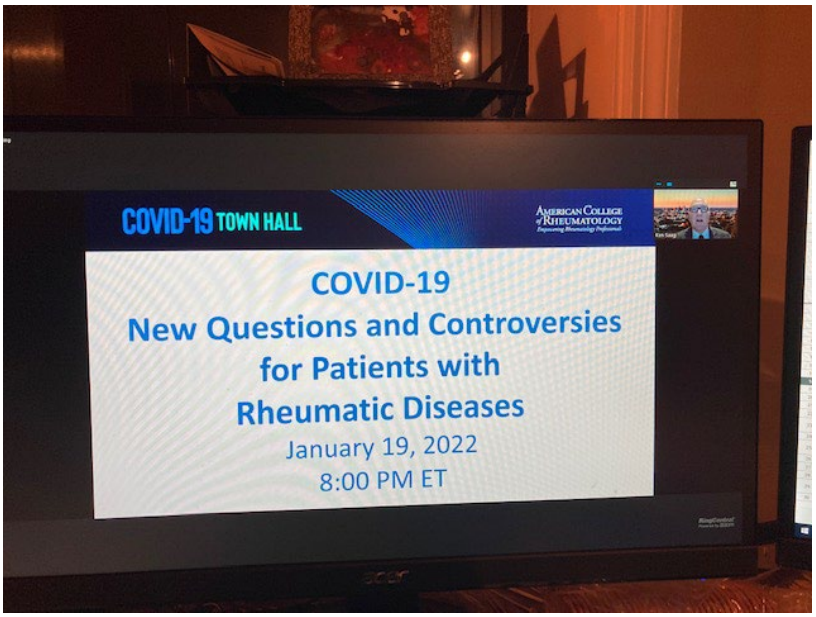

COVID-19 ACR Townhall: New Questions and Controversies for Patients with Rheumatic Diseases

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Moderators and Panelists: Michael Saag, MD, University of Alabama at Birmingham, Cassandra Calabrese, DO, Cleveland Clinic, Andy Pavia, MD, Chief Division of Pediatric Infectious Diseases, University of Utah, Monica Gandhi, MD, MPH, University of California, San Francisco

As members of the American College of Rheumatology (ACR)/ Association of Rheumatology Professionals (ARP), AiArthritis was able to attend this very important meeting aimed at addressing the ever-evolving world of COVID-19 in rheumatology. Several questions were answered, such as, "When is it too much vaccine?" and "What's better, wait for access to monoclonal antibodies, an Omicron specific vaccine, or do the 4th dose?"

Two representatives from our organization attended – Tiffany Westrich-Robertson, CEO, person living with non-radiographic axial spondyloarthritis and Katie Simons, Senior Programs & Communications Manager, person living with rheumatoid arthritis. At the time of this presentation, no new guidance from the ACR has been released since December 2021 regarding COVID treatment, prevention, and vaccinations.[1]

But before getting into what was learned from the townhall meeting, let's start with some basic information already known:

- **It *is* recommended that persons with rheumatic diseases who are on immunocompromising treatments receive the 4th vaccine dose**.[2] There has been a lot of news coverage on the ineffectiveness of 4th vaccine doses to prevent Omicron.
    - *First to note – none of the vaccinations were created to prevent COVID-19, they were designed to curb the pandemic by providing some level of protection against contracting severe disease that leads to hospitalizations and death.*[3]

[1] https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf
[2] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html
[3] https://www.medpagetoday.com/opinion/second-opinions/96680?fbclid=IwAR1P9NC8YVKw9LjCg3WwNP_9FP9s6rskbKQxm7jOiXGgf1Ls2hU-Opn2Gpg

  - Second, this information is relevant to the general patient population and the typical antibody levels they generate after three doses. The guidance for 4th doses includes only those with hereditary genetic immune issues or those with compromised immune systems due to treatments, as research has shown these people are not mounting as much protection (to any strand) as others. *This was discussed further in the townhall meeting, stated below.*

- **As of January 2022, while there are medications available to prevent COVID or lessen the severity if taken in early onset, they are almost impossible to obtain by rheumatic patients.** This is due to distribution limitations, which is normal for new drugs and for those in high demand. Locations are provided a limited quantity of product, which is rationed to the most vulnerable.[4] In this case, the doses are going to cancer patients and others with severe genetic immune issues.
  - In December 2021, Evusheld, a monoclonal antibody used for pre-exposure prevention of COVID, was indicated for use by those who are immunocompromised due to illness or medications (including our community). However, due to distribution limitations and rationing requirements, rheumatology patients were categorized after those with cancer and other conditions. AiArthritis reached out to AstraZeneca (manufacturers) to inquire when availability would increase. Several representatives from the company responded, assuring that distribution was ramping up and hopefully heightened availability will happen in the next few months. In the meantime, they provided a website for patients to track availability.[5]

Now, let's get into what we learned at the townhall meeting, which was divided into segments based on identified outstanding issues that have not been addressed yet with official guidance. This information should not replace what you and your doctor believe is the best therapeutic management for your individualized needs. Please use this information to help jumpstart a conversation with your disease management team (first part of the shared-decision making process).

