SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

The effect of COVID-19 pandemic on idiopathic inflammatory myopathies

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The PhD Defense takes place at the Lecture Hall of Building A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, 16th of June, 2025 at 13:00

Introduction

1. Idiopathic inflammatory myopathies

Idiopathic inflammatory myopathies (IIM) are chronic immune-mediated inflammatory diseases, mostly affecting the proximal muscles, causing progressive and symmetric muscle weakness and muscle pain. There may also be characteristic skin lesions, as well as extramuscular and extraskeletal involvement, pulmonary involvement, cardiac involvement, gastrointestinal involvement.

Several forms of the disease can be distinguished. Based on clinical, immunopathological and demographic features, the following subgroups are known: polymyositis, necrotizing autoimmune myopathy, dermatomyositis, amyopathic dermatomyositis, juvenile dermatomyositis/polymyositis, inclusion body myositis. Recently, serological classification of the disease based on the presence of myositis-specific or myositis-associated autoantibodies in the serum of patients has been increasingly used. Some myositis-specific (MSA) or myositis-associated autoantibodies (MAA) can be found in the serum of 80% of patients. Myositis-specific autoantibodies are anti-Mi-2, anti-MDA5, anti-TIF-1-γ, anti-NXP2, anti-SAE, anti-Jo1, anti-PL-7, antiPL-12, anti-OJ, anti-EJ, anti-KS, anti-HA, anti-ZO, anti-SRP and anti-HMGCR. Myositis-associated autoantibodies are anti-SS-A, anti-SS-B, anti-PmScl or anti-U1RNP.

To establish the diagnosis of IIM, we use the EULAR/ACR classification criteria published in 2017. Taking into account various factors, a scoring system helps to make the correct diagnosis; based on age, clinical signs such as muscle weakness, skin symptoms, dysphagia or oesophageal dysmotility, laboratory tests (anti-Jo-1 antibody, CK, LDH, GOT, GPT) and, if done, histopathological features of muscle biopsy.

In Europe, North America and Asia, the incidence of the disease is between 11 and 660/1,000,000 patients. The disease is more common in women than in men. Both genetic factors and environmental factors play a role in its development. Among the environmental factors, the role of UV radiation and the triggering effect of various viral infections such as HCV or HTLV1 should be highlighted. The mortality rate of the disease is highest in the first year, after which it shows a decreasing trend. Among the organ involvement, mortality is most influenced by lung involvement and cardiovascular manifestations, and possible associated malignancies also play a significant role.

Regarding the pathomechanism, our knowledge is limited. In addition to genetic and environmental factors, the innate and adaptive immune system also play a role in the development of the disease. Histopathological examinations showed that perifascicular atrophy can be observed in dermatomyositis, in the region of which MAPs are visible on the remaining endothelial cells by staining the capillaries of the endomysium. These vascular structures are surrounded by plasmacytoid dendritic cells, which can be a source of interferon response. Genes inducing the type 1 interferon response are most up-regulated in the muscle and skin tissue. One of the first examples of the role of adaptive immune mechanisms in IIM was the anti-Jo1 autoantibody present in the anti-synthetase syndrome, which is produced against the hystidyl tRNA synthetase antigen. In this subtype, perifascicular necrosis is seen in histological specimens. Clonal T-cell expansions infiltrating the endomysium are seen. CD4+ T cells with reactivity against histidyl tRNA synthetase can also be detected in the blood and lungs.

2. The impact of the COVID-19 pandemic on the myositis patient population

COVID-19 is a disease that affects multiple organ systems, and its manifestations range widely. In addition to the lungs, the infection can also affect the liver, kidneys, pancreas or

skeletal muscle system. In addition to typical upper respiratory complaints such as fever, cough, and sore throat, myalgia is also a very common symptom. The disease is caused by the SARS-CoV-2 coronavirus, which is a positive-stranded ssRNA virus containing approximately 29,800 base pairs. Its virion is surrounded by a lipid envelope. It is built up by four main structural proteins. The S protein (spike) forms an external spike attached to the receptor. The E protein (envelope) and the M protein (membrane) are embedded in the lipid envelope. The N (nucleocapsid) protein is attached to the genome. The extrapulmonary manifestations are linked to the entry into the small vessel endothelium through the ACE2 receptor-mediated pathway, thus entering the muscles as well, with their direct invasion. Rhabdomyolysis can be a rare complication of infection. Early data assumed that the risk of SARS-CoV2 infection increased despite vaccination due to the immunomodulatory effects of their underlying diseases and immunosuppressive treatment in patients with autoimmune rheumatism. Meanwhile, the immunodeficiency state and the frequent use of immunosuppressive treatments may have prevented the so-called "cytokine storm" and severe complications of COVID pneumonitis. However, the course of the viral disease in the myositis patient population was not known in all its details.

The virus can also cause autoimmunity. The adaptive immune system is activated during infection. Three SARS-CoV-2 "specific" T-cell receptor epitopes were also recognized: 0-ribose methyltransferase, RNA-dependent RNA polymerase, 3' to 5' exonuclease protein. As a result of the infection, even classic dermatomyositis can develop. It is assumed that the virus causes excessive activation of CD8 positive T cells, there are also descriptions of this in the literature. Establishing the correct diagnosis can be a challenge for clinicians, as the symptoms here also range widely. Muscle weakness may or may not be present, and even severe bulbar weakness may occur. In laboratory tests, the increase in CK is often missed. Classic skin symptoms such

as Heliotrope rash, periorbital edema or the presence of myositis-specific autoantibodies can help in the diagnosis.

