Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

addressing the main determinants of acceptability and providing accurate and updated data to physicians can help them to relay more timely and transparent information to their patients, thus facilitating the vaccine uptake in both groups.

LA reports consulting fees and honoraria from Pfizer and AstraZeneca, outside this work. All other authors declare no competing interests. NZ, LEK, IH, and MM designed the study and were part of the steering committee that wrote the study protocol, included participants from their respective countries, and supervised the recruitment of participants in all the countries. LA and RF provided the original questionnaire from the VAXICOV study and participated in the questionnaire adaptation and in the finalisation of the protocol. NZ, LEK, MM, and IH drafted the manuscript and handled the comments of the authors. NA, HH, ME, MER, BM, FA, WH, AA, and AAN participated in the study design and protocol, included participants from their respective countries, and helped in addressing logistical issues during recruitment. NZ and IH analysed the results of the survey and designed the tables and figures. All authors made substantial contributions to work and participated in the discussion of the study results, the draft of the manuscript, and revised the final submitted document for intellectual content. All the authors approved the version to be published and agreed to be accountable for all aspects of the work. RF and LA contributed equally.

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Humoral and cellular immune responses to mRNA COVID-19 vaccines in patients with axial spondyloarthritis treated with adalimumab or secukinumab

Published **Online**
December 21, 2021
https://doi.org/10.1016/S2665-9913(21)00393-3

Biologic disease-modifying anti-rheumatic drugs (DMARDs) represent a potent treatment option for patients with immune-mediated inflammatory diseases.[1] Yet, infections make up the largest proportion of serious adverse events associated with biological DMARD therapy.[2] Throughout the COVID-19 pandemic, patients receiving immunosuppressive treatment were shown to be at higher risk of severe disease outcomes.[3] Vaccination could prevent these outcomes, but the efficacy of COVID-19 vaccines in these patients is incompletely understood.[4]

Although studies investigating the effect of biological DMARDs on the development of immune responses to COVID-19 vaccines are slowly accumulating, most of our current knowledge relies on studies evaluating the serological responses to COVID-19 vaccines.[5] However, the serological response to COVID-19 vaccines is highly variable between individuals, in terms of both antibody titres and kinetics.[6,7] There is also no cutoff value of antibody titres that clearly reflects protection from SARS-CoV-2 infection.[7]

See Online for appendix

Vaccine-elicited cellular immune responses were shown to be crucially important for the development of humoral immune response and for the clearance of SARS-CoV-2.[6,8] For that reason, more data on vaccine-elicited SARS-CoV-2-reactive T cells in patients treated with biological DMARDs are urgently needed. Recent studies by Mahil and colleagues[3,5] show encouraging results on COVID-19 vaccine immunogenicity in patients with psoriasis treated with biological DMARDs. These studies showed that patients receiving these drugs were able to mount both serological and cellular responses to both the first and second dose of the BNT162b2 (tozinameran, Pfizer–BioNTech) mRNA vaccine.[3,5]

We aimed to evaluate the immunogenicity of two doses of the BNT162b2 vaccine in individuals receiving monotherapy with tumour necrosis factor (TNF) inhibitors or interleukin(IL)-17A inhibitors. We evaluated antibody and T-cell responses in 17 patients with axial spondyloarthritis who had not been exposed to SARS-CoV-2 and who were being treated with either the TNF inhibitor adalimumab (n=10) or the IL-17A inhibitor secukinumab (n=7), compared with six healthy individuals. 11 (65%) of the patients were treated for radiographic axial spondyloarthritis, 15 (88%) were men. The mean age of the patients was 39·8 (SD 9·4) years, and the mean disease duration was 97·3 (80·8) months (appendix p 1). All patients were managed according to treatment guidelines; secukinumab (150 mg) was administered every four weeks, and adalimumab (40 mg) was administered either every 2 weeks (n=7) or every three weeks (n=3; appendix p 1). Adherence to biological DMARD treatment was confirmed by all study participants. The healthy control cohort had a mean age of 48·2 (10·5) years and included three men and three women. Patients who were previously exposed to SARS-CoV-2 infection, as indicated by positivity for SARS-CoV-2-specific IgG or IgA antibodies before vaccination, and patients with a history of acute respiratory tract infection symptoms 6 months before study initiation, were excluded.

