Caribbean Association For Rheumatology
Bay Medical Center, PO Box GM712, Castries, St. Lucia LC04 201

Caribbean Association for Rheumatology COVID-19 Vaccination Recommendations

Purpose

The purpose of this document is to provide guidance on COVID-19 vaccination for individuals with autoimmune rheumatic diseases in the Caribbean as vaccination programs are implemented. It is a **living document** that will be updated as more information becomes available. For most Caribbean countries the available vaccine is Oxford-AstraZeneca - a replication-deficient simian adenovirus vector, first approved for use by the Medicines and Healthcare products Regulatory Agency in the United Kingdom on December 30th 2020.

Methods

A task force consisting of 8 rheumatologists (see Appendix) was convened to review the literature and to address 4 questions-:

1) Are COVID-19 vaccines safe to administer to individuals with rheumatic disease?
2) Will these vaccines be effective in individuals with rheumatic disease?
3) Are individuals with rheumatic disease/on immunosuppressive therapy at increased risk of COVID-19 infection?
4) Are individuals with rheumatic disease/on immunosuppressive therapy at increased risk of worse outcomes with COVID-19?

Summary

1) Currently available COVID-19 vaccines are not live vaccines and are considered safe to administer to individuals with autoimmune rheumatic disease and those on immunosuppressive therapy. Side effects are typically minor and similar to that in the general population. It is unknown if COVID-19 vaccines may cause an exacerbation of an existing rheumatic disease or development of a de novo autoimmune syndrome (1-4)

2) Currently there is insufficient data to speak with certainty about the effectiveness of COVID-19 vaccines in individuals with rheumatic disease. Efficacy may be reduced in individuals on immunosuppressive therapy. The decision to hold specific immunosuppressive medications in relation to COVID-19 vaccination should be guided by the recent American College of Rheumatology recommendations and at the discretion of the consultant rheumatologist (3, 5-9).

3) There is no overwhelming evidence for an increased incidence of SARS-CoV2 infection (COVID-19) among patients with rheumatic disease compared to either healthy individuals or patients with other chronic illnesses. The risk of contracting COVID-19 principally relates to environmental exposure and is mitigated by public health measures such as physical distancing, hand hygiene and facemask-wearing (10-14)

4) Risk factors for severe COVID-19 in individuals with rheumatic disease are the same as for the general population i.e. older age, obesity, diabetes, hypertension, lung disease, kidney disease. Some studies demonstrated an increased risk of adverse outcome in rheumatic disease patients with high background disease activity and those on higher doses of corticosteroids or very potent immunosuppressive therapy (15-21)

Caribbean Association For Rheumatology
Bay Medical Center, PO Box GM712, Castries, St. Lucia LC04 201

Caribbean Association for Rheumatology

Detailed report

1. **Are Vaccines Safe to Administer in this Population?**

The currently available Covid-19 vaccines are not live vaccines and are considered safe to be administered in patients with rheumatic disease. In this section we focus on the safety data from clinical trials and post-marketing reports for the currently approved COVID-19 vaccines.

The mRNA vaccines appeared to have similar profile with frequent mild or moderate local reactogenicity (tenderness at the injection site) after both the first and the second dose of the vaccine. These symptoms were slightly less frequent in older (>55 years) adults. The most reported adverse effects (fatigue, headache, fever) occurred after the second vaccine dose. In the ***Pfizer BNT162b2 mRNA Covid-19 Vaccine*** Clinical trial see Table 1), there were 2 deaths in the treatment group in patients with known coronary artery disease (CAD) vs. 4 deaths in those who received placebo. There have been additional reports of anaphylactoid reactions in patients with a prior history of anaphylaxis (1). There was one report of severe hypoglycemia with the ***Moderna SARS-CoV-2 mRNA-1273 Vaccine (see Table 2)*** in a patient after fasting and vigorous exercise (2). For the **Oxford-AstraZeneca** ***ChAdOx1 nCoV-19 vaccine (AZD1222),*** serious adverse events (SAE's) were similar in the control and treatment groups. There was one case of idiopathic short segment spinal cord demyelination reported 14 days after the booster vaccine. A second case of transverse myelitis was later determined to be unrelated to the vaccine due to further investigation revealing prior unrecognized multiple sclerosis. One case of an exceptionally high fever > 40 ^{0}C was also reported - this patient is currently in the trial and remains masked to group allocation. There were four deaths in vaccine recipients and controls which were not linked to the vaccine (motor vehicle accident, blunt force trauma, homicide and fungal pneumonia) (3).