Environmental factors are therefore important triggers of autoimmune diseases. The triggering effect of several types of viruses has already been described in myositis

In addition to all this, the pandemic and the related closure led to various problems and difficulties not only in the case of IIM patients, but in the lives of all immunology-rheumatology patients. The new situation brought new challenges that required a solution.

- increasing the dose of regularly taken medicines
- patients could not obtain medicines
- intensification of symptoms in the absence of regular visits
- hospitalization due to relapse of the autoimmune disease

At the beginning of our research, less data were available on the disease course of the COVID-19 infection in patients with myositis and only a few case reports presented SARS-CoV2 or vaccine-induced myositis. Clinical presentation and symptoms vary from isolated enzyme (CK) elevation to rapidly progressive myositis. In another case, the diagnosis of IIM was associated with a negative response to mRNA vaccination. Furthermore, increasing age was associated with a lower probability of a positive antibody response.

3. **Characteristics of vaccines against COVID-19 in myositis**

One of the important steps in the fight against the coronavirus was the introduction of vaccination at the end of 2020. Vaccination of patients also began in Hungary at the beginning of 2021. All vaccine types on the market were available to the patients (BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), ChAdOx1-S (AstraZeneca), BBIBP-CorV

(Sinopharm), Gam-COVID-Vac (Szputnyik V, Gamaleja), Ad26.COV2.S (Janssen). It was clear that the vaccines are safe for the healthy patient population, since safety studies were carried out during its development, however, the autoimmune-rheumatological patient population and those taking immunosuppressive therapy were excluded from these studies.

Thus, precisely in the case of this IIM patient population with high risk factors, open questions remained, since little literature data was available in their case. We can say that taking the vaccine prevents the development of severe COVID-19 infection. However, there have been several case reports that several patients developed anti-MDA5 positive myositis after receiving the vaccine against the coronavirus, which may indicate the role of the vaccine as a trigger in the pathogenesis of anti-MDA5 positive DM. However, retrospective and epidemiological studies have not demonstrated an association between vaccination and myositis, i.e. no significant increase in the incidence of myositis has been reported after large vaccination campaigns consequently, the importance of vaccination during a pandemic was emphasized. In addition, other studies have described relapse of IIM after vaccination. therefore, there were no clear, reliable data in the literature on the relationship between vaccination and the activity of myositis

mRNA vaccines have been shown to have limited immunogenicity in immunocompromised patients. Most patients with autoimmune diseases developed an adequate response after receiving the first dose of the mRNA vaccine, however, a significant proportion of patients did not develop an acceptable humoral response even after a double dose. In one study, 74% of patients with autoimmune rheumatism showed seroconversion after a single and 94% after two doses of the vaccine. This may also be due to the fact that DMARDs and biological agents (such as methotrexate, mycophenolate mofetil, rituximab or glucocorticoids) can reduce the chance of a detectable antibody response. However, ongoing DMARD treatments, especially bDMARDs, did not affect the outcome of mild symptomatic COVID-19 infection.

AIMS

1. Characteristics of COVID-19 infection in patients with myositis

Between the 1st of January 2020 and the 1st of June 2021, after the first 3 waves of the COVID-19 pandemic, we aimed to assess the following for IIM patients cared for by the University of Debrecen, Institute of Internal Medicine, Department of Clinical Immunology:

a) The incidence, severity and the disease course of the coronavirus infection and its effect on the autoimmune disease
b) Search for predictive factors that may be suitable for predicting the COVID-19 disease resulting in hospitalization.
c) The characteristics and extent of the development of antibodies indicating an immune response against COVID-19 after the coronavirus infection

2. Use of COVID-19 vaccines in IIM

In the second part of the work, we aimed to assess the following in the same patient population:

a) The vaccination rate
b) Determining the possible reasons for the non-vaccination
c) Assessment of the incidence of vaccination complications
d) Measuring the degree of antibody response developed after vaccination
e) Assessment of the effect of the autoimmune disease and the applied immunosuppressive therapy on the response to the antibody

f) Assessment of the frequency of COVID-19 infection after vaccination (breakthrough infections)

3. IIM relapses after COVID-19 vaccinations

In the last part of our work between the 1st of January 2021 and the 1st of September 2022, we aimed to

a) examine prospectively the frequency, severity, and outcome of relapses after the COVID-19 vaccine, using IMACS criteria

b) identify relevant factors that contribute to a higher risk of relapse, and thus may have predictive significance in case of subsequent vaccinations

Methods

1. Characteristics of COVID-19 infection in patients with myositis

Patients aged ≥17 years old with IIM controlled regularly before the 4th wave of pandemic were recruited to participate in this observational cohort via phone call. All of the patients have met the EULAR/ACR Classification Criteria for IIM (14). It was a retrospective cross-sectional study in our cohort (176 IIM patients) by identifying COVID-19 positive patients and assessed disease course. This study meets, and is in compliance with all ethical standards of medicine. In formed consent was obtained from all of the subjects. This study is ethi cally compliant and was carried out in compliance with the Declaration of Helsinki. Volunteers underwent blood draw containing haematology, chemis try, immunoserology and SARS-CoV2 antibody testing.

