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Background: Notwithstanding the wealth of literature on COVID-19, studies focusing on young people with autoimmune diseases (ADs) are lacking. Despite their younger age, they may have been exposed to immunosuppressants (IS) for longer than older adults, particularly if diagnosed at pediatric age.
Objectives: To determine early (within 7 days) and late (after 7 days) anti-SARS-CoV-2 vaccine-related adverse events (AEs), post-vaccine disease flares, COVID-19 severity and breakthrough infections (B-INFs) in young people with rheumatic diseases (RMDs) and non-rheumatic (nr)-ADs compared to healthy controls (HC).
Methods: The EULAR Young PARE definition was used to classify young patients (18-35 years old). Data were captured through the international COVID-19 Vaccination in AD (COVAD) 1 and 2 questionnaires (covering the years 2021 and 2022) and variables differing across groups in univariable analysis were included in multivariable analysis adjusting for baseline factors defined a priori.
Results: Of 20,685 complete responses, 6010 were from young people (1692 RMD, 400 nrADs, 3918 HC). RMDs and nr-ADs comprised mainly females of Caucasian, Asian and Hispanic ethnicities. Before vaccination, <5% and 7% of nrAD were taking glucocorticoids (GC) or immunosuppressants (IS) other than GC vs 30% GC and >80% IS in RMDs. Over 80% of total responders had received ≥2 vaccine doses.
1) AEs after 1 or 2 doses. Early mild AEs were more frequent in RMDs and nr-ADs compared to HC [RMD vs HC odds ratio (OR) (95% confidence interval (CI)) 2.4 (2.0-3.1); nr-AD vs HC 2.0 (1.4-2.9)]. Injection site pain, headache and fatigue were the most frequent mild AE in all 3 groups, but they were more frequent in nr-AD than in HC and RMD. Fever and chills were also more frequent in nr-AD compared to HC and to RMD. The frequency of late mild AEs after either of the 2 doses was < 10% in all 3 groups with no differences between groups. Severe AEs were < 2% in all groups, with no differences between the first and second dose.
2) AEs after 3 or 4 doses. The frequency of late mild AEs after any dose (1, 2 3 or 4) was < 20% in all 3 groups with no differences between groups. Severe AEs after the third dose were <3%. In the 1417 responders that received a fourth dose, only two (1 RMD and 1 HC) reported AEs (0.1%).
3) Pre-vaccine vs breakthrough infections (B-INFs). The frequency of reported SARS-CoV-2 infections was similar in all groups (RMD=28%, nr-ADs=25%, HC=28%). However, RMD patients reported only one infection more frequently than nrADs and HC, while nrADs reported ≥ 2 infections more frequently than RMD. Pre-vaccine infections were less frequent in RMD vs HC (OR=0.6, 95% CI= 0.4-0.9), but similar in nr-AD vs HC. In contrast, the frequency of B-INFs was higher in RMD vs HC (OR=2.7 95% CI 2.1-3.5), while it was similar in nr-AD vs HC. Regarding the clinical profiles of pre-vaccine infections versus B-INFs, no differences were observed among nrADs whereas in RMD a significantly lower frequency of loss of smell and loss of taste was reported for B-INFs. Less than 5% of total respondents received advanced therapies for SARS-CoV-2 infection.
4) Post-vaccination disease flares: Self-reported disease flares after the second vaccine dose were reported by 10% or RMD and 7% of nrAD patients. Of these, approximately half reported requiring a change in their medications (increased dose/addition of a new IS and/or GC).
Conclusion: This study provides the first detailed exploration of the SARS-CoV2 spectrum in young people with RMDs and nrADs compared to HC and highlights important similarities and differences between disease groups. In fact, despite being less exposed to GC and IS, nr-AD reported a higher number of SARS-CoV-2 infections, no difference in the clinical picture of pre-vaccine infections vs B-INFs and a more pronounced burden of post-vaccine mild AEs after earlier doses compared to RMD. These findings may highlight that in young people the type of disease rather than IS therapy may be more important to influence the vaccine safety and the features of B-INFs.
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Prehabilitation to increase treatment success in rheumatology

LB0007 **SHORT- AND LONG-TERM EFFECTS OF HIGH-INTENSITY INTERVAL TRAINING IN PATIENTS WITH INFLAMMATORY JOINT DISEASE: THE EXEHEART RANDOMIZED CONTROLLED TRIAL**

Topic: 39. Rehabilitation

Keywords: Cardiovascular disease, Non-pharmacological interventions, Randomized control trial

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Table 1. Effects of HIIT at 3 and 6 months. Data presented as mean (SD).