Generally, administration of the COVID-19 vaccines to patients without autoimmune inflammatory rheumatic disease (AIIRD) are well tolerated with most adverse events being mild, and mostly local site reactions. A few patients have experienced systemic symptoms with fatigue and fever. These reactions were reported more commonly in younger patients.

Patients with AIIRD were excluded from clinical trials but based on prior experience with attenuated vaccines in these patients, adverse events would mimic those of the general population.

A central question to the safety of vaccines in patients with AIIRD is the possible risk of "disease exacerbation" or flare of the underlying condition. Vaccines are generally safe and are not associated with exacerbations of AIIRD; however, trials inclusive of AIIRD have been small and hence, data are difficult to interpret. However, reports indicate the influenza vaccine was not associated with flares of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ANCA-associated vasculitis (AAV) or systemic sclerosis (SS) (4). Similarly, Hepatitis B (HBV) vaccination did not change the overall disease activity in patients with RA or Behcet disease. No safety alerts following pneumococcal vaccination in most AIIRDs were reported, independent of vaccine type.

To date, there have been no published reports of exacerbations of autoimmune rheumatic diseases caused by administration of the COVID-19 vaccine. However, the report of transverse myelitis and multiple sclerosis does raise a concern about possible exacerbation/ flare of this autoimmune disease.

Overall, more than 100 000 persons have completed the clinical vaccine trials and although patients with AIIRD and those treated with immunosuppressive medications were excluded, safety data did not report unmasking or flares of unknown or mild rheumatic disease. The data is reassuring although ongoing evaluation is warranted given the short duration of these clinical trials. Scientists theorize that the mRNA vaccines (Pfizer® and Moderna®) which elicit a strong Type 1 interferon response, could potentially cause an exacerbation of systemic lupus erythematosus or rheumatoid arthritis.

Physicians should reassure patients that there is no risk of contracting COVID-19 from these any of the available vaccines.

Summary: Currently available COVID-19 vaccines are not live vaccines and are considered safe to administer to individuals with autoimmune rheumatic disease and those on immunosuppressive therapy. Side effects are typically minor and similar to that of the general population. It is unknown if COVID-19 vaccines may cause an exacerbation of an existing rheumatic disease or development of a de-novo autoimmune syndrome.

2. Will the vaccines be effective in Autoimmune rheumatic disorders (AIRD)?

There is no data on the efficacy of the COVID-19 vaccine in patients with AIIRD. Current recommendations are based on what is known about already existing vaccines in this group of patients, especially as it relates to influenza and the influenza vaccine. However, there are several limitations to the extrapolation of this information to the currently available vaccines. The principal issues are that the influenza virus is not a coronavirus and that the COVID-19 vaccines represent a new era in vaccine creation, with novel mechanisms (mRNA vaccines ((Pfizer® and Moderna®)) and a viral vector vaccine (Oxford-AstraZeneca®) (3, 5, 6). It is also noteworthy that the efficacy of vaccines in most studies is based on the surrogate of immunogenicity (the development of protective antibodies) and not on prevention of actual disease. Antibodies to adenovirus may limit efficacy of adenovirus vector vaccines in certain populations and in older adults.

It has been demonstrated that the seasonal trivalent subunit influenza vaccination has reduced the incidence and bacterial complications of influenza, admissions for and mortality in AIIRD (7). Generally, Influenza vaccination has been shown to be immunogenic in patients with most AIIRD treated with all classes of disease modifying antirheumatic drugs (DMARDs), except for rituximab. DMARDs can affect immunogenicity. Temporary discontinuation of methotrexate (MTX) was shown to improve immunogenicity of seasonal influenza vaccination in patients with RA, with the best results when MTX was suspended for 2 weeks before and 2 weeks after vaccination. However, it is currently not recommended to stop MTX before or after

vaccinating for influenza (7). Recent guidance has suggested holding specific DMARDS for a short period around COVID-19 vaccination, but this should be individualized and at the discretion of the consultant rheumatologist (8). Other factors that can negatively affect immunogenicity include advanced age, increased comorbidity and moderate to higher dose corticosteroids. Vaccination efficacy is increased in patients with well controlled quiescent disease(9) . Aiming for the lowest possible glucocorticoid dose and vaccinating patients before the start of DMARDs if possible, would also be helpful.