2. Determination of SARS-CoV2 antibody

Anti-SARS-CoV2 S enzyme elec trochemiluminescent immunoassay (Elecsys®) has been used with Cobas e602 (Roche) automata according to the manufacturer's protocol, which measures total antibody (IgM and IgG) to the SARS-CoV2 S receptor-binding domain (RBD) protein and SARS CoV2 N protein. Results of anti-S antibodies range from 250U/ mL with a positive response defined as >0.8 U/mL. Titer for anti-N antibod ies range from 0.1 U/ml to 283.9 U/ml with a positive result defined as ≥1.0 U/ml. Determination of COVID-19 infection COVID-19 disease diagnosis was made by (1) positive rapid antigen test and/ or positive polymerase chain reaction testing performed at oral/nasopharyn geal swabs and/or (2) anti-N and anti-S protein antibody positivity without pre vious vaccination.

3. COVID-19 vaccines and IIM

The level of vaccination coverage, the type of vaccinations, and vaccination reactions were also assessed using questionnaires compiled by our working group.

Anti-SARS-CoV2 S enzyme elec trochemiluminescent immunoassay (Elecsys®) has been used with Cobas e602 (Roche) automata according to the manufacturer's protocol, which measures total antibody (IgM and IgG) to the SARS-CoV2 S receptor-binding domain (RBD) protein and SARS CoV2 N protein. Results of anti-S antibodies range from <0.4 to >250U/ mL with a positive response defined as >0.8 U/mL. Titer for anti-N antibodies range from 0.1 U/ml to 283.9 U/ml with a positive result defined as ≥1.0 U/ml.

4. IIM relapses developed after the COVID-19 vaccination

In this prospective cohort study, IIM patients under the care of theDepartment of Clinical Immunology, University of Debrecen, Hungarywere interviewed at the end of the third wave of the COVID-19 pan-demic (May–June 2021). The vaccination of the patients started March1, 2021. At the time of survey every patient had been given the opportu-nity to receive the vaccines. The vaccination rate, the type of adminis-tered vaccines, and the adverse reactions experienced were assessed byquestionnaires. These patients were followed prospectively at the clinicor in outpatient departments until July 2022. A loss of follow-up wasavoided by conducting telephone interviews with all patients at the endof the study. IIM disease activity, comorbidities, COVID-19 infectiondata, later vaccination data (booster vaccination started in August 2021),immunosuppressive therapy, and laboratory results were also recorded.All patients had a definite or probable diagnosis of IIM (muscleweakness, high muscle enzyme levels, plus abnormal electromyogram(EMG) with myopathic motor unit potentials, fibrillation potentials,positive sharp waves, increased insertional activity, and/or musclebiopsy features of inflammatory infiltration in polymyositis (PM) ortypical skin symptoms in DM) according to Bohan and Peter,19 orprobable/definite IIM according to the EULAR/American College ofRheumatology's (ACR) myositis criteria.20 Patients with inclusion bodymyositis were

excluded. Interstitial lung disease (ILD) was defined aspresent by radiographic findings (high-resolution computed tomogra-phy [HRCT]) and pulmonary function tests (spirometry, diffusingcapacity for carbon monoxide). Dysphagia was diagnosed by bariumradiography of the esophagus. Informed consent was obtained fromthe subjects. This study was carried out in compliance with the Decla-ration of Helsinki. The study was approved by the Institutional ReviewBoard of the University of Debrecen (Ethical permission number: DERKEB/IKEB-5723-2021).

4.1 Evaluation of myositis disease status

Disease activity was evaluated using the International MyositisAssessment and Clinical Studies Group (IMACS) core set measures(CSM)21: the physician global activity visual analogue scale (VAS), theManual Muscle Test (MMT-8), patient global activity VAS, a healthassessment questionnaire (HAQ), laboratory values of muscleenzymes (CK, creatine kinase; LDH, lactate dehydrogenase), andMyositis Disease Activity Assessment Tools (MDAAT) were assessedat each visit. Active disease at/prior vaccination was defined byphysician global activity ≥2 cm of VAS.Myositis relapse was defined as any of the following: (1) physi-cian-assessed global worsening by ≥2 cm on a 10-cm VAS and wors-ening on MMT-8 by ≥20%; OR (2) extramuscular organ diseaseactivity worsening by ≥2 cm on a 10-cm VAS; OR (3) any three of sixIMACS CSM worsening by ≥30%.21,22The criteria for improvement used the six IMACS CSM, combiningthe absolute percentage change in each with varying weights to obtain atotal improvement score (TIS) on a scale of 0–100 using a Web-calcula-tor.23 Different thresholds of improvement were set for minimal (20–39points), moderate (40–59 points) and major responses (≥60 points).24The severity of myositis relapse was graded as minimal, moderateand major. This was determined by a total deterioration score (TDS),which was calculated using the opposite method of the TIS calcula-tion, that is, the absolute percentage worsening change in eachIMACS CSM was scored and the sum of the six scores

determined theTDS. The relapse category was minimal, moderate, or major based onTDS 20–39, 40–59, or ≥60, respectively

