What's New in my Specialty Rheumatology

Effects of SARS-CoV-2 infection and vaccination on rheumatic and musculoskeletal disease (RMD)

Gregory T. Austad, MD, FACP, FACR
Tanner Memorial Clinic

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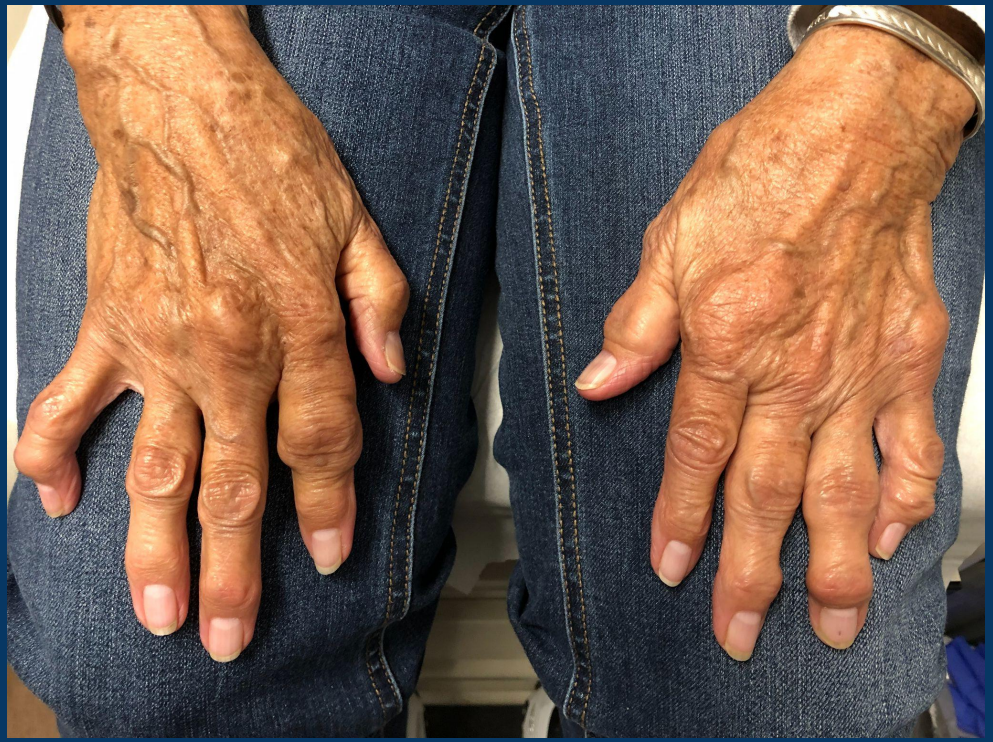
Disclosures:

- None



Objectives:

- Learn the effects of COVID-19 infection in immunosuppressed rheumatology patients
- Discuss effects and efficacy of COVID-19 immunization in immunosuppressed rheumatology patients
- Review updated CDC immunization guidelines for COVID-19 vaccination in immunosuppressed patients

Factors associated with COVID-19-related death in people with rheumatic diseases

Independent factors associated with COVID-19-related death were:

- Age (66–75 years)
- Male sex
- Hypertension and cardiovascular disease
- Chronic lung disease
- Prednisolone equivalent dosage >10 mg/day
- Moderate/high RMD disease activity
- Rituximab, sulfasalazine, azathioprine, cyclophosphamide, cyclosporine, mycophenolate or tacrolimus
- Not receiving any immunosuppressive compared with methotrexate monotherapy

Strangfeld A, et al. Ann Rheum Dis 2021;80:930–942. doi:10.1136/annrheumdis-2020-219498

COVID-19 Infection among RMD Patients

- 77 patients infected with SARS-CoV-2
- 68.9% had a mild course (fatigue, 58.4%; fever 45.4%; URI symptoms 68.8%)
- 23.3% required hospitalization
- 1.3% mortality rate
- Corticosteroid, mycophenolate and rituximab treatment lead to more serious disease course
- Older age and lung disease were independent predictive factors of hospitalization
- Interesting fact: All patients receiving Rituximab had severe disease