Summary: There is no clear data on efficacy of novel COVID-19 vaccines in AIIRD. Efficacy may be limited by advanced age, comorbidity and higher dose corticosteroid use. Antibodies to adenovirus may limit efficacy of adenovirus vector vaccines in certain populations and in older adults. The decision to hold specific immunosuppressive medications in relation to COVID-19 vaccination should be guided by the recent American College of Rheumatology recommendations and at the discretion of the consultant rheumatologist.

3. **Are patients with rheumatic disease +/- immunosuppressant therapy at increased risk of SARS-CoV2 infection?**

Patients with rheumatic disease are, in general, at increased risk for infections due to immune dysregulation. This has been observed repeatedly in SLE and RA, independent of immunosuppression (10). However, currently there is no overwhelming evidence for an increased incidence of SARS-CoV2 infection among patients with rheumatic disease compared to individuals with other co-morbidities. Exposure continues to be the key risk factor for SARS-CoV2 infection with immunosuppression and co-morbidities influencing COVID-19 severity, morbidity and mortality (11, 12).

There are no data to support that medications which patients with AIIRD may be taking for their underlying condition, namely hydroxychloroquine, are protective against SARS-CoV2 (13, 14).

4. **Are patients with rheumatic disease/on immunosuppressant therapy at increased risk of worse outcomes with COVID19**

For the purpose of this discussion, worse outcomes were defined as increased risk of hospitalization, admission to an intensive care unit (ICU), need for mechanical ventilation, or death. Available data on outcomes in AIIRD patients infected with SARS-CoV-2 are a large international registry, the COVID-19 Global Rheumatology Alliance (GRA) physician registry(15).

The GRA included 600 cases from 40 countries, mostly from the USA or European countries, entered between 24th March and 20th April 2020. Severe COVID-19 affected nearly half (46%) who were hospitalized and 9% died (15).

Additional studies found the risk factors for severe COVID-19 in the general population to be similar in the AIIRD population, and included older age, male sex, obesity, hypertension, diabetes, lung disease, and renal failure (15, 16). The severity of COVID-19 infection in AIIRD patients was not dissimilar to the general population (17).

There is limited data to determine whether patients with AIIRD may have more severe COVD-19 infection. The data is limited due to the small number of patients with AIIRD with reported COVID-19 infection, however some trends appear to indicate that a certain subset of patients with AIIRD may have greater severity of COVID-19. In a UK population-based cohort study (18), of RA, SLE or psoriasis patients analysed as a combined group, had a slightly increased risk of death from COVID-19 compared to those without these diseases. It is unclear what role disease activity or treatment played, as these were not taken into account in this risk estimation. In a Danish population-based cohort, AIIRD patients were more likely to be admitted with COVID-19 than the general population, and COVID-19 admitted patients with RA could be at higher risk of a severe outcome (19).

The impact of AIIRD disease activity on the severity of COVID-19 infection, is unknown, but a small single site study in Spain found that higher disease activity was associated with increased mortality (20).

The GRA reported that patients with AIIRD on monotherapy with biologic or targeted synthetic DMARDS had lower odds of COVID-19 related hospitalization than those of non-DMARD patients (see Figure 1). Neither exposure to DMARDs nor non-steroidal anti-inflammatory drugs (NSAIDs) were associated with increased odds of hospitalization (15). However, chronic use of corticosteroids a dose > 10 mg of equivalent prednisone was associated with higher odds of hospitalisation (OR 2.05, 95% CI 1.06 to 3.96) (15, 16). There is also concern that Rituximab therapy may confer a higher risk of severe infection based on outcomes in a single study of a small cohort of AIIRD patients treated with Rituximab at one Spanish hospital (21).