4.2 Laboratory tests

Routine laboratory markers such as erythrocyte sedimentation rate,total blood count, and chemistry including renal and liver function, ionlevels and muscle enzymes (CK, LDH) were tested. Immunologicalanalyses included tests for the following autoantibodies: antinuclearantibodies (ANA), anti-centromere antibodies (ACA), anti-histone anti-bodies, and anti-cytoplasmic antibodies were determined by indirectimmunofluorescence on HEp-2 cells (Viro-Immun Labor-DiagnostikaGmbH, Oberursel, Germany); ANA positivity was assessed at 1:40dilution. Titers of the antibodies against extractable nuclear antigen(ENA) complex, anti-SS-A (Ro) and anti-Jo-1 antibodies, were measured(HYCOR Biomedical Inc., CA, USA) using this latter method. Myositisspecific antibodies were detected by membrane-fixed line blots accord-ing to the manufacturer's instructions (Euroline Myositis Antigen Profile4,EuroImmun, Lübeck, Germany). Anti-HMGCR antibodies were detectedby indirect immunofluorescence assay and confirmed by in-houseenzyme-linked immunosorbent assay (ELISA; the cutoff value was≥40 U/mL). ELISA was used for the measurement of anti-double-stranded deoxyribonucleic acid (dsDNA), anti-beta-2-glycoprotein I(B2GPI), anti-cardiolipin, and antiphospholipid antibodies (ORGENTECDiagnostica GmbH, Mainz, Germany). These commercially availablemethods were used following the manufacturer's protocol.

4.3 Determination of COVID-19 infection

COVID-19 disease diagnosis was made by (1) positive rapid antigentest and/ or positive polymerase chain reaction testing performedwith oral/nasopharyngeal swabs and/or (2) anti-N and anti-S proteinantibody positivity without previous vaccination.

5. Statistical analysis

The statistical analysis was performed using the SPSS version29 (IBM, Armonk, NY). The normality of distributions in the case ofcontinuous variables was tested using the Shapiro–Wilk test. Nor-mally distributed continuous variables were described by mean andSD values. Categorical variables were described using frequencies(case numbers) and percentages. To compare several matched groups,the Friedman test was used since data were not normally distributed(Shapiro–Wilk test: $p > .05$). Two related scale variables were com-pared, either by the paired t-test, or the Wilcoxon test, depending onthe distribution. The contingency tables presenting the connection oftwo categorical variables were analyzed by Fisher's exact test. Toidentify the significant independent predictors of the relapse of myo-sitis, forward stepwise (likelihood ratio) logistic regression analysiswas applied, using the following candidate variables: age, duration ofthe disease, gender, disease subtype and state (PM/DM, activity atthe time of vaccination), autoantibody profile, comorbidities (chronicobstructive pulmonary disease, ILD, diabetes mellitus, hypertension,ischemic heart disease, asthma), medications (glucocorticoids, metho-trexate, leflunomide, cyclosporine-A (CSA), azathioprine, mycopheno-late mofetil (MMF), intravenous immunoglobulin, hydroxychloroquine,cyclophosphamide, rituximab), and vaccination features (number ofvaccination, manufacturers). We also calculated the odds ratios (ORs)for the predictors found. A p value less than .05 was regarded as sta-tistically significant

Results

1. Characteristics of COVID-19 infection in patients with myositis

One hundred and seventy-six patients participated in the study, who appeared on regular check-ups between 1st of January 2020 and 1st of June 2021. According to our telephone survey, 68.75% of these patients got a vaccine to that date. One hundred and one of them volunteered for laboratory test ing. Mean age was 55.25 years (17-81) the female/male ratio was 2 to 1. My ositis subsets were 40% dermatomyosi tis (DM) and 60% polymyositis (PM), respectively. The mean IIM disease du ration was 11.04 years. Demographics, therapeutic regimens, co-morbidities, vaccination and disease course (both COVID-19 and IIM) data were col lected by a specific questionnaire made by our study group (Table I). Prevalence of COVID-19 disease in IIM patients was 34.7% (n=35) with mean age of 48.3 (± 14.83) years. 72.72% of them were female. 34.2% suffered from DM (n=12) and 65.8% had PM (n=23). All of cases were de tected before vaccination. Acquisition of COVID-19 infection was not associ ated with myositis type, demographic factors, previous ILD, or disease dura tion. Considering basic immunoserol ogy, anti-phospholipid antibody positivity (aCL 0.27% vs. 23% ($p<0.001$) andaB2GPI 0.18% vs. 11% ($p=0.014$)) were more common among those who were infected. Summarising the myosi tis-specific autoantibodies, there were a few (n=4) anti-Jo1, 1-1 anti-TIF1γ, anti-Mi2 and anti-Ku positive cases. Curiosity is that 2 anti-PL-12 antibody positive patients were found in the co hort, both of them had COVID-19 in fection ($p=0.016$), but limitation of this result is the small number of cases.

In 34.8% of patients, COVID-19 disease was asymptomatic or mild with upper airway infection. 20% of patients (n=7) were hospitalised for severe dyspnoea and pneumonitis. Clinical symptoms of patients were the followings: fever, coughing, dyspnoea, loss of smelling