	HIIT group Baseline	Follow-up	Control group Baseline	Follow-up	*n*	Mean group difference (95%CI)[a]	*p*
VO_{2peak}, mL/kg/min Baseline to 3 months	30.4 (5.9)	32.9 (6.4)	30.1 (7.9)	30.3 (7.5)	60§	2.5 (0.9-4.0)	<0.01
Baseline to 6 months	30.4 (5.9)	33.2 (7.4)	30.4 (8.0)	30.7 (7.8)	60§	2.6 (0.8-4.3)	<0.01
Fatigue, NRS 0-10, 0= no fatigue Baseline to 3 months	3.1 (2.1)	3.0 (1.9)	3.6 (2.5)	3.5 (2.7)	59 58	-0.1 (-0.9-0.8)	0.87 0.41
Baseline to 6 months	3.1 (2.1)	3.1 (2.2)	3.6 (2.5)	3.8 (2.4)		-0.4 (-1.2-0.5)[b]	
Pain, NRS 0-10, 0= no pain Baseline to 3 months	2.9 (2.1)	2.8 (1.8)	2.9 (2.5)	3.1 (2.7)	59 58	-0.3 (-1.3-0.7)[b] -0.4 (-1.2-0.5)	0.57 0.38
Baseline to 6 months	2.9 (2.2)	2.9 (2.0)	2.9 (2.5)	3.2 (2.4)			

§ Primary analysis with multiple imputation of estimate, *n*=60. [a]ANCOVA; gender, group, age and baseline value as covariates. [b]Bootstrap CI with 10000 replications. HIIT: High-intensity Interval Training, NRS: Numeric rating scale, VO_{2peak}: Peak oxygen uptake

Background: Cardiorespiratory fitness (CRF) is recognized as an independent risk factor for cardiovascular disease (CVD) and improved CRF associates with lower risk of CVD [1]. High-intensity interval training (HIIT) is an effective mode of exercise to increase CRF. However, HIIT is seldom utilized in physiotherapy primary care in the context of inflammatory joint disease (IJD), and the sustainable effects of HIIT have been questioned [2].
Objectives: To investigate short- and long-term effects of twelve weeks of supervised HIIT in physiotherapy primary care on CRF, pain and fatigue in patients with IJD.
Methods: In this assessor-blinded randomized controlled trial (NCT04922840), 60 patients were allocated to a control group (n=30) or a HIIT group (n=30) that received a 12-week intervention in physiotherapy primary care including two weekly supervised 4x4 minute HIIT sessions at 90-95% peak heart rate and one non-supervised exercise session at moderate intensity. Patients were assessed at baseline, 3 and 6 months. Primary outcome was change in CRF from baseline to 3 months, measured as peak oxygen uptake (VO_{2peak}) by a cardiopulmonary exercise test. Secondary outcomes were pain and fatigue (Numeric Rating Scale 0-10, 0= no pain/fatigue). Group differences were assessed by pre-specified intention-to-treat analysis of covariance with multiple imputation of missing data for the primary outcome. Per-protocol analysis was applied for the primary outcome.
Results: Median age was 59 years (IQR 52-63) and 34 participants (57%) were female. A total of 55 patients completed assessment at 3 and 6 months for the primary outcome; 27 in the HIIT group and 28 in the control group. Following HIIT, there was a significant between-group difference in VO_{2peak} (2.5 mL/kg/min, $p<0.01$) in favor of the exercise group at 3 months with no corresponding differences in pain and fatigue (Table 1). At 6 months, the between-group difference in VO_{2peak} was maintained (2.6 ml/kg/min, $p<0.01$) and there were no significant differences in pain and fatigue (Table 1). Per-protocol analysis at 3 months showed a between-group difference in VO_{2peak} (3.2 mL/kg/min, $p<0.001$, 95% CI 1.7-4.8) in the 19 (70%) patients that adhered to ≥17/24 HIIT sessions compared to the 20 (71%) control group patients that refrained from aerobic exercise.
Conclusion: CRF increased in patients with IJD following 12 weeks of supervised HIIT and the effect was maintained at 6 months. The beneficial response on CRF was not accompanied by changes in pain or fatigue and the intervention can be regarded as feasible in physiotherapy primary care. HIIT is a viable physiotherapy intervention with sustainable effects in patients with IJD.
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Neutrophil dysregulation in systemic lupus erythematosus