Athanasios-Dimitrios Bakasis, et al. Journal of Autoimmunity, Volume 123, September 2021, 102687

Risk and prognosis of SARS-CoV-2 infection and vaccination against SARS-CoV-2 in RMD

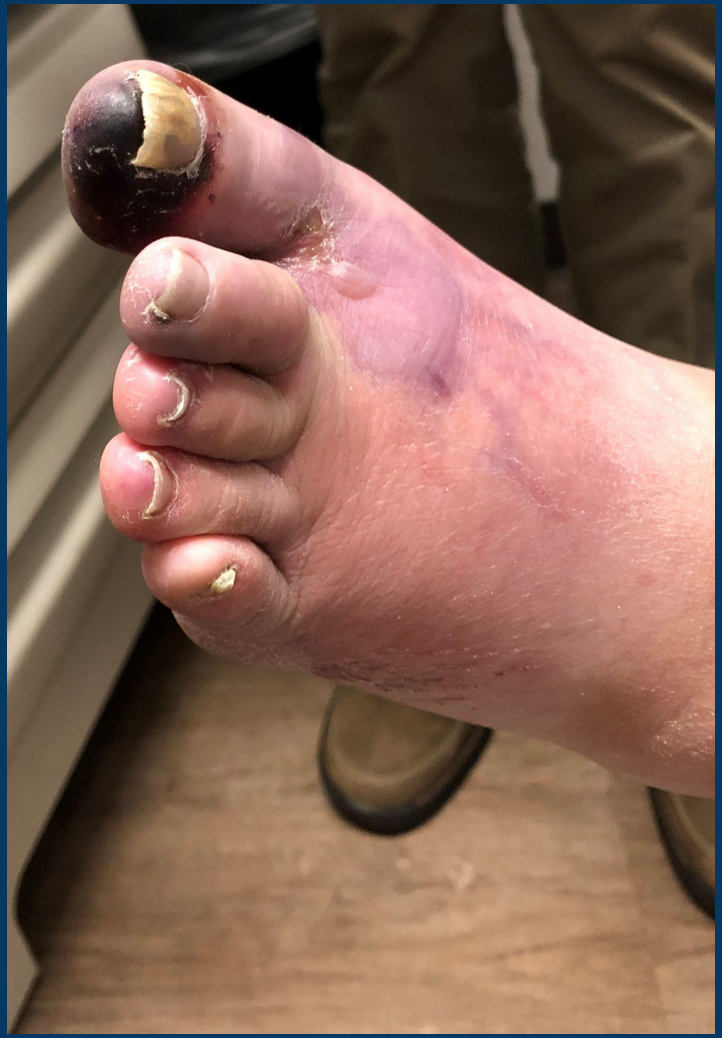
- 5,165 records reviewed, 208 included, 90 passed quality assessment
- Patients with RMDs do not face more risk of contracting SARS-CoV-2 (n=26 studies)
- or worse prognosis of COVID-19 (n=14) than individuals without RMDs.
- No consistent differences in risk of developing (severe) COVID-19 were found between different RMDs (n=19).
- Disease activity is associated with worse COVID-19 prognosis (n=2)
- Increased risk seen for glucocorticoid use (n=13).
- Rituximab associated with worse COVID-19 prognosis (n=7)
- Vaccine immunogenicity is negatively associated with older age, rituximab and mycophenolate

Kroon FPB, et al. Ann Rheum Dis 2022;81:422–432. doi:10.1136/annrheumdis-2021-221575

