The effect of COVID-19 pandemic on idiopathic inflammatory myositis patients: a single centre experience

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Abstract

Objective

Pandemic caused by coronavirus disease (COVID-19) determines the life of clinicians and patients since 2 years. We have a lot of information about disease course, treatment and protection against virus, but less on the prognosis of infection in patients with idiopathic inflammatory myopathies (IIM). Also few data are available on triggered humoral response and side effects after vaccination.

Methods

Our goal was to assess by a retrospective cross-sectional study the above data in our cohort (176 IIM patients) by identifying COVID-19 positive patients and follow disease course. Incidence and complications of vaccination were determined by questionnaires. 101 patients volunteered for complex blood test.

Results

By June 1st, 2021 significantly higher incidence of COVID 19 infections (34.7%) were identified comparing to the national prevalence (8.2%). A third of these infections occurred asymptomatically or mild. Patients requiring hospitalisation had a significantly longer disease duration and a higher incidence of anti-Jo-1 antibody. All patients infected by COVID-19 became seropositive regardless the immunosuppressive therapy or symptoms severity. 54.3% of the patients received anti-COVID-19 vaccine. 72.3% of patients became seropositive after vaccination. Higher antibody titre against spike protein was detected after Pfizer-BioNTech vaccination compared to others. Patients receiving steroid therapy had decreased post-vaccination antibody response compared to those without steroid treatment. No major post-vaccination infection was observed

Conclusion

Based on our results, myositis may be associated with an increased risk of COVID-19 infection. Independent risk factor for hospitalisation are longer disease duration and anti-Jo1 positivity. Anti-SARS-CoV2 vaccines seem safe and tolerable and strongly recommended for that population.

Key words

myositis, interstitial lung disease, COVID infection, vaccination

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Received on February 12, 2022; accepted in revised form on May 9, 2022.

Competing interests: none declared.

Introduction

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV2), is known for being a life-threatening respiratory illness including varied extra- pulmonary manifestations. In the last two years in the shadow of the fight against SARS-CoV2 virus, clinicians and researchers are trying to assess the effect of COVID-19 pandemic on rheumatic and musculoskeletal diseases (RMDs) and *vice versa*. Early data have assumed that patients with RMDs have increased risk for SARS-CoV2 infection even after vaccination (1, 2) due to the immunomodulatory effects of their underlying diseases and continuous immunosuppressive treatment. Meanwhile, the immune-compromised condition along with the frequent administration of immune-suppressive treatments could prevent the so called "cytokine-storm" and major complications of COVID pneumonitis (3, 4).

Limited immunogenicity of SARS-CoV2 messenger RNA (mRNA) vaccines were detected in immunocompromised patients (1, 5, 6), and although most patients with RMDs developed an appropriate response to the first dose of the mRNA vaccine (7), an important subset of patients did not mount acceptable humoral response even after double doses (7-9). In a case series study 74% of RMD patients showed seroconversion for a single and 94% for two-dose of vaccination (6, 9). Non-biologic immunomodulators and also biologics (*e.g.* methotrexate, mycophenolate mofetil, rituximab or glucocorticoids) reduced the odds of a detectable antibody response (6, 8). But the ongoing immune-modifier treatments, especially bDMARD, did not affect the outcomes of symptomatic, generally mild COVID-19 disease (3).

Idiopathic inflammatory myopathies (myositis or IIM) are rare RMDs with a high frequency of extra muscular manifestation especially interstitial lung disease (ILD) and myocarditis. In the year that marked the outbreak of the COVID-19 pandemic, there was no shortage of new insights regarding IIMs, which was well reviewed earlier (10). Due to involvement of thoracic muscles, ILD, immobility, chronic immunosuppressive treatment and other co-morbidities, SARS-CoV2 infection with an underlying IIM could be a high risk and life-threatening situation. Based on these characteristics obtaining information about the effect of COVID-19 on IIM and *vice versa* is essential in clinical practice. We have less data about the disease course of COVID-19 infections in IIM patients and only some case reports presented SARS-CoV2 or vaccination induced myositis (11-13). Clinical manifestations vary from isolated enzyme (creatine kinase CK) elevation to rapid progressive myositis (12). On the other hand, diagnosis of IIM was associated with a negative response to mRNA vaccination (6) and furthermore, increasing age was associated non-linearly with reduced odds of a positive antibody response (6). Healthcare professionals invest a lot of energy worldwide in the long-term management of patients with IIM. In addition to the direct response to the pandemic, mitigating the indirect negative impact is vital, *e.g.* delayed appointments, diagnostics and treatments, which may all lead to poorer outcome (12).