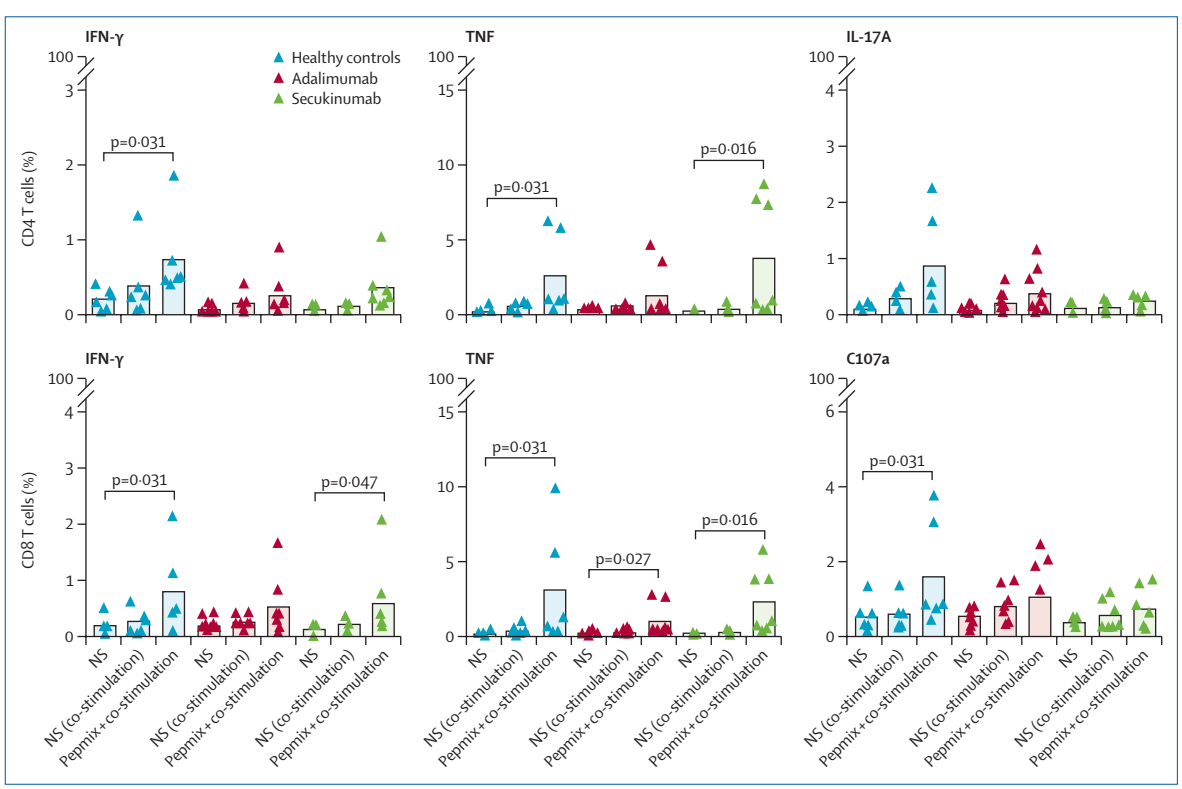

Figure: **Proportion of SARS-CoV-2 reactive T cells between study groups**
T-cell responses were measured 30 days after the second dose of the BNT162b2 vaccine in healthy donors and patients receiving therapy with adalimumab or secukinumab. T cells were stimulated with a mixture of SARS-CoV-2 spike protein peptides, and production of interferon γ, interleukin(IL)-17A, and tumour necrosis factor (TNF) was measured by flow cytometry in CD4+ T cells and CD8+ T cells. Expression of CD107a was also measured in CD8+ T cells. Statistical analysis was done between cell samples from one group of patients or healthy controls stimulated with costimulatory antibody and costimulatory antibody in combination with PepMix. A correlation was also made in cells stimulated by a combination of co-stimulation and PepMix within the groups of patients and healthy controls. NS=not stimulated.