Summary: Risk factors for severe COVID-19 in individuals with rheumatic disease are the same as for the general population i.e. older age, male sex, obesity, diabetes, hypertension, lung disease, kidney disease. Few studies demonstrated an increased risk of adverse outcome in AIIRD patients with high background disease activity and those on higher doses of corticosteroids or very potent immunosuppressive therapy.

Caribbean Association For Rheumatology
Bay Medical Center, PO Box GM712, Castries, St. Lucia LC04 201

Caribbean Association for Rheumatology

Appendix A:

Table 1 What are Adverse Reactions to COVID Vaccines?

BNT162b2 mRNA Covid-19 Vaccine (Pfizer®)[1]

Adverse Event	Total Population (%)	1st Dose Age < 55 (%)	2nd Dose Age < 55 (%)	1st Dose Age > 55 (%)	2nd Dose Age > 55 (%)
Severe Local Reactogenicity	< 1				
Mild to moderate local reactogenicity		83	78	71	66
Fatigue			79		51
Headache			52		39
Fever < 38			16		11
Fever 38 - 40	0.2 (1st dose) 0.8 (2nd dose)				
Lymphadenopathy	0.3				
Death	2 patients (atherosclerosis and cardiac arrest vs 4 placebo patients				

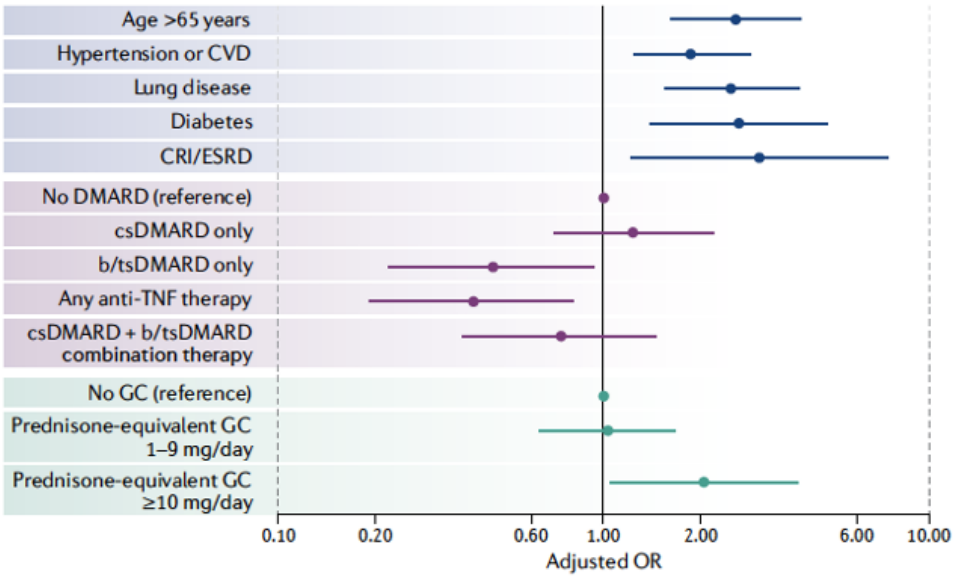
Post marketing reports of 2 anaphylactoid reactions in patients with a prior history of anaplylaxis

Table 2. SARS-CoV-2 mRNA-1273 Vaccine (Moderna®)[2]

Adverse Event	Population, n (%)	1st Dose (%)	2nd Dose
Any Severe Local Symptoms		6.7 (18 – 55 group)	6.7 (18 – 55 group)
Any Moderate Local Symptoms		0 -13.3 (depending on vac. dose and age)	7.7 – 26.7 (depending on vac. dose and age)
Any Mild Local Symptoms		50- 80 (depending on vac. dose and age)	40 – 79.2 (depending on vac. dose and age)
Any Severe Systemic Symptoms		0	10% (1 subject in the 56 – 70 age group
Any Moderate Systemic Symptoms		13 – 20 (depending on vac. dose and age)	10 – 80 (depending on vac. dose and age)
Any Mild Systemic Symptoms		30 – 50 (depending on vac. dose and age)	40 – 69.2 (depending on vac. dose and age)

Appendix B.