Risk of COVID-19 in Rheumatoid Arthritis: National VA cohort study

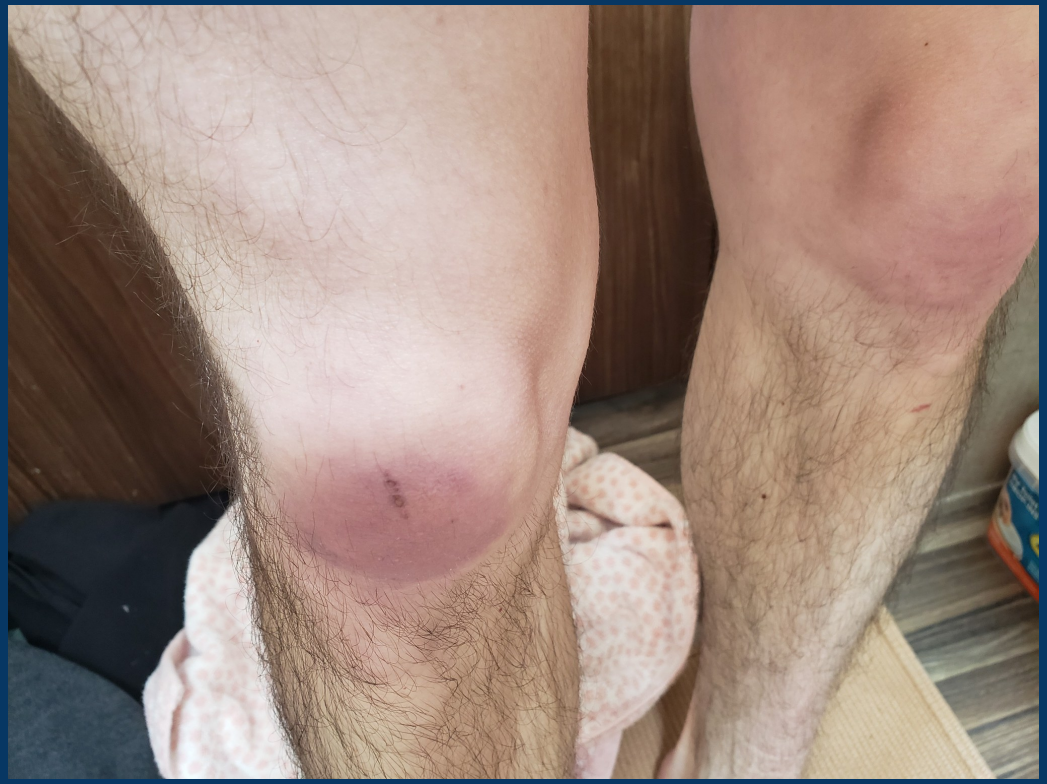
- 67,772 patients studied, Large matched cohort study, VA database 2019
- Compared the risk of COVID-19 and COVID-19 hospitalization and death for RA vs non-RA patients
- 1503 patients had COVID-19. 388 patients had severe COVID (hospitalization or death)
- RA was associated with a higher risk of COVID-19 and COVID-19 hospitalization and death compared to non-RA controls.
- Use of DMARD drugs and prednisone, Black race, self-reported Hispanic ethnicity, and presence of several chronic conditions were associated with COVID-19 and severe COVID-19 hospitalizations and death