All study participants received two standard doses of the BNT162b2 vaccine with a 21-day interval between doses. The humoral immune response was evaluated by measuring titres of anti-SARS-CoV-2-specific IgA and IgG antibodies, and the cellular immune response was assessed as the proportion of SARS-CoV-2-reactive $CD4^+$ and $CD8^+$ T cells producing interferon γ, TNF, or IL-17A after ex vivo stimulation with spike glycoprotein-derived peptides (PepMix SARS-CoV-2) and co-stimulation with CD28 and CD49d antibodies. CD107a expression was assessed as an indicator of $CD8^+$ T-cell degranulation. Cellular immune responses were analysed by flow cytometry.

We observed a robust seroconversion in all study participants (appendix p 2). Vaccination also generated proinflammatory cytokine-producing $CD4^+$ and $CD8^+$ T cells, with no significant differences in the proportion of SARS-CoV-2-reactive T cells between the study groups (figure). The second dose of the BNT162b2 vaccine did not elicit $CD8^+$ T-cell degranulation in patients treated with adalimumab nor in those treated with secukinumab.

Cytokine-producing $CD8^+$ T cells and CD107a-expressing $CD8^+$ T cells presumably represent anti-viral effector immunity, whereas vaccine-elicited $CD4^+$ T cells have been shown to contribute to the efficient production of neutralising antibodies.[9] Our data also showed individual differences in the cellular immune responses to full vaccination with the BNT162b2 vaccine, with T-cell responses undetectable in up to 20% (appendix p 3) of vaccinees in each group (figure).

COVID-19 vaccines were shown in clinical trials to substantially reduce the severity of COVID-19 and also to reduce the risk of SARS-CoV-2 transmission.[4,10] However, patients receiving immunosuppressants were excluded from these trials and few published studies have evaluated vaccine responses in patients treated with biological DMARDs.[5]

Our data indicated that neither adalimumab nor secukinumab substantially affected the immunogenicity of the BNT162b2 mRNA COVID-19 vaccine. Patients receiving these biological DMARDs were able to develop cellular immune responses after vaccination with the BNT162b2 vaccine, and the overall humoral and cellular immune response did not differ significantly between patients and healthy individuals. By contrast to the data presented by Mahil and colleagues,[3,5] our findings did not indicate a significant disparity between humoral and cellular immune responses in individual patients. However, although all study participants had high levels of anti-SARS-CoV-2-specific IgA and IgG antibodies, cellular responses against the SARS-CoV-2 spike glycoprotein could not be identified in all participants.

Our study has several limitations worth noting, in particular the small number of participants studied. Although we initially enrolled 21 patients with axial spondyloarthritis receiving biological DMARDs, we had to exclude three patients because of previous exposure to COVID-19 and one patient because of concomitant treatment with methotrexate. We also did not assess neutralising antibody titres. In addition, our study reflects the immunogenicity of the BNT162b2 mRNA COVID-19 vaccine at a single timepoint. We presume that the magnitude of cellular and humoral immune responses might change over time and thus further investigations are needed to fully understand the consequences of biological DMARD therapy in the era of COVID-19.

JS, ZS, AS, TM, and RH contributed to study design. JS, ZS, TM, and RH contributed to the conceptualisation of the study protocol and the data curation. ZS and RH contributed to the formal analysis and administration of the project. ZS, RH, and AS supervised the project. JS, ZS, and TM did the main study investigation. JS and TM contributed to the validation of the study and software analyses. JS contributed to the methodology and provided the visualisation of the obtained data. JS, AS, TM, and RH contributed to the funding acquisition and AS, TM, and RH provided the resources for the study. ZS, JS, and TM contributed to the writing of the original draft. JS, ZS, AS, TM, and RH reviewed and edited the manuscript.

We declare no competing interests.

The authors are happy to share data on request to the corresponding author.

The study was supported by a NU20-05-00320 grant issued by the Czech Health Research Council and Ministry of Health (Czechia), Institutional support issued by the Motol University Hospital (Prague, Czechia), the Ministry of Health (00064203; University Hospital Motol, Prague, Czech Republic).

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From phenotype to pathophysiology—placing rheumatic diseases in an immunological perspective

Published **Online** January 5, 2022 https://doi.org/10.1016/S2665-9913(21)00369-6

Rheumatic diseases have many overlapping clinical features, which can complicate the differentiation between shared and unique underlying immunopathological mechanisms. Fortunately, a wealth of information on the genetic basis of rheumatic diseases has become available due to new research techniques. These genetic data can elucidate common denominators versus unique features of the pathophysiology of rheumatic diseases. We therefore capitalised on the gain of genetic knowledge to make a cutting-edge overview of the immunopathology of rheumatic diseases and assessed the validity of our model based on its congruence with medication use.