Fig. 1 | **Factors associated with hospitalization for COVID-19 infection.**



This graph visualizes data from 600 patients with rheumatic diseases recorded in the COVID-19 Global Rheumatology Alliance international physician registry, reported by Gianfrancesco et al. (20) Associations between the various factors and odds of hospitalization were estimated using multivariable-adjusted logistic regression and reported as odds ratios (ORs) with 95% confidence intervals. b/tsDMARD, biologic/ targeted synthetic DMARD; CRI, chronic renal insufficiency; csDMARD, conventional synthetic DMARD; CVD, cardiovascular disease; ESRD, end-stage renal disease; GC, glucocorticoid.

CAR COVID-19 Task Force members

Sharon Dowell, Associate Professor, Howard University, USA
Aurore Fifi-Mah, University of Calgary, Adult Rheumatology, Canada
Cindy Flower, Consultant Rheumatologist, Queen Elizabeth Hospital, Barbados
Nicole Johnson, University of Calgary, Pediatric Rheumatology, Canada
Gail Kerr, Chief of Rheumatology at Washington DC Veterans Affairs Medical Center and Howard University Hospital, Professor of Medicine, Howard University and Georgetown University, Washington DC, USA
Amanda King-Greenidge, Consultant Rheumatologist, St. Lucia
Rebecca Manno, MD, MHS, Rheumatologist, *The Comprehensive Arthritis and Rheumatology Center of the Caribbean* at Comprehensive Orthopaedic Global, *Adjunct Assistant Professor, Johns Hopkins University School of Medicine*
J. Steuart Richards, Veterans Affairs Pittsburgh Healthcare System and Clinical Associate Professor of Medicine University of Pittsburgh, USA

REFERENCES

1. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603-15. Epub 2020/12/11. doi: 10.1056/NEJMoa2034577. PubMed PMID: 33301246; PubMed Central PMCID: PMCPMC7745181.
2. Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. N Engl J Med. 2020;383(25):2427-38. Epub 2020/09/30. doi: 10.1056/NEJMoa2028436. PubMed PMID: 32991794; PubMed Central PMCID: PMCPMC7556339.
3. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397(10269):99-111. Epub 2020/12/08. doi: 10.1016/S0140-6736(20)32661-1. PubMed PMID: 33306989; PubMed Central PMCID: PMCPMC7723445.
4. Rondaan C, Furer V, Heijstek MW, Agmon-Levin N, Bijl M, Breedveld FC, et al. Efficacy, immunogenicity and safety of vaccination in adult patients with autoimmune inflammatory rheumatic diseases: a systematic literature review for the 2019 update of EULAR recommendations. RMD Open. 2019;5(2):e001035. Epub 2019/09/09. doi: 10.1136/rmdopen-2019-001035. PubMed PMID: 31565247; PubMed Central PMCID: PMCPMC6744079.
5. Chen H, Xiang ZQ, Li Y, Kurupati RK, Jia B, Bian A, et al. Adenovirus-based vaccines: comparison of vectors from three species of adenoviridae. J Virol. 2010;84(20):10522-32. Epub 2010/08/04. doi: 10.1128/JVI.00450-10. PubMed PMID: 20686035; PubMed Central PMCID: PMCPMC2950567.
6. King A. Vector-Based Vaccines Come to the Fore in the COVID-19 Pandemic. The Scientist; 2021.
7. Furer V, Rondaan C, Heijstek M, van Assen S, Bijl M, Agmon-Levin N, et al. Incidence and prevalence of vaccine preventable infections in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD): a systemic literature review informing the 2019 update of the EULAR recommendations for vaccination in adult patients with AIIRD. RMD Open. 2019;5(2):e001041. Epub 2019/09/19. doi: 10.1136/rmdopen-2019-001041. PubMed PMID: 31673420; PubMed Central PMCID: PMCPMC6803008.
8. ACR. COVID-19 Vaccine Clinical Guidance Summary for Patients with Rheumatic and Musculoskeletal Diseases. Available from: https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf.
9. EULAR. EULAR View-points on SARS-CoV-2 vaccination in patients with RMDs 2021. Available from: https://www.eular.org/eular_sars_cov_2_vaccination_rmd_patients.cfm.
10. Pego-Reigosa JM, Nicholson L, Pooley N, Langham S, Embleton N, Marjenberg Z, et al. The risk of infections in adult patients with systemic lupus erythematosus: systematic review and meta-analysis. Rheumatology (Oxford). 2021;60(1):60-72. Epub 2020/10/26. doi: 10.1093/rheumatology/keaa478. PubMed PMID: 33099651; PubMed Central PMCID: PMCPMC7785308.
11. Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. J Infect. 2020;80(6):656-65. Epub 2020/04/14. doi: 10.1016/j.jinf.2020.03.041. PubMed PMID: 32283155; PubMed Central PMCID: PMCPMC7151416.