and taste, muscle pain. No pulmonary embolism or other thrombotic events occurred. Ten patients received favi piravir therapy at home or in hospital, while none received remdesivir. One of our patients, whose IIM disease were active before COVID-19 infection with moderate skin, muscle involve ment and ILD required non-invasive mechanical ventilation support. That patient recovered after combined favi piravir, IVIg and antibiotic treatment. One of our newly diagnosed patients with severe active anti-Jo1 positive anti-synthetase syndrome died despite the combined immunosuppressive and IVIg treatment due to COVID-19 and cytomegalovirus co-infection. Comparing patients requiring and not requiring hospitalisation (Table II), Table II. Major epidemiology data of IIM patients with COVID-19 disease, significant differences marked with bold characters. Hospitalised patients (n=7) No need of hospitalisation (n=28) Value of significance (p) Female/Male ratio Mean age Average disease duration Polymyositis Dermatomyositis Anti-Jo1 antibody positive Death 4/3 patients 58.14 years 17.87 years 64% 36% 57% 1 20/8 patients 47.23 years 8.67 years 68% 32% 11% 0 0.384 0.068 0.003 0.372 0.676 0.018 0.2 we found that significantly longer IIM disease duration (8.67±5.19 vs. 17.87±10.27 years; p=0.003) was as sociated with hospitalisation. None of the presenting co-morbidities, internal organ involvement and chronic immu nosuppressive treatment affected hos pitalisation. 14.3% of patients (n=5) had active IIM disease at the time of SARS-CoV2 infection but myositis ac tivity was not affected neither disease course nor hospitalisation. In contrast, the presence of anti-Jo-1 autoantibody (57% vs. 11% p=0.018) seemed to be an independent risk factor for hospi talization due to COVID-19 disease. Forward logistic regression analysis also confirmed that, anti-Jo1 positivity (p=0.015) and disease duration ($p<0.001$) are independent risk factors considering hospitalization. Following the COVID infection, all of our patients became seropositive regardless of im munosuppressive therapy with a mean SARS-CoV N antibody titer: 87.43 U/ ml and SARS-CoV S mean antibody titer:

150.99 U/ml. We have neither found any SARS-CoV2 infection in duced myositis nor new auto-antibody positivity among our IIM patients.

2. Vaccination and IIM

At the time of the survey, every patient with IIM had the opportunity to receive the full, two doses of vaccination against SARS-CoV2. The following vaccines were available: Pfizer-Biontec, Moder na, Astra-Zeneca, Sputnik, Sinopharm. 54.3% of the patients received some form of vaccination and 75.9% received mRNA type. 80% of patient got all 2 doses of vaccination. Interval between doses used varied between 4 weeks and 3 months. 34.5% of patients who had not been vaccinated did not request the vaccine because they were afraid of its harmful effects, 10% had already reg istered but still waiting for approval at the time of the study, and 9% had a recent COVID-19 infection. Mean age of infected and vaccinated patients was significantly different (48.3 vs. 62.5 years, p=0.000). In the vaccinated group we observed longer IIM duration compared to infected group (7.6 vs. 6.1 years, p=0.058). There were no patients who did not request the vaccine due to a lack of choice between vaccinations. Based on laboratory findings, the titer of anti-SARS-CoV2 antibodies in duced by vaccines varies, but 72.3% of patients have become seropositive with the vaccine. ANOVA analysis showed significant differences in mean values of anti-spike protein titers for different vaccine types (p=0.002; Fig. 1). Lack of antibody response has no correla tion with patient age, IIM type, inter nal organ involvement and immuno suppressive treatment. Pfizer-Biontec vaccination resulted in a significantly higher mean autoantibody titer against spike protein (177.1 U/ml vs. 81.1 U/ ml p<0.001), whereas Astra-Zeneca vaccine resulted weaker humoral response comparing to all other vac cine types (mean titer: 45.05 U/ml vs. 126.93 U/ml p=0.054). In the serum of patients with continuous corticosteroid intake lower anti-S antibody titer was detected comparing to those who were not taking any steroids (94.03 U/ml vs. 165.6 U/ml p=0.008).

Same, but non significant tendency has been found comparing methotrexate usage with other immunosuppressive drugs (78.82 U/ml vs. 133.58 U/ml, p=0.062) (Fig. 2). 41% of vaccinated patients were on low-dose corticosteroid treatment (<7.5 mg prednisolone or equivalent) at the time of the study. 22.3% took medium dose of corticosteroid (7.5-30 mg pred nisolone or equivalent) only 1 patient got high dose treatment (>30 mg pred nisolone or equivalent). All vaccinated patients were on stable dosage during 3 months before vaccination.

Considering vaccination reactions after Pfizer-Biontec local pain (47% vs. 17% p=0.001) were significantly more fre quent than after getting other vaccines. Astra-Zeneca vaccines implied more fever (43% vs. 8.6% p=0.028) and headache (42.8% vs. 5.4% p=0.010) than other vaccine types. Severe disease activity or complica tions have been observed in 2 patients after vaccination: a 66-year-old DM fe male patient with previous anti-TIF1y positivity showed severe relapse in skin symptoms after 2 weeks of second Pfizer-Biontec vaccination and needed therapy change for IVIg followed by rituximab. Repeated malignancy re search excluded underlying cancer, so the association with vaccination is presumed. We still did not reach re mission after 6 months of treatment. A new myositis specific autoantibody positivity appeared after Pfizer-Biontec vaccination when we assumed a strong correlation with vaccine. A 63-year-old DM patient who previously had no in ternal organ involvement, no myositis specific antibody positivity and did not require any immunomodulatory treat ment since 2017. Two weeks after the second dosage of mRNA vaccination coughing and dyspnoea started. It was f irst treated as pneumonia by the local health care services, but after worsen ing the patient came for further diag nostic procedures to our clinic. New right Tawara-branch block, elevated right ventricular pressure and systolic D sign were found by our cardiologists. Bilateral pulmonary fibrosis with ac tive alveolitis and honeycomb changes were also found by high resolution CT and breath tests showed severely de creased diffusion capacity (FEV52% DLCO 22%). Immunoserology re vealed new anti-EJ antibody positivity in high titer in addition to

anti-Ro52 positivity. The immunological findings correlated with the clinical symptoms, based on ILD, fever, antibody positiv ity IIM activity was noted and high dose intravenous corticosteroid treat ment started in combination with cy closporine A. Besides a prophylactic antibiotic, antiviral therapy was also initiated followed by alprostadil and sildenafil, which resulted major im provement in clinical status.