LB0008 **NOVEL PATHOGENETIC MECHANISMS MEDIATED BY DYSREGULATION OF TRIM21-STING-TYPE I INTERFERON AXIS IN LUPUS**

Topic: 08. SLE, Sjögren's and APS - aetiology, pathogenesis and animal models

Keywords: Autoantibodies, Systemic lupus erythematosus, Biomarkers

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Background: Tripartite motif-containing protein (TRIM) 21 is an E3 uniquitin-protein ligase, involved in the ubiquitin-dependent proteolysis pathway of various proteins including factors related to type I interferon pathways. Although the presence of autoantibodies against TRIM21 in various autoimmune diseases suggests potential pathogenetic roles, no studies have clarified its exact implications especially in lupus.
Objectives: We aimed to elucidate the functions of TRIM21 in dysregulation of type I interferon signals in lupus.
Methods: To investigate effects of TRIM21 dysfunction in lupus pathogenesis, two independent lupus animal models, the R848-induced model and the B6/*lpr* mice model were performed using TRIM21 knockout mice and their phenotypes and immunological profiles were determined. In addition, we investigated the degree of TRIM21 dysfunction and therapeutic effects of *in vivo* delivery of TRIM21 in MRL/*lpr* mice. To evaluate the E3 ubiquitin ligase activity of TRIM21 for targeted proteins in type I interferon pathways, we performed specialized immunoblot assay.
Results: The R848-induced model and the B6/*lpr* model both presented with more severe lupus-like phenotypes such as nephritis, lymphadenopathies, and inflammatory immune cell profiles in TRIM21 knockout mice than in control mice. TRIM21 deficiency resulted in activation of intracellular factors related to type I interferon pathways such as STING, TBK1, and IRF3 in both models. MRL/*lpr* mice presented with activation of type I interferon pathways including STING, TBK1, and IRF3, and decreased expressions of TRIM21. Overexpression of TRIM21 attenuated the disease phenotypes in MRL/*lpr* mice. Using immunoblot assay, we observed E3 ubiquitin ligase activity of TRIM21 directly targeting STING via the proteasome pathway.

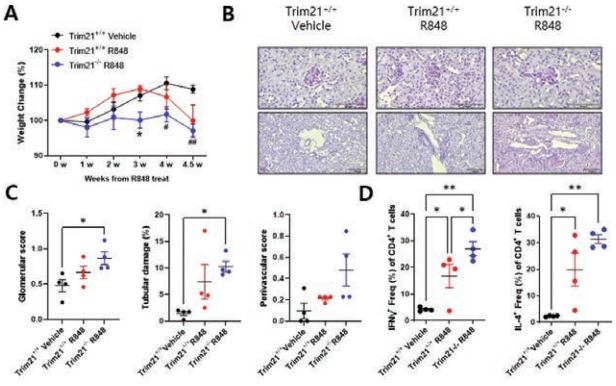

Figure 1.
(A) Bodyweight changes of R848- or vehicle-treated mice. (B) Representative images of H&E-stained kidney tissues from R848- or vehicle-treated mice. (C) Glomerular score, tubular damage score, and perivascular pathology score of kidney tissues from R848- or vehicle-treated mice. (D) Percentages of interferon-gamma-positive or IL-4-positive CD4+ T cells from R848- or vehicle-treated mice.
Conclusion: TRIM21 dysfunction induced dysregulation of STING-type I interferon pathways and exacerbates the disease in lupus animal models. Targeting TRIM21-STING-type I interferon axis can be a novel therapeutic strategy in lupus treatment.
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