12. Michelena X, Borrell H, López-Corbeto M, López-Lasanta M, Moreno E, Pascual-Pastor M, et al. Incidence of COVID-19 in a cohort of adult and paediatric patients with rheumatic diseases treated with targeted biologic and synthetic disease-modifying anti-rheumatic drugs. Seminars in arthritis and rheumatism. 2020;50(4):564-70. Epub 2020/05/16. doi: 10.1016/j.semarthrit.2020.05.001. PubMed PMID: 32425260.
13. Favalli EG, Monti S, Ingegnoli F, Balduzzi S, Caporali R, Montecucco C. Incidence of COVID-19 in Patients With Rheumatic Diseases Treated With Targeted Immunosuppressive Drugs: What Can We Learn From Observational Data? Arthritis Rheumatol. 2020;72(10):1600-6. Epub 2020/06/09. doi: 10.1002/art.41388. PubMed PMID: 32506699; PubMed Central PMCID: PMCPMC7300434.
14. Gendelman O, Amital H, Bragazzi NL, Watad A, Chodick G. Continuous hydroxychloroquine or colchicine therapy does not prevent infection with SARS-CoV-2: Insights from a large healthcare database analysis. Autoimmun Rev. 2020;19(7):102566. Epub 2020/05/08. doi: 10.1016/j.autrev.2020.102566. PubMed PMID: 32380315; PubMed Central PMCID: PMCPMC7198406.
15. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Annals of the rheumatic diseases. 2020;79(7):859-66. doi: 10.1136/annrheumdis-2020-217871. PubMed PMID: 32471903.
16. contributors FRSSSCIca. Severity of COVID-19 and survival in patients with rheumatic and inflammatory diseases: data from the French RMD COVID-19 cohort of 694 patients. Annals of the rheumatic diseases. 2020:annrheumdis-2020-218310. doi: 10.1136/annrheumdis-2020-218310. PubMed PMID: 33268442.
17. Kastritis E, Kitas GD, Vassilopoulos D, Giannopoulos G, Dimopoulos MA, Sfikakis PP. Systemic autoimmune diseases, anti-rheumatic therapies, COVID-19 infection risk and patient outcomes. Rheumatol Int. 2020;40(9):1353-60. Epub 2020/07/13. doi: 10.1007/s00296-020-04629-x. PubMed PMID: 32654078; PubMed Central PMCID: PMCPMC7353833.
18. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6. Epub 2020/07/09. doi: 10.1038/s41586-020-2521-4. PubMed PMID: 32640463.
19. Cordtz R, Lindhardsen J, Soussi BG, Vela J, Uhrenholt L, Westermann R, et al. Incidence and severeness of COVID-19 hospitalisation in patients with inflammatory rheumatic disease: a nationwide cohort study from Denmark. Rheumatology (Oxford). 2020. Epub 2020/12/29. doi: 10.1093/rheumatology/keaa897. PubMed PMID: 33369663; PubMed Central PMCID: PMCPMC7798558.
20. Santos CS, Morales CM, Álvarez ED, Castro CÁ, Robles AL, Sandoval TP.
21. Loarce-Martos J, García-Fernández A, López-Gutiérrez F, García-García V, Calvo-Sanz L, Del Bosque-Granero I, et al. High rates of severe disease and death due to SARS-CoV-2 infection in rheumatic disease patients treated with rituximab: a descriptive study. Rheumatology international. 2020;40(12):2015-21. Epub 2020/09/18. doi: 10.1007/s00296-020-04699-x. PubMed PMID: 32945944.