3. Characteristics of relapses after COVID-19 vaccines

One hundred and eighty-one patients were contacted, 176 of whom finally participated in the study. The epidemiologic data of the interviewed study population are summarized in Table 1. By May 1, 2022,82.9% (146/176) of the patients had received an anti-COVID-19 vaccination, 67% (99/146) of whom were given the Pfizer-Biontech type (BNT162b2). One hundred and thirtynine patients received both the first and the second dose, while seven patients received only one vaccination. No major immediate adverse events, such as hospitalization or anaphylaxis were reported. 11.6% (17/146) of patients who were vaccinated experienced a relapse (based on the IMACS criteria) within3 mo of the vaccination. The general characteristics of the unvaccinated population (n = 30) showed distinct similarities and differences in comparison with the vaccinated group. We found that therelapse rate of the unvaccinated patients was 3.3% during the follow-up period, which was not different in comparison with the relapse rateof the vaccinated group (Fisher: p = .32; OR, 3.82; confidence interval [CI], 0.49–29.9). However, due to small sample size a significant effect in either direction cannot be confidently excluded.

Features and outcomes of post-vaccination disease relapses

No patient died during their relapse, but two patients needed hospitalization, with one patient requiring intensive care because of breathing insufficiency. The average time from last vaccination to the patient reporting a worsening of symptoms was 25 days. Thirteen patients (8.9%) experienced a disease worsening within 1 month of the last vaccination. The severity of the relapses was minimal in three (17.6%), moderate in six (35.3%), and major in eight (47.1%) patients. The CK levels were significantly different during follow-up (p=0.022). In 3/17 cases, new autoantibodies were detected after vaccination. One patient had high titer anti-aminoacyl-transfer-ribonucleic-acid synthetase antibody (anti-EJ) positivity, and two patients had an occurrence of anti-SSA antibody as a second autoantibody in addition to anti-Jo1 and anti-TIF1 gamma respectively

Breakthrough COVID infections

In the current study, we could detect a confirmed COVID-19 break-through infection after vaccination in 18 patients (12.3%), 17 of whom(94.4%) had a mild course of infection without hospitalization. The mean duration between vaccination and infection was 22 week (range2–38 week). One of our vaccinated patients with cancer associated myositis (colorectal carcinoma with multiple liver and pulmonary metastases) without post vaccination seroconversion (undetectable antibodies against spike protein) died because of tumor progression and terminal COVID-19 infection. The COVID infection rate in the follow-up period was 20% (6/30) of the unvaccinated group. All fatalCOVID-19 infections in the whole study group (n = 3) occurred only in patients whose serum antibodies against spike protein were undetectable, regardless of whether or not they had been vaccinated.

Relevant factors that could contribute to postvaccination IIM relapses

When comparing each variable individually between the patients with and without relapse, several parameters were significantly different in the two populations: vaccination status, active disease at vaccination, the number of vaccinations, double vaccination (first and second dose), BNT162b2 vaccination, the presence of any myositis specific antibodies, ILD, and treatment with methylprednisolone, MMF, and CSA. However, forward stepwise logistic regression analysis revealed that only two factors were significantly associated independently with the occurrence of relapse: the active state of myositis at time of injection and the use of the BNT162b2 vaccine (Table 3). When restricting the logistic regression analysis to those patients who were not infected with COVID (eliminating the confounding effect of COVID-19 infection), in addition to active myositis at vaccination, a diagnose of DM was associated with relapse in logistic regression analysis. The wide CI for the OR of relapse for DM showed that our limited dataset cannot confirm or exclude an effect of vaccination on DM relapse. By ordinal regression analysis, we could not find any factor associated significantly with the severity of relapse.

Discussion

1. Characteristics of COVID-19 infection in patients with myositis

According to our data, this is the first study in the Eastern-European region to assess the effects of COVID-19 pan demic on IIM patient population. Limi tation of the study is based on semi-ret rospective and cohort design but we are a national immunology centre treating patients from all region of Hungary and also from the countries of neighbour hood.

Among individuals with IIM, infection is frequent and the leading cause of mortality, where antibody status, lym phopenia, ILD, old age, and treatment with steroids are contributing factors in the development of infections. Our results approved the previous findings, that the odds of COVID-19 in patients with rheumatic disease was significant ly higher than in control population. The prevalence of COVID-19 disease is higher in IIM patients than in the Hungarian average population (34.7% vs. 8.2% according to national registry data on 11th June 2021). Recent studies also revealed that COVID-19 disease has the risk of poor outcomes in those with immune system disease, including people with rheumatic diseases. In our cohort prognosis seemed better, only prolonged myositis and the presence of Jo-1 autoantibody are risk factors for hospitalization due to COVID-19 disease. Presence of organ involvement or comorbidities did not affect hospitalization. This cohort study also supports that primary pre vention and close monitoring during COVID-19 disease is essential in patients with myositis. Consistent guidance is to follow all local public health advice like physical distancing, hand washing, wearing masks and isolation to reduce the risk of contracting SARS CoV2. Early hospitalisation and antiviral therapy should be considered in elderly patients with prolonged IIM disease or anti-Jo1 positivity.