Our study group takes care of IIM patients since 1985. The primary goals of the current research were (1) to assess frequency and outcome of COVID-19 disease and (2) to determine the vaccination rate and effect among patients with IIM treated by the Department of Clinical Immunology, University of Debrecen. Secondary objectives were to search for risk factors of infection and predictive factors of hospitalisation. We are tried to find the reasons for non-vaccination, the incidence of vaccination side-effects or complications.

Patients and methods

Patients

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. Informed consent was obtained from all of the subjects. This study is ethically compliant and was carried out in compliance with the Declaration of Helsinki. Volunteers underwent blood draw containing haematology, chemistry, immunoserology and SARS-CoV2 antibody testing.

Determination of SARS-CoV2 antibody

Anti-SARS-CoV2 S enzyme electrochemiluminescent 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. Titre 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.

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/nasopharyngeal swabs and/or (2) anti-N and anti-S protein antibody positivity without previous vaccination.

Statistical analysis

Comparisons between groups were performed by chi-square test, Fisher's exact test, Student's t test and Mann-Whitney test when appropriate using SPSS 22.0 software. A p-value < 0.05 was considered statistically significant.

Table I. Study population.

	Screened patients (n=176)	Finally participated (n=101)	Patients infected by COVID (n=35)
PM subset	60.2% (n=106)	59.4% (n=60)	65.7% (n=23)
DM subset	39.8 % (n=70)	40.6% (n=41)	34.3% (n=12)
Mean age	57.6 years	55.25 years	49.54 years
Female	66.5% (n=117)	65.3% (n=66)	71.4% (n=25)
Male	33.5% (n=59)	34.7% (n=35)	28.6% (n=10)
Average disease duration	12.9 years	11.04 years	10.89 years
Infected by COVID	not applicable	34.7% (n=35)	100% (n=35)
COPD	5.1% (n=9)	3.9% (n=4)	5.6% (n=2)
Diabetes mellitus	15.9% (n=28)	18.8% (n=19)	22.9% (n=8)
Hypertonia	55.1% (n=97)	58.4% (n=59)	54.3% (n=19)
Ischaemic heart disease	11.4% (n=20)	11.9% (n=12)	5.7% (n=2)
Asthma bronchial	5.1% (n=9)	3.9% (n=4)	2.8% (n=1)
Previous myositis specific autoantibody positivity			
anti-Jo1	14.8% (n=26)	17.8% (n=18)	20% (n=7)
anti-Mi2	5.7% (n=10)	2.9% (n=3)	2.8% (n=1)
anti-SRP	3.9% (n=7)	3.9% (n=4)	none
anti-PL7	1.7% (n=3)	1.9% (n=2)	none
anti-PL12	1.1% (n=2)	1.9% (n=2)	2.8% (n=1)
anti-MDA5	2.3% (n=4)	1.9% (n=2)	none
anti-TIF1y	4.5% (n=8)	4.9% (n=5)	2.8% (n=1)
anti-NXP2	1.7% (n=3)	2.9% (n=3)	none
anti-SAE	4.5% (n=8)	2.9% (n=3)	none
anti-EJ	none	none	none
anti-OJ	1.1% (n=2)	1.9% (n=2)	none
Previous anti-phospholipid antibody positivity	9.7% (n=17)	14.8% (n=15)	5.6% (n=2)
Immunosuppressive treatment at the time of study			
None	23.9 % (n=42)	22.8% (n=23)	25.7% (n=9)
Corticosteroid alone	28.4% (n=50)	26.7% (n=27)	25.7% (n=9)
Corticosteroid and methotrexate	15.3% (n=27)	17.8% (n=18)	14.3% (n=5)
Corticosteroid and other DMARD	13.6% (n=24)	13.9% (n=14)	14.3% (n=5)
Other DMARD alone	10.8% (n=19)	9.9% (n=10)	8.6% (n=3)
IVIG	5.1% (n=9)	5.9% (n=6)	5.7% (n=2)
Biological therapy	2.8% (n=5)	2,9% (n=3)	5.7% (n=2)
Vaccine type	68.75% (n=121)	54.45 % (n=55)	none
Pfizer	63.6% (n=77)	69.1% (n=38)	not applicable
Szputnyik	1.6% (n=2)	3.6% (n=2)	not applicable
Sinopharm	9.0% (n=11)	7.3% (n=4)	not applicable
AstraZeneca	14.0% (n=17)	12.7% (n=7)	not applicable
Moderna	11.6% (n=14)	7.3% (n=4)	not applicable