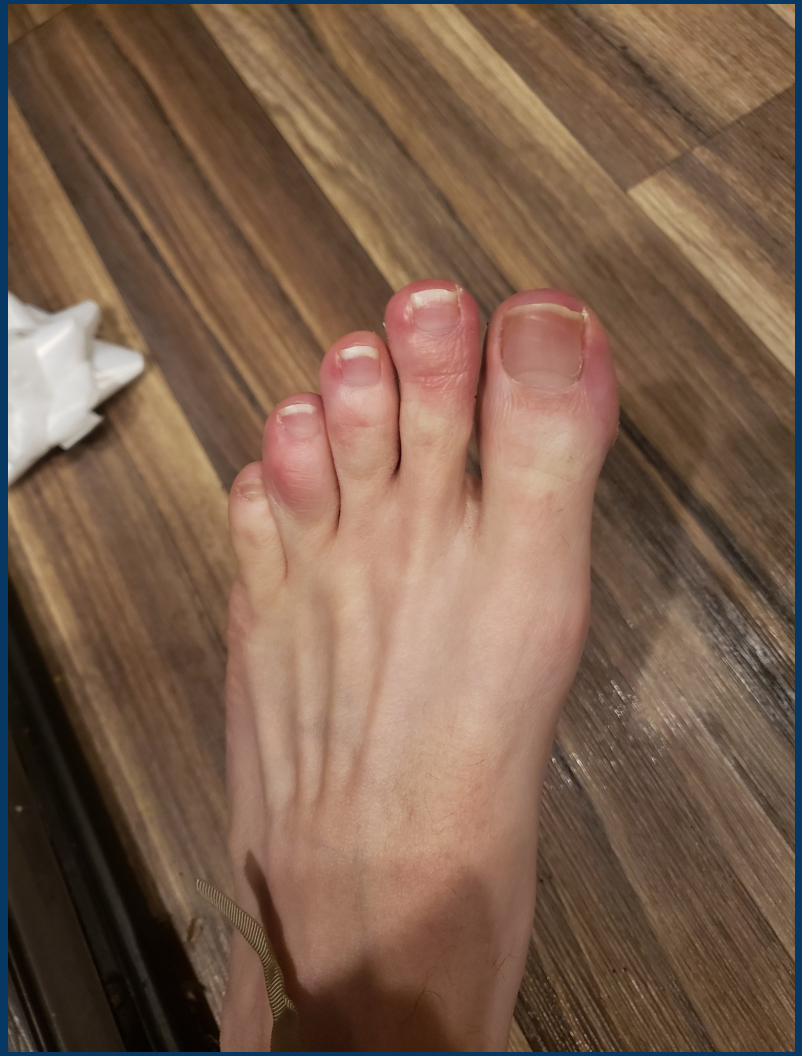
Arthritis & Rheumatology. Vol 73. No. 12, Dec 2021, pp 2179-2188



Rheumatologic Manifestations of COVID-19 infection or vaccination

- Systemic lupus flare
- Rheumatoid arthritis flares
- New IgG-4 related disease
- COVID toes mimicking vasculitis
- Microscopic polyangiitis





RMD Manifestations of COVID-19 infection

Musculoskeletal	**Cutaneous**	**Vasculitis**
Arthralgia/Myalgia	COVID toes/pseudo-chillblains	Kawasaki disease
Acute myositis	Urticarial or maculopapular rash	Large vessel stroke
Acute myocarditis	Livedoid rash with necrosis	
	Erythema elevatum diutinum	
Autoinflammatory	**Autoimmune antibodies**	
Hemophagocytic Lymphohistocytosis	+ANA, +SSA/Ro, +anti-phospholipid antibodies	

Adapted from: Rheumatology International (2020) 40:1539–1554

Vasculitis as Temporally Associated With COVID-19 Infection or Vaccination

COVID-19 infection	COVID-19 vaccination
Skin purpura, arthritis	Myalgia
Constitutional symptoms	Skin purpura/arthritis
Systemic inflammatory response	Constitutional symptoms
Systemic inflammatory response	Skin purpura
Limb gangrene with necrosis	Painful left temporal artery
Panniculitis with necrosis	Carotidynia
Purpura	Headache/jaw claudication

The Journal of Rheumatology 2022;49:2 doi:10.3899/jrheum.210788, December 15 2021

Spectrum of short-term inflammatory MSK manifestations after COVID-19 vaccine administration: a report of 66 cases

Primary features:

- Oligoarthritis
- Polyarthritis
- PMR-like symptoms
- Tenosynovitis
- Enthesitis

Other features

- Bursitis
- Inflammatory back pain
- Elevated inflammatory markers
- +RF, +CCP, +ANA

Ann Rheum Dis March 2022 Vol 81 No 3

Spectrum of short-term inflammatory MSK manifestations after COVID-19 vaccine administration: a report of 66 cases

- Most patients treated with glucocorticoids (50%– 78%), NSAIDs (33%–52%) or analgesics (14%–28%)
- DMARDs used in five (28%) patients with polyarthritis, five (24%) patients with oligoarthritis and only three (11%) patients with PMR-like presentation.
- PMR-like onset with 74% achieving full remission of symptoms after 2 weeks; 67% of patients with polyarthritis had active disease after an average follow-up of 6 weeks.

