should be preferred, with use of heterologous additional dosing to further optimize the vaccine response.

Third, modulation of perivaccination immunosuppression may bolster SARS-CoV-2 vaccine response. A temporary hold of mycophenolate mofetil in the perivaccination period elicits a greater antibody response in immunosuppressed patients with autoimmune diseases.[10]

Finally, several therapeutic strategies exist to enhance protection against COVID-19. Immunoprophylaxis, such as with the antispike mAb combination of tixagevimab and cilgavimab (Evusheld, AstraZeneca), has recently been authorized as preexposure prophylaxis. Notably, VOCs have demonstrated resistance to certain mAbs (eg, the omicron BA.2 subvariant's evasion of sotrivumab), thus rendering them ineffective. Currently, Evusheld continues to demonstrate efficacy against this predominant VOC, and this therapeutic intervention should be considered in all seronegative persons, as well as in those who have concurrent comorbidities associated with poor COVID-19 outcomes (such as older age, comorbid obesity, diabetes, chronic kidney disease, or interstitial lung disease) and mount a suboptimal response. In addition, postexposure prophylaxis with mAb therapy should be considered in those who are at a risk of poor COVID-19 outcomes.

The therapeutic armamentarium has also been reinforced by the development of novel antiviral agents (such as nirmatrelvir plus ritonavir and molnupiravir) that can reduce the risk of progression to severe COVID-19 infection. Although these oral therapies offer a promising avenue to prevent poor COVID-19 outcomes, they are contingent on rapid access to testing and availability of therapy.

These measures should be layered on other public health risk mitigation strategies such as masking, hand hygiene, and physical distancing. Immunocompromised patients should be prioritized for prophylactic and early preventive therapies.

CONCLUSION

COVID-19 infection continues to cause significant morbidity and mortality worldwide. Many questions remain for immunocompromised patients, some of whom remain at high risk of

infection despite vaccination. Although significant progress has been made in understanding the safety and efficacy of SARS-CoV-2 vaccination among this vulnerable population, many evidence gaps remain.

Lymphocyte incompetence, either genetic or acquired mediated by immunosuppression, has a clear role in attenuating the SARS-CoV-2 vaccine response. Insights into the clinical correlates of protection, as well as the dynamics of the vaccine response, are urgently needed to inform the timing of additional doses for immunocompromised persons. Furthermore, more granular data regarding the role of cellular response and associated clinical relevance are needed.

The rapidly evolving SARS-CoV-2 virus demands that the medical community continue to dynamically expand its knowledge base and develop novel protective countermeasures against COVID-19. The ongoing protection of our most vulnerable patients requires a multifaceted plan, including optimization of vaccine schedule, modulation of perivaccination immunosuppression (when feasible), use of immunoprophylaxis, early intervention with antiviral therapy, and continued risk mitigation strategies such as masking.

REFERENCES

1. Connolly CM, Ruddy JA, Boyarsky BJ, Barbur I, Werbel WA, Geetha D, et al. Disease flare and reactogenicity in patients with rheumatic and musculoskeletal diseases following two-dose SARS-CoV-2 messenger RNA vaccination. Arthritis Rheumatol 2022;74:28-32.
2. Ruddy JA, Boyarsky BJ, Bailey JR, Karaba AH, Garonzik-Wang JM, Segev DL, et al. Safety and antibody response to two-dose SARS-COV-2 messenger RNA vaccination in persons with HIV. AIDS 2021;35:2399-401.
3. Pham MN, Murugesan K, Banaei N, Pinsky BA, Tang M, Hoyte E, et al. Immunogenicity and tolerability of COVID-19 messenger RNA vaccines in primary immunodeficiency patients with functional B-cell defects. J Allergy Clin Immunol 2022;149:907-11.e3.
4. Parker EP, Desai S, Marti M, Nohynek H, Kaslow DC, Kochhar S, et al. Response to additional COVID-19 vaccine doses in people who are immunocompromised: a rapid review. Lancet Glob Health 2022;10:e326-8.
5. Feng S, Phillips DJ, White T, Sayal H, Aley PK, Bibi S, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. Nat Med 2021;27:2032-40.
6. Deepak P, Kim W, Paley MA, Yang M, Carvidi AB, Demissie EG, et al. Effect of immunosuppression on the immunogenicity of mRNA vaccines to SARS-CoV-2: a prospective cohort study. Ann Intern Med 2021;174:1572-85.
7. Ahmed S, Mehta P, Paul A, Anu S, Cherian S, Shenoy V, et al. Postvaccination antibody titres predict protection against COVID-19 in patients with autoimmune diseases: survival analysis in a prospective cohort. Ann Rheum Dis https://doi.org/10.1136/annrheumdis-2021-221922.
8. Chiang TP, Connolly CM, Ruddy JA, Boyarsky BJ, Alejo JL, Werbel WA, et al. Antibody response to the Janssen/Johnson & Johnson SARS-CoV-2 vaccine in patients with rheumatic and musculoskeletal diseases. Ann Rheum Dis 2021;80:1365-6.
9. Wang L, Davis PB, Kaelber DC, Volkow ND, Xu R. Comparison of mRNA-1273 and BNT162b2 vaccines on breakthrough SARS-CoV-2 infections, hospitalizations, and death during the delta-predominant period. JAMA 2022;327:678-80.
10. Connolly CM, Chiang TP, Boyarsky BJ, Ruddy JA, Teles M, Alejo JL, et al. Temporary hold of mycophenolate augments humoral response to SARS-CoV-2 vaccination in patients with rheumatic and musculoskeletal diseases: a case series. Ann Rheum Dis 2022;81:293-5.