The study was organised after vaccina tion become available for all citizens. Frequency of vaccination among our patients is higher also than the na tional one (68.75% vs. 55.1% based the vaccination statistics on 15th June 2021) proving a favourable patient doctor relationship and proper transfer of information. Vaccination against COVID-19 seems safe and effective. No post-vaccination COVID-19 dis ease were detected in our cohort. The observed minor vaccine complications were easily manageable. Rapid recog nition of severe cases helps the thera peutic choice.

2. Vaccination and IIM

Vaccines and autoimmunity are crossed. Vaccine efficacy is based on whether host immune response against an antigen can elicit a memory T-cell response over time. Although the side effects thus far have been mostly transient and acute, vaccines are able to elicit the immune system towards an autoimmune reaction. Some case reports are still published proving anti-SARS CoV2 vaccination induced autoimmunity. Based on these findings and our highlighted cases, early hospitalisation of severe cases and adequate therapy could lead to a favourable outcome. Further investigations needed to recognise and separate vaccination reaction and vaccine-induced disease reactivation.

mRNA vaccination could be offered for IIM population based on detected higher humoral immune response. Our results support the Hungarian national guideline about vaccination for patients on chronic immunosuppressive therapy (e.g., corticosteroid and/or methotrexate therapy). For these members 3rd vaccination is recommended as part of primary immunisation and 4th vaccine should be considered based on clinical activity, therapy and comor bidities. Cessation of immunosuppressive agents also should be reconsidered in COVID-19 infection with using the principles of personalised medicine. Further investigations and internation al

collaborations needed to describe the break-through infections after vaccination and long-term effect of COVID-19 pandemic on IIM.

3. Characteristics of relapses after COVID-19 vaccines

We can summarize our recent work as follows: (1) a minority of thevaccinated patients experienced a confirmed disease flare of IIM aftera COVID-19 vaccination, (2) the majority of these relapses were easilytreatable, and (3) the most relevant factor which was associated with a flare was the active disease state at the time of vaccination.The approved COVID-19 vaccines have shown clear safety and efficacy in the reduction of severe SARS-CoV-2 disease. Recently, amulticenter Italian study focusing on post vaccination relapses (defined almost identically to our study) revealed that the flare rate was 6.1% within 1 mo of vaccination and the development of a flare was mostly influenced by the number of organs involved. No flares occurred after the third dose of a vaccination. Our relapse rate washigher in comparison with the Italian data, but we assessed the flareswithin 3 month of a COVID-19 vaccination. We decided to extend the assessment time to 3 month because the majority of the patients had a regular visit more than 1 month after vaccination and the disease statusassessment required multiple physical and laboratory examinations. Restricting our relapse rate to those patients whose symptoms worsened within 1 month of administration of the last vaccine, the post vacci-nation relapse rate was 8.9% (13/146) in our cohort, which is quite similar to the Italian results. Furthermore, the relapse rate in theunvaccinated patients (3.3%) was comparable to the vaccinated patients, but due to small sample size a significant effect of vaccination in either direction cannot be confidently determined.

Importantly, no firm causal conclusions regarding vaccination andthe development of flares can be drawn from this dataset. The resultsof our study are similar to COVAX registry data,7

where the percent-age of post vaccination flares was slightly higher in patients with moderate/high disease activity compared with patients in remission/lowdisease activity. Our study results are in line with the previous EULAR recommendation that vaccination in patients with autoimmune rheu-matic diseases should preferably be administered during quiescent disease. The second factor that was significantly associated with disease relapse, was the use of the BNT162b2 vaccine. However, theavailability of the vaccines, the higher proportion of patients vaccinated with the BNT162b2 vaccine and the lower confidence level might limit comparisons between different vaccine types.

We determined the relapse rate based on IMACS defined criteria and during the follow-up we used the myositis response criteria to define the outcome of the flare. The advantage of this method in contrast to patient reported surveys is that it requires laboratory parameters, physical examination, a physician global opinion and the patient's opinion simultaneously. Our study showed that myositis response criteria are useful and easy to use to achieve objective, comparable, and reproducible measurements of a patients' disease activity in everyday clinical practice.

Another interesting issue regarding myositis flare after vaccination isthe severity of the relapse. We strongly believe that there would be significant relevance in developing criteria for a definition of disease relapse severity, or at least, differentiating them as minor or major, since thislikely would lead to different treatment recommendations. We tried tograde the deterioration of the disease using the opposite method of cal-culation to that used in the myositis improvement criteria (TDS vs. TIS),but the consequences deriving from these calculations should be interpreted carefully. The threshold determination and exact calculation of disease deterioration to assess a mild, or a major relapse requires standardized development with the consensus of an international group of myositis experts. We could not detect any factors that

were associated significantly with the severity of relapse or hospitalization, but this could be due to the low number of patients with relapses.

The breakthrough COVID infections were rare and milder than in unvaccinated patients and all fatal COVID infections occurred in patients without any vaccination, or without post vaccination seroconversion. These facts argue strongly for considering the administration of SARS-CoV-2 vaccination and booster vaccinations, if no anti-spike antibody is detected.

The possible limitations of this study should be acknowledged. This work was a single center study from a national myositis unit in Hungary, some of the data were self-reported and the number of participants (especially the unvaccinated group) in the study was relatively low.

