COVID-19 – Challenges ahead of vaccination in immunocompromised patients

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Abstract
A novel strain of coronavirus — SARS-CoV-2 — was first detected in December 2019 in Wuhan, a city in China’s Hubei province, after an outbreak of pneumonia-like symptoms. The virus has now spread to over 200 countries and territories across the globe and was characterized as a pandemic by the World Health Organization (WHO) on 11 March 2020. To date, there is no proven effective treatment for the COVID-19 with ongoing trials on anti-viral and immunosuppressive therapies. Due to the highly contagious nature of COVID-19, the most promising way to contain the infection is by the development of a vaccine. Scientists all over the world are working tirelessly to develop a vaccine with several trials already undergoing and reaching phase 2. If and once a safe and effective vaccine is available, essential evidence-based considerations will be needed for the high-risk immunocompromised population. In this short summary, we are interpreting the current literature pertaining to vaccinations in patients on immunosuppressive medications and suggest how to implement management strategies in these patients once a vaccine is available for COVID-19.

Commentary
The world is in the midst of an unprecedented crisis caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease 2019 (COVID-19) which was first reported in December 2019. According to the World Health Organization situation report, as of July 15, 2020, 13,150,645 cases have been confirmed with 574,464 deaths globally [1]. To date, there is no definitively-proven effective treatment for the COVID-19 with trials ongoing on anti-viral and immunosuppressive therapies. Scientists all over the world are running a race against the time to find a vaccine with several trials already undergoing and reaching phases 2 and 3.

There has been substantial evolution in the development of vaccines since 1796 when Edward Jenner demonstrated immunity to smallpox after inoculating a child with the vaccinia virus [2]. Today, vaccines are considered one of the most cost-effective devices for saving life. The introduction of foreign antigens leading to activation of the innate immune system which then activates and regulates the adaptive immune system resulting in the production of protective antibodies is the basis of vaccination. Despite their origin more than 200 years ago, and significant advancements leading to the eradication of diseases such as smallpox and polio, there are still gaps in our knowledge and understanding of the immunological mechanisms of vaccines, which can be highlighted by failure to develop vaccines against global pandemics such as the human immunodeficiency virus (HIV).

Infections, some of which are vaccine-preventable, are one of the most common causes of mortality in patients with autoimmune diseases such as rheumatoid arthritis (RA), who are immunocompromised due to immune dysfunction caused by the disease, as well as due to iatrogenic immunosuppression [3,4]. Live-attenuated vaccines are contraindicated in patients who are on strong immunosuppressive medications and shall be given at least 2 weeks before initiation of immunosuppression. Influenza and pneumococcal vaccines which are inactivated vaccines are strongly recommended in patients with autoimmune rheumatic diseases [5-7]. However, there are several concerns with inactivated vaccines as well in these patients including the effects of immunosuppressive medications on the vaccines.

Although there are theoretical concerns of exacerbation of the underlying autoimmune disease due to the immune response to vaccines, limited data so far has been reassuring and has not shown vaccine-associated changes in disease activity of autoimmune diseases including systemic lupus erythematosus, dermatomyositis, polymyositis, and Sjogren syndrome [8-12]. The production of neutralizing antibodies to neoantigens can be suppressed by medications suppressing humoral immunity [13]. Studies in the past have shown reduced humoral response to seasonal influenza and pneumococcal vaccines due to methotrexate, rituximab and abatacept, and to Hepatitis B vaccine in patients taking tumor-necrosis factor inhibitors [14-21]. There is conflicting data about the effect of tumor necrosis factor inhibitors on immunogenicity to influenza and pneumococcal vaccines [22-26]. Interleukin-6 inhibitors (tocilizumab) and Janus kinase inhibitors (tofacitinib) were not associated with a diminished immune response to pneumococcal and influenza vaccines [27,28].

Further, in patients with RA, temporary discontinuation of methotrexate for two weeks after vaccination was shown to be associated with significant improvement in immunogenicity of the seasonal influenza vaccine without an increase in the rheumatoid arthritis disease activity [29]. The suppressive effect of methotrexate has been proposed

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to be secondary to its interaction with the B-cell activation factor (BAFF) leading to an increase in immunosuppressive adenosine and regulatory B-cells, hence suppressing humoral immune response [30]. Park, et al. suggested holding methotrexate for 2 weeks after seasonal influenza vaccination to improve vaccine immunogenicity [31]. Similarly, Bingham, et al. suggested administration of polysaccharide and primary immunization before rituximab infusions to maximize the humoral response to the vaccine [32].

There are limitations with the data available so far. While the current literature suggests a decrease in the immunological response in patients continuing immunosuppressive therapy after the vaccination, no information is available about the transformation of this data to the actual clinical setting, such as difference in incidences of the viral infection by withholding or continuing the immunosuppressive therapy after the vaccination. Immune response to vaccines is a surrogate marker and while it may not transform into protection against the disease, stronger seroprotection may theoretically be associated with better protection against the viral infection.

Similar strategies may be needed for the SARS-COV2 vaccine if and when it becomes available. To better protect the vulnerable immunocompromised patients, aiming for better seroprotection by using practices proven to be effective and safe such as holding methotrexate for 2 weeks after the vaccination, and vaccination before rituximab infusions may be considered until further clinical trials are available about the effects of immunosuppression on the vaccine once it is available.

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Author contributions

All authors have made significant contribution to the study including writing initial manuscript, reviewing literature and revising manuscript. All authors have read and approved the final version of the manuscript by the corresponding author on behalf of authors.

Ethics approval

The mayo clinic institutional review board (IRB) acknowledges that based on the responses submitted for this new activity through the Mayo Clinic IRBe Human Subjects Research Wizard Tool, and in accordance with the Code of Federal Regulations, 45 CFR 46.102, the above noted activity does not require IRB review.

Data sharing statement

There are no data in this work.

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We acknowledge that this letter is ahead of its time with a vaccine for SARS-CoV-2 still in the infant stages of development. However, when the world is going through a crisis, we need to be better prepared by thinking ahead of time and being proactive rather than reactive.

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