See **Online** for appendix

For rheumatic diseases with a prevalence of 1/10 000 or higher, and for which sufficient genetic data were available (ie, gout, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, familial Mediterranean fever, systemic lupus erythematosus, Behçet's disease, primary Sjögren's syndrome, systemic sclerosis [scleroderma], and giant cell arteritis), recent literature reviews on genetic risk factors between 2017 and 2019 were obtained. Genetic risk factors were classified as contributing to innate or adaptive immune responses; contributing to B-cell function or belonging to the HLA class 1 locus. Using the prevalence of autoantibodies as a second key factor, the contribution of innate versus adaptive immunity (B-cell factors and of HLA class 1 alleles) was estimated for each disease. Detailed methods, references, and the genetic risk factors per disease are provided in the appendix.

The figure provides an overview of the location of the various rheumatic diseases in the immunological landscape. The position on the X-axis is determined by the relative contribution of the adaptive versus innate immune system, and the position on the Y-axis reflects the contribution of B-cell factors (upper part) and HLA class 1 alleles (lower part). When the analysis was repeated for genetic factors replicated in different ethnicities, the results were similar (appendix p 17).

This depiction allows us to distinguish three distinct categories of rheumatic diseases (figure). The diseases in the blue box (ie, systemic lupus erythematosus, rheumatoid arthritis, primary Sjögren's syndrome, and systemic sclerosis) are mainly characterised by the influence of B cells and adaptive immunity on disease pathogenesis. Although the genetic background of these diseases is to some extent quite heterogeneous with innate, adaptive, and B-cell influences, this disease subgroup is unique in that autoantibodies and mutations in genes coding

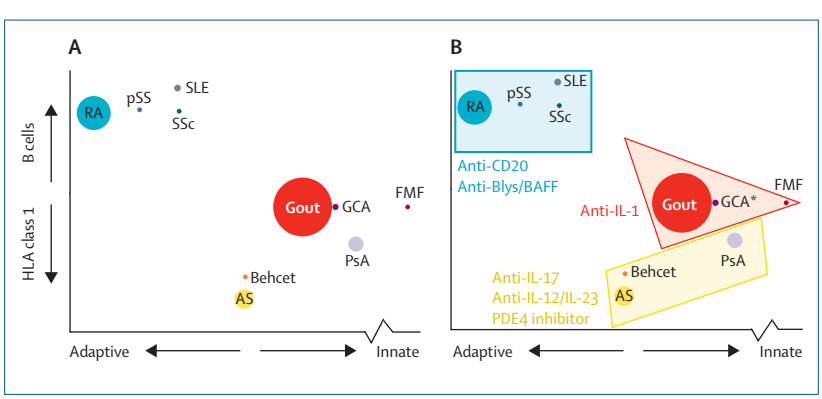

Figure: **Distribution of rheumatic diseases in the immunological landscape**
(A) The position of a rheumatic disease is determined by the ratio of the sum of genetic predispositions and autoantibody prevalence for innate versus adaptive immunity on the x-axis and for B-cell (+) and HLA class 1 (–) on the y-axis. The size of each dot is based on prevalence in the White population, however for diseases with a prevalence lower than 0·2/1000 (primary Sjögren's syndrome [pSS], systemic sclerosis [SSc], Behçet's Disease [Behçet], and familial Mediterranean fever [FMF]) the dots are plotted as 0·2/1000. For the sake of legibility of the figure, the symbol depicting giant cell arteritis was moved slightly to the right to avoid it coalescing with gout. (B) As in panel A but with boxes applied around clusters of diseases. AS=ankylosing spondylitis. BLyS=anti-B lymphocyte stimulator. GCA=giant cell arteritis. IL=interleukin. PDE4=phosphodiesterase type four. PsA=psoriatic arthritis. RA=rheumatoid arthritis. SLE=systemic lupus erythematosus. SSc=systemic sclerosis. *GCA prevalence in ≥50-year-old patients.