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Additional reported RMD flares in the literature:

- Giant Cell Arteritis
- Leukocytoclastic vasculitis
- Flare of Still's disease
- Exacerbation of subacute cutaneous lupus

Efficacy of COVID-19 vaccines in immunosuppressed patients

- Large cohort study comparing vaccinated (n=97688) and unvaccinated (n=42094) individuals on various immunosuppressants
- Compared the three FDA approved COVID vaccines for efficacy in preventing infection and hospitalization
- Taking immunosuppressants increases risk of COVID infection for vaccinated and unvaccinated patients
- Pfizer and Moderna vaccines were highly effective at reducing the risk of COVID-19
- J & J vaccine protection did not reach statistical significance (smaller sample size n=173)
- Receiving a booster dose reduced the risk of COVID infection

Shen C, et al. Ann Rheum Dis 2022;0:1–6. doi:10.1136/annrheumdis-2021-222045

Efficacy of COVID-19 vaccines in immunosuppressed patients: meta-analysis

- 82 studies included
- 77 used mRNA vaccines, 16 viral vector vaccines, 4 inactivated whole virus vaccines
- Patients with hematologic and solid organ cancers and RMD half as likely as normals to seroconvert after 1st vaccine. This improved with 2nd and 3rd vaccine doses
- Organ transplant patients were 16 times less likely to seroconvert after the first vaccine, with sluggish response to the 2nd dose. Third dose required to seroconvert.

BMJ 2022;376:e068632 | doi: 10.1136/bmj-2021-068632

Effects of B-cell depletion

- Personal experience: mortality higher in patients on B-cell depletion therapy (Rituximab)
- B-cell depleted patients don’t make antibodies to COVID-19 vaccines
- Undoubted T-cell response, but unknown efficacy of that response

Humoral and Cellular Immune responses to SARS-CoV-2 infection and vaccination in patients with B cell depletion

- B cell response based on antibody testing (ELIZA) and T cell response (interferon-gamma enzyme-linked immunospot assay) to the SARS-CoV-2 spike S1, and nucleocapsid proteins
- Patients with autoimmune disease and B cell depletion: 6 previously infected, 8 vaccinated. Compared to 30 previously infected healthy controls and 30 vaccinated healthy controls
- All normal controls responded with antibody production to the vaccine 30/30
- None of the B-cell treated patients responded with antibodies to the vaccine 0/8
- After COVID infection both normal controls and B cell treated patients had antibody responses and T-cell responses to both the Spike S1 protein and nucleocapsid proteins

Arthritis and Rheumatology. Vol 74. N0. 1. January 2022, pp 33-37

B Cell Reconstitution Is Strongly Associated With COVID-19 Vaccine Responsiveness in RMD patients on Rituximab

- B-cell reconstitution is necessary for effectiveness of the COVID-19 vaccine
- B cell reconstitution was significantly associated with a positive serologic response to the vaccine $p<0.001$
- Significant difference in reactivity to vaccine 594 days vs median 138 days $p<0.001$
- At <6 months, 86% had no response
- AT 6-12 months, 55% had a response
- At > 12 months, 13% still had no response

S. Jinich, et al. Arthritis and Rheumatology, Brief Report, Vol 0, No. 0, Month 2022, pp 1-7

B-cell targeted therapy is associated with severe COVID-19 among patients with inflammatory arthritides

- 1 year multicenter study in 1116 successive patients receiving intravenous biologics
- 1116 patients total
- 449 infliximab
- 392 rituximab
- 170 tocilizumab
- 105 abatacept
- 10 cases of severe COVID-19 occurred. 9/10 were treated with rituximab
- Rituximab remained the only factor associated with risk of hospitalization for COVID-19

