S1/S2 IgG titers at the following time points: 2-6 weeks (AIIRD n=720, controls n=122) and six months (AIIRD n=628, controls=116) after the second vaccine dose, and 2-6 weeks after the third vaccine dose (AIIRD n=169, controls n=45). A seropositive response was defined as a detectable anti-S1/S2 IgG titer ≥ 15 BAU/ml. T-cell immune response was evaluated in a sample of patients (n=28) and controls (n=9) by intracellular staining of S-stimulated $CD4^+$ T-cells for TNFα and IFNγ production.

Results: The two-dose vaccine regimen induced a higher humoral response in controls compared to patients, as reflected by the post-vaccination seropositivity rates of 100% vs 84.72%, p<0.0001, and 96.55% vs 74.26%, p<0.0001 at 2-to-6 weeks and at 6 months, respectively. The decline of S1/S2 IgG titers within six months was similar in controls and patients. Following the 3rd vaccine, the seropositivity rate increased to 80.47% and 100% in AIIRD and control groups, p=0.0028, with a significantly higher increase of S1/S2 IgG titers in controls compared with AIIRD patients, 284.09±76.58 vs 219.39±151.55 BAU/ml, p=0.0016. At all-time points, S1/S2 IgG titers were significantly lower in AIIRD patients compared with controls (Figure 1).

We further investigated the impact of therapies on the vaccine's immunogenicity (Figure 1). Glucocorticoids (GC) were associated with a significantly lower seropositivity rate and lower S1/S2 IgG titers compared to controls at all time points. Monotherapy with methotrexate (MTX) was associated with a comparable to controls humoral response at all time points. Anti-cytokine biologics (TNFi, IL6i, IL17i) were associated with an initial high seropositivity rate, similar to controls, followed by a steeper decline at 6 months, 79.82% vs 96.55%, p=0.0001, and restoration of seropositivity after the 3rd vaccine dose in all patients. JAKi were associated with a mildly decreased seropositivity rate after the 2nd vaccine dose and similar to controls response after the 3rd vaccine dose. Abatacept was associated with a reduced immunogenicity after the 2nd vaccine dose, but was restored to 100% seropositivity after the 3rd vaccine dose. Rituximab (RTX) significantly blunted the humoral response at all time points, with a seropositivity rate of 42% after the 2nd vaccine dose, 29% at 6 months, and with increase to 40% after the 3rd vaccine dose. A third of the RTX-treated patients who were seronegative after two vaccine doses, seroconverted after the 3rd dose. The multivariate model for predicting the seropositive response to vaccination found that higher S1/S2 IgG titers after the 2nd vaccine dose was associated with a higher seropositivity rate following the 3rd vaccine dose, OR 1.026 (1.008-1.045), p=0.0027, and that treatment with RTX was associated with a 14.3-fold risk for a negative humoral response, p≤0.0001. Cellular immune response, evaluated mainly in RTX treated patients, was preserved prior to and after the 3rd vaccine dose and was similar to controls.

Conclusion: Over a six-month period, the two dose BNTb262 vaccination was associated with a similar extent of waning of the humoral immune response in AIIRD patients and controls. The 3rd vaccine dose restored the response in all controls and in patients treated with MTX monotherapy, anti-cytokine biologics, abatacept, and JAKi. Treatment with GC and RTX was associated with an impaired humoral response at all time points.

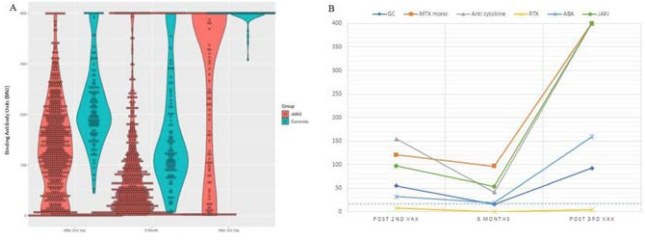

Figure. Kinetics of humoral response (S1/S2 IgG titer, BAU/mL) after two and three BNT162b2 vaccine doses. Panel A: AIIRD patients and controls. Panel B: AIIRD patients according to immunosuppressive treatment used.

BAU, binding antibody units; vax, vaccine dose; AIIRD, autoimmune inflammatory rheumatic disease; GC, glucocorticoids; MTX mono, monotherapy with methotrexate; anti cytokine includes tumor necrosis factor, interleukin 6 and interleukin 17 inhibitors; RTX, rituximab, ABA, abatacept, JAKi, janus kinase inhibitors.