In conclusion, the rate of flares after COVID vaccination was lowand based on myositis response criteria, the majority of the patientsresponded well to individualized treatment. Active disease state atvaccination might be an important factor in the development of postvaccination relapse. Clinicians should promote vaccination in mostpatients with idiopathic inflammatory myopathies. Vaccination duringthe active disease state should be carefully considered, and patientsshould be monitored frequently. Further evaluation of larger multi-center cohorts with graded outcome results are required to assessmore detailed features of flares after COVID-19 vaccinations.

Summary

In the first part of our work, we assessed the effects of COVID-19 infection in a patient population with idiopathic inflammatory myopathy.

Neither the myositis subtype, nor demographic factors, nor previous ILD, nor the longer duration of the disease played a significant role in the aquiration of the COVID-19 infection. A third of the infections were asymptomatic or with mild symptoms, while anti-Jo1 autoantibody positivity and longer disease duration were independent risk factors for hospitalization. After infection, patients developed an active humoral immune response despite immunosuppressive treatment. In contrast, seroconversion occurred in only 72.3% of the patients after the COVID-19 vaccination. The type of vaccines and immunosuppressive treatment influenced the extent of the immune response to vaccination. No major early complications occurred during vaccination.

In the second part of our work, we assessed the effects of COVID-19 vaccines on the activity of myositis. During our prospective study, we confirmed that after vaccination, relapses occurred in 11.6% of patients, while this was 3.3% in the case of non-vaccinated patients.

Most relapsing patients responded well due to the individualized therapy, 70.6% of the patients three months after the relapse and 88.2% after 6 months showed at least minor improvement. Using stepwise logistic regression, we verified that the activity of the underlying disease at the time of vaccination was significantly related to the development of relapses. Overall, based on our results, anti-SARS-CoV2 vaccines are safe, well-tolerated and effective and recommended for the prevention of severe COVID infection in patients with myositis. In the case of an active underlying disease, vaccination can be recommended with caution, as it may result in a relapse of myositis.

New scientific achievements

1. During the COVID-19 pandemic, the prevalence of COVID-19 infection was higher in patients with IIM than in the national average population
2 The longer disease duration of myositis and the presence of anti-Jo-1 autoantibody were independent risk factors for hospitalization related to COVID infection
3 The use of different vaccine types and immunosuppressive therapy affect the degree of antibody response after vaccination
4 Validated myositis relapses after the COVID-19 vaccinations were occurred in 11.6 % of the patients with IIM
5 Relapses were well manageable with individualized therapy

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Subject: PhD Publication List

Candidate: Tibor Béldi
Doctoral School: Gyula Petrányi Doctoral School of Allergy and Clinical Immunology

List of publications related to the dissertation

1. Nagy-Vincze, M.*, **Béldi, T.***, Szabó, K., Vincze, A., Miltényi-Szabó, B., Varga, Z., Varga, J., Griger, Z.: Incidence, features and outcome of disease relapse after Covid-19 vaccination in patients with idiopathic inflammatory myopathies.
Muscle Nerve. 67 (5), 371-377, 2023.
DOI: http://dx.doi.org/10.1002/mus.27811
* These authors contributed equally to this work.
IF: 2.8

2. **Béldi, T.**, Vincze, A., Miltényi-Szabó, B., Varga, Z., Szabó, K., Griger, Z.*, Nagy-Vincze, M.*: The effect of COVID-19 pandemic on idiopathic inflammatory myositis patients: a single centre experience.
Clin. Exp. Rheumatol. 41 (2), 254-260, 2023.
DOI: http://dx.doi.org/10.55563/clinexprheumatol/eisexh
* These authors contributed equally to this work.
IF: 3.4

List of other publications

3. **Béldi, T.**, Nagy-Vincze, M., Griger, Z.: A tumorasszociált myositisek sajátosságai: szűrési és kezelési szempontok.
Immunol. Szle. 16 (2), 39-45, 2024.

4. Nagy-Vincze, M., Szinay, D., Szabó, K., Deliné Molnár, S., Balkay, L., **Béldi, T.**, Griger, Z.: High fetal risk in pregnancies of myositis patients: a Hungarian cohort study.
Front. Lupus. 2, 1-7, 2024.
DOI: http://dx.doi.org/10.3389/flupu.2024.1449390

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5. Nemes-Tömöri, D., Csabalik, R., Nagy, E. B., **Béldi, T.**, Majai, G.: A rare association of neuromyelitis optica, antisynthetase, and antiphospholipid syndrome.
Clinical Case Reports. 11 (11), 1-4, 2023.
DOI: http://dx.doi.org/10.1002/ccr3.7873
IF: 0.6

6. Vincze, A., Lisztes, E., Szabó, K., **Béldi, T.**, Nagy-Vincze, M., Pór, Á., Varga, J., Dankó, K., Bíró, T., Tóth, I. B., Griger, Z.: Pruritogenic molecules in the skin of patients with dermatomyositis.
Front. Med. 10, 1168359, 2023.
DOI: http://dx.doi.org/10.3389/fmed.2023.1168359
IF: 3.1

7. Szabó, K., Bodoki, L., Nagy-Vincze, M., **Béldi, T.**, Vincze, A., Zilahi, E., Varga, J., Szűcs, G., Dankó, K., Griger, Z.: Clinical, Serological, and Genetic Characteristics of a Hungarian Myositis-Scleroderma Overlap Cohort.
Biomed Res. Int. 2022, 1-9, 2022.
DOI: http://dx.doi.org/10.1155/2022/6251232

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