Q: Which of our patients do we need to worry most about? Emerging research has been looking into rheumatology drugs and which lead to the highest risk of poor COVID-19 outcomes and decreased antibody response to vaccinations.[6] Patients at the highest risk for worse COVID outcomes and lessened vaccine response are those on B cell targeted agents (Rituximab and Orencia, for example), with the least impact on those on TNF inhibitors (Enbrel, Humira, Cimzia, for example). But it's a spectrum, with steroid use and JAK-inhibitors falling somewhere in the middle. Other factors, like

[4] https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Evusheld/Pages/default.aspx
[5] https://www.phe.gov/emergency/events/COVID19/therapeutics/distribution/Pages/data-tables.aspx
[6] https://www.rheumatology.org/About-Us/Newsroom/Press-Releases/ID/1178

age and comorbidities associated with poorer COVID outcomes, also need to be considered. *See the latest ACR guidance to learn more where your treatment falls in the spectrum.*

Additionally, understanding the natural history of disease is important. When a person becomes infected with a virus, within the first 4-7 days of symptoms the innate side of our immune system is modified (innate = natural, inborn defense side of the system). After that, mostly the adaptive immune response kicks in (adaptive = the learned, fight off intruders' side). So, those first few days of infection are very important. For people taking steroids, there is an additional concern, as steroids can inflame prolonged illness and increase viral shedding if not immediately tapered off. Keeping in contact with the rheumatologist is very important when navigating early COVID infection.

As anti-viral drugs become more available, it will likely be recommended to use them.

Q: Any data on Omicron in rheumatic diseases? Depending on the research read, those vaccinated have lower risks (ranging between 30-50%) of developing severe Omicron. In immunocompromised patients, it will be important to continue observing the impact of Omicron based on existing knowledge – which includes knowing patients who experience lack of vaccine response due to medications and those unvaccinated have worse outcomes. Bottom line, this is still a new virus. All research is new and will take time to collect.

Q: Should patients get the 4th vaccine dose? It is known that two doses of the vaccine (or one of the J & J) isn't good enough – for anyone - now that COVID has morphed into more strains. At least one booster is recommended for everyone. Then beyond that, we need to look at everyone else – those who aren't mounting strong protection due to immune problems need to be protected. In some cases, the 3rd dose may bring our patients up to the levels of protection the rest of the population achieves in two doses. So, a 3rd dose is really the "priming series" for those immunocompromised, whereas two doses would serve as the "priming series" in the general population. Broader population gets a booster, that's number three. Our community? Our equivalent 'booster' would be number four.

It's important to consider availability of the new Omicron specific vaccine that will be available in the next few months. If a patient is slotted for #4 in May, it may make more sense to get the newer version if accessible soon thereafter. If a patient has access to #4 in January/February, they need to understand if they want the Omicron version, they may have to wait a period of time between vaccines. This is where doctor-patient conversations are important.

It is also thought that those over the age of 75 should soon be considered for a 4th dose (considering age impacts immune responses).

Q: Does the patient really need the 4th dose if they have antibodies? Antibodies can go up and come down and will vary depending on the laboratory that performed the test. Also, if a patient shows low antibody response, that and doesn't mean they aren't protected by t and b cells – very important protection - so it's misleading. Many patients are aiming to get in that protective range, and if they do, they may feel they don't need a booster. It's a conversation they will need to continue with their doctor, using shared-decision making, if they are still concerned. *Doctors in the panel agreed it's not necessarily recommended for patients to get antibody tests for these reasons, but they would not deny their right to do so if asked for one.*

"A 4th dose makes a lot of sense for immunocompromised individuals. *But not for immunocompetent individuals.* "There's a concept called original antigenic sin, which is the idea that if you keep on training your immune system to form T cells and antibodies against the ancestral strain … then you redirect your resources to not produce T cells and antibodies against the variant you see in front of you," (Dr. Gandhi)

Q: Is there potential harm in getting too many boosters? There is always a theoretical risk, but we don't know what this will look like in the future. The research regarding a need for a 4th dose in our patient population was covered previously *(Q: Should patients get the 4th vaccine dose?)* One thing to consider discussing with the doctor is timing. A 4th dose of the current vaccination could potentially make someone ineligible for a new vaccine (that is supposed to target Omicron). So, if a patient is scheduled to do their five month 4th dose in April or May, recommendations may change.