Acknowledgements: We would like to thank the statistician Mr Yishai Friedlander and Mr Yoram Neufeld for their valuable assistance.
Disclosure of Interests: None declared
DOI: 10.1136/annrheumdis-2022-eular.2074

OP0178

COVID-19 BREAKTHROUGH INFECTIONS IN VACCINATED PATIENTS WITH IMMUNE-MEDIATED INFLAMMATORY DISEASES AND CONTROLS – DATA FROM TWO PROSPECTIVE COHORT STUDIES

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Background: Concerns have been raised regarding risks of COVID-19 breakthrough infections in vaccinated patients with immune-mediated inflammatory diseases (IMIDs) treated with immunosuppressants, but data on COVID-19 breakthrough infections in these patients are still scarce.

Objectives: The primary objective was to compare the incidence and severity of COVID-19 breakthrough infections with the SARS-CoV-2 delta variant between fully vaccinated IMID patients with immunosuppressants, and controls (IMID patients without immunosuppressants and healthy controls). The secondary objective was to explore determinants of breakthrough infections.

Methods: In this study we pooled data collected from two large ongoing prospective multi-center cohort studies (Target to-B! [T2B!] study and ARC study). Clinical data were collected between February and December 2021, using digital questionnaires, standardized electronic case record forms and medical files. Post-vaccination serum samples were analyzed for anti-RBD antibodies (T2B! study only) and anti-nucleocapsid antibodies to identify asymptomatic breakthrough infections (ARC study only). Logistic regression analyses were used to assess associations with the incidence of breakthrough infections. Multivariable models were adjusted for age, sex, cardiovascular disease, chronic pulmonary disease, obesity and vaccine type.

Results: We included 3207 IMID patients with immunosuppressants and 1810 controls (985 IMID patients without immunosuppressants and 825 healthy controls). The incidence of COVID-19 breakthrough infections was comparable between patients with immunosuppressants (5%) and controls (5%). The absence of SARS-CoV-2 IgG antibodies after COVID-19 vaccination was independently associated with an increased incidence of breakthrough infections (P 0.044). The proportion of asymptomatic COVID-19 breakthrough cases that were additionally identified serologically in the ARC cohort was comparable between IMID patients with immunosuppressants and controls; 66 (10%) of 695 patients vs. 64 (10%) of 647 controls. Hospitalization was required in 8 (5%) of 149 IMID patients with immunosuppressants and 5 (6%) of 86 controls with a COVID-19 breakthrough infection. Hospitalized cases were generally older, and had more comorbidities compared with non-hospitalized cases (Table 1). Hospitalization rates were significantly higher among IMID patients treated with anti-CD20 therapy compared to IMID patients using any other immunosuppressant (3 [23%] of 13 patients vs. 5 [4%] of 128 patients, P 0.041; Table 1).

Table 1. Determinants of the severity of COVID-19 breakthrough infections.

	Ambulatory care (n = 222)		Hospitalized (n = 13)	
Group - no. (%)				
IMID patients with immunosuppressants	141	(64)	8	(62)
IMID patients without immunosuppressants	49	(22)	3	(23)
Healthy controls	32	(14)	2	(15)
Patient characteristics				
Age, years – mean (SD)	51	(14)	60	(11)
Female sex – no. (%)	143	(64)	4	(31)
Comorbidities – no. (%)				
Cardiovascular disease	17	(8)	5	(39)
Chronic pulmonary disease	17	(8)	4	(31)
Diabetes	15	(7)	3	(23)
Obesity	34	(15)	5	(39)
Immunosuppressants– no. (%)				
Methotrexate	36	(16)	2	(15)
TNF inhibitor	48	(22)	2	(15)
Anti-CD20 therapy	13	(6)	3	(23)
Mycophenolate mofetil	3	(1)	0	(0)
S1P modulator	5	(2)	0	(0)
Other immunosuppressants	70	(32)	3	(23)

Conclusion: The incidence of COVID-19 breakthrough infections in IMID patients with immunosuppressants was comparable to controls, and infections were mostly mild. Anti-CD20 therapy might increase patients' susceptibility to severe COVID-19 breakthrough infections, but traditional risk factors also continue to have a critical contribution to the disease course of COVID-19. Therefore, we argue that most patients with IMIDs should not necessarily be seen as a risk group for severe COVID-19, and that integrating other risk factors should become standard practice when discussing treatment options, COVID-19 vaccination, and adherence to infection prevention measures with patients.

Disclosure of Interests: None declared
DOI: 10.1136/annrheumdis-2022-eular.4704