Ann Rheum Dis January 2022 Vol 81 No 1

Efficacy of COVID booster Vaccinations in patients on Rituximab

- 55 patients–Blinded randomized trial
- Booster vaccine in patients on Rituximab that did not seroconvert
- Compared Booster with Astra Zeneca vs repeat Pfizer or Moderna vaccination
- Patients stratified by presence of peripheral B cell measurement, not by time from last Rituxan
- Endpoint: difference in SARS-CoV-2 antibody seroconversion rate
- Secondary endpoint: Overall seroconversion and cellular immune response
- Seroconversion rates comparable between two vaccine strategies: 22% Astra Zeneca, 32% moderna or pfizer.
- T-cell response noted in 100% Astra Zeneca, 81% Moderna and Pfizer
- Newly induced humoral and/or cellular responses occurred in 82% patients

Bonelli M, et al. Ann Rheum Dis 2022, 0:1-8

Rituximab during the COVID-19 pandemic: time to discuss treatment options with patients

- Humoral and T-cell responses are marginal even with a booster, and a change may be necessary during the pandemic.

www.thelancet.com/rheumatology Vol 4 March 2022

Options:

- Switch to another biologic therapy
- Delay the next rituximab dose as long as possible
- Add tixagevimab and cilgavimab (EVUSHELD).
    - Recombinant human IgG1k monoclonal antibodies that bind to spike protein receptor-binding domain of SARS-COV-2. This blocks attachment to human ACE2 receptor.

Who is moderately to severely immunosuppressed?

- Receiving active cancer treatment for tumors hematologic malignancy
- Received an organ transplant and are taking immunosuppressants
- Received a stem cell transplant within the last 2 years or are taking immunosuppressants
- Moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids or other drugs that may suppress the immune response

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html#mod; accessed 4/20/32022

ACR concensus statements:

- Healthcare provider is responsible for engaging the RMD patient in a discussion to assess COVID-19 vaccination status and engage in a shared decision-making about receiving the COVID-19 vaccine.
- RMD patients are at higher risk for hospitalized COVID-19 and worse outcomes compared to the general population.
- RMD patients should be prioritized for vaccination before the nonprioritized general population of similar age and sex.

American College of Rheumatology Guidance for COVID-19 Vaccination in Patients with Rheumatic and Musculoskeletal Diseases – Version 5. Feb 2022

ACR concensus statements:

- Beyond allergy to vaccine components, there are no known contraindications to COVID-19 vaccination for RMD patients.
- The response to COVID-19 vaccination for RMD patients on systemic immunomodulatory therapies is blunted in its magnitude and duration compared to the general population.
- A risk exists for RMD flare following COVID-19 vaccination. However, the benefit of COVID-19 vaccination outweighs the potential risk for new onset autoimmunity.

American College of Rheumatology Guidance for COVID-19 Vaccination in Patients with Rheumatic and Musculoskeletal Diseases – Version 5. Feb 2022

What are the current CDC vaccine recommendations for immunocompromised patients?

Pfizer	Moderna
Age 12+	Age 18+
3 primary doses First and second doses separated by 3 weeks Second and third separated by 4 weeks	3 primary doses separated by 4 weeks
4th dose 3 months later	4th dose 3 months later
5th optional dose 4 months later	5th optional dose 4 months later

What about the J&J vaccine?

Age Group 18+
Two doses to complete primary series: 1st dose J&J, 2nd dose Pfizer or Moderna vaccines given 4 weeks after the 1st dose
Booster: Pfizer or Moderna given 2 months after the 2nd dose
Moderately or severely immunocompromised patients can choose to receive a 2nd booster (4th dose) of an mRNA vaccine at least 4 months after their first booster.

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html; accessed 4/20/2022

Conclusion:

- COVID-19 infection places rheumatology patients at risk
- COVID-19 vaccines are effective at reducing the risk of severe infection and hospitalization but vaccine responses are blunted in the immunosuppressed, requiring COVID-19 booster vaccines
- Treatment with B-cell depletion treatments increases likelihood for severe COVID-19 infection, requiring additional interventions
- Waiting for B-cell repletion prior to a COVID-19 booster enhances likelihood of seroconversion
- COVID-19 infection and vaccination both can flare rheumatologic diseases in a variety of ways. These flares are usually self-limited.
- Although information about the effect of COVID-19 infections and immunizations was initially sparse, it is now being published plentifully
- Patients on immunosuppressive therapy should be on their 4th or 5th COVID vaccine