Not from the townhall, but information we have also received from rheumatology advisors: There is proven protection that vaccines help curb Omicron severity. Given our patient population tends to build vaccine response slower than the average population, it makes sense to consider a 4th dose if offered soon. We also do not know the roll out availability of any new vaccine at this time.

Q: What about using new treatments, like monoclonal antibodies or antivirals?

The first thing to note is some of these are very hard to find, if not impossible, due to distribution limitations (which will change in the next few months). None of these should be considered a replacement for vaccination. And in some cases, like Evusheld, vaccination is required to be a candidate for use.

- **Monoclonal antibodies**. Evusheld - the only monoclonal antibody therapy that has received an EUA for pre-exposure prophylaxis to prevent COVID-19, and it is effective against the omicron variant. *But as of today, it's being rationed to those most severely immunocompromised due to manufacturing limits. It will be more available to our community (hopefully) soon.*
- **Monclonal antibodies.** Tixagevimab/cilgavimab has been shown to prevent serious COVID-19 outcomes for up to six months with the delta variant, but its effectiveness will likely be shorter with the omicron variant. *Promising efficacy for a few months, but limited supply, too, as it's still new.*
- **Antivirals.** In clinical trials, Paxlovid, an oral antiviral for treatment of COVID-19,[7] data showed disease activity reduced by 88% ***if given within 5 days in immunocompromised people***. ***This is important to note, because rheumatology patients who think they have COVID-19 should be tested as soon as possible and notify their rheumatologist immediately so a prescription – if available - can be given immediately. "If we don't hear our patients have covid until day 6 or 7, that's too late to get full efficacy." Patients should contact their rheumatologist immediately after knowing they are COVID positive.***
    - There are several potential severe drug interactions (treatments for heart disease, for example) to consider with this drug. *If patients are prescribed this, they should check with their pharmacist about potential drug interactions.* There is also a website by the University of Liverpool just for COVID-19 drug interactions.[8]
    - This should not be prescribed unless the patient has tested positive for COVID-19.

[7] https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19
[8] https://www.covid19-druginteractions.org/

- **Antivirals**. There are other antivirals, such as molnupiravir, that are not proving to be as effective (viral activity reduced by 30%), but it could be easier to obtain access to this these and some improvement is better than none. This drug shouldn't be used in people pregnant or trying to be pregnant and is not authorized for use in children.

There was additional conversation around outpatient remdesivir (outpatient infusions), which does not work as well in the hospital/early settings (indicated for outpatient/post-COVID use). It's considered an option if there isn't access to the other antivirals.

Q: Does vaccination help in long-term COVID (persistent symptoms beyond 28 days from start of symptoms)? Commonly reported symptoms of COVID-19 include things like brain fog - even to the point of dementia - GI disturbances, extended loss of taste and smell, etc. There's a lot to still understand, as again, this virus is still new and it's morphing. Keep in mind, the way the virus is acting is not unique in how other syndromes follow an infectious disease pattern. The virus takes over and then likely a pathway or two gets triggered within our immune system, so those pathways activate and don't turn off. It's not the infection continuing, it's the activated pathways that become problematic.

Theoretically, a person's immune system should prevent a virus from going to other places, which is first addressed in the innate immunity state (those first few days of infection). That's why early notification of the rheumatologist is so important to treating known COVID-19. It's also why vaccinations are currently our best bet for preventing worse disease and long term COVID. Given the virus is only two years old, there's a lot of research still to be done to understand vaccination effect on long term symptoms and, specifically, in patient subgroups.

Q: Given antibody testing is so unreliable, why can't we just start testing for T cell assays? Is there any data to better understand the impact of T cell response? *(An assay is the process of analyzing the substance quality)*. Thinking broadly, like for a global population ability to test, there is no specific capability to measure something like that currently.

General Prevention Comments

- Masks. The CDC recently announced guidance on six types of masks to wear for COVID protection.[9] Naturally, as always known, some are better than others. Perhaps the most comfortable while easiest to access are cloth with filter paper (thinnest).
    - We also need to factor in lack of compliance to hygiene. Remember when the pandemic was new? We were washing our mail deliveries and feared pumping gas. Now we know transmission is droplets (small and large). So, we need to stay diligent about refraining from contracting COVID in this manner.
- Isolation time for those immunocompromised. Standard recommendation may not be the right recommendation for those with rheumatic diseases and who are immunocompromised due to treatments. While not official guidance, panelists agreed 10 days is more appropriate than five.

[9] https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/types-of-masks.html

- Most of the anti-virals will be available in a couple of months. When these treatments are more readily available, outpatient redemisivir will be discontinued. We are close to having more options, patients need to hang on just a little longer.
- Risk – benefit consideration. Remember, the relative risk of poor response to vaccination compared to what can happen if a person gets COVID – particularly if immunocompromised and/or including other comorbidities – should be considered in all shared-decision making conversations.