Results

COVID-19 in IIM

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 testing. Mean age was 55.25 years (17-81) the female/male ratio was 2 to 1. Myositis subsets were 40% dermatomyositis (DM) and 60% polymyositis (PM), respectively. The mean IIM disease duration was 11.04 years. Demographics, therapeutic regimens, co-morbidities, vaccination and disease course (both COVID-19 and IIM) data were collected 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 detected before vaccination. Acquisition of COVID-19 infection was not associated with myositis type, demographic factors, previous ILD, or disease duration. Considering basic immunoserology, anti-phospholipid antibody positivity [aCL 0.27% *vs.* 23% (p<0.001) and aB2GPI 0.18% *vs.* 11% (p=0.014)] were more common among those who were infected. Summarising the myositis-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 cohort, both of them had COVID-19 infection (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 favipiravir 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 involvement and ILD required non-invasive mechanical ventilation support. That patient recovered after combined favipiravir, 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), we found that significantly longer IIM disease duration (8.67±5.19 *vs.* 17.87±10.27 years; p=0.003) was associated with hospitalisation. None of the presenting co-morbidities, internal organ involvement and chronic immunosuppressive treatment affected hospitalisation. 14.3% of patients (n=5) had active IIM disease at the time of SARS-CoV2 infection but myositis activity 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 hospitalisation 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 hospitalisation. Following the COVID infection, all of our patients became seropositive regardless of immunosuppressive therapy with a mean SARS-CoV N antibody titre: 87.43 U/ml and SARS-CoV S mean antibody titre: 150.99 U/ml. We have neither found any SARS-CoV2 infection induced myositis nor new auto-antibody positivity among our IIM patients.

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, Moderna, 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 registered 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 titre of anti-SARS-CoV2 antibodies induced 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 titres for different vaccine types (p=0.002; Fig. 1). Lack of antibody response has no correlation with patient age, IIM type, internal organ involvement and immunosuppressive treatment. Pfizer-Biontec vaccination resulted in a significantly higher mean autoantibody titre 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 vaccine types (mean titre: 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 titre was

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	4/3 patients	20/8 patients	0.384
Mean age	58.14 years	47.23 years	0.068
Average disease duration	**17.87 years**	**8.67 years**	**0.003**
Polymyositis	64%	68%	0.372
Dermatomyositis	36%	32%	0.676
Anti-Jo1 antibody positive	**57%**	**11%**	**0.018**
Death	1	0	0.2

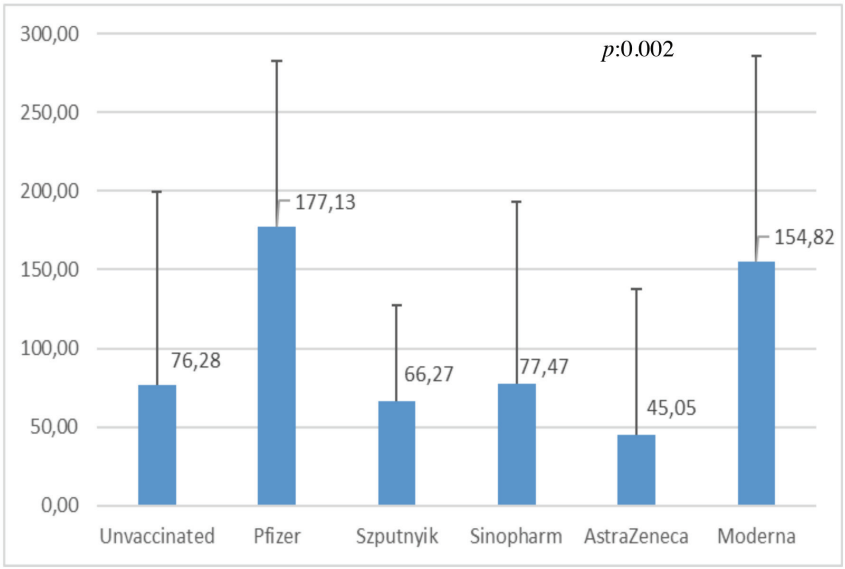

Fig. 1. Mean anti-spike protein (anti-S) and anti-nucleocapside protein (anti-N) titres with standard deviation (SD). Significant differences have been found by ANOVA analysis in mean titer of anti-S protein induces by different vaccines (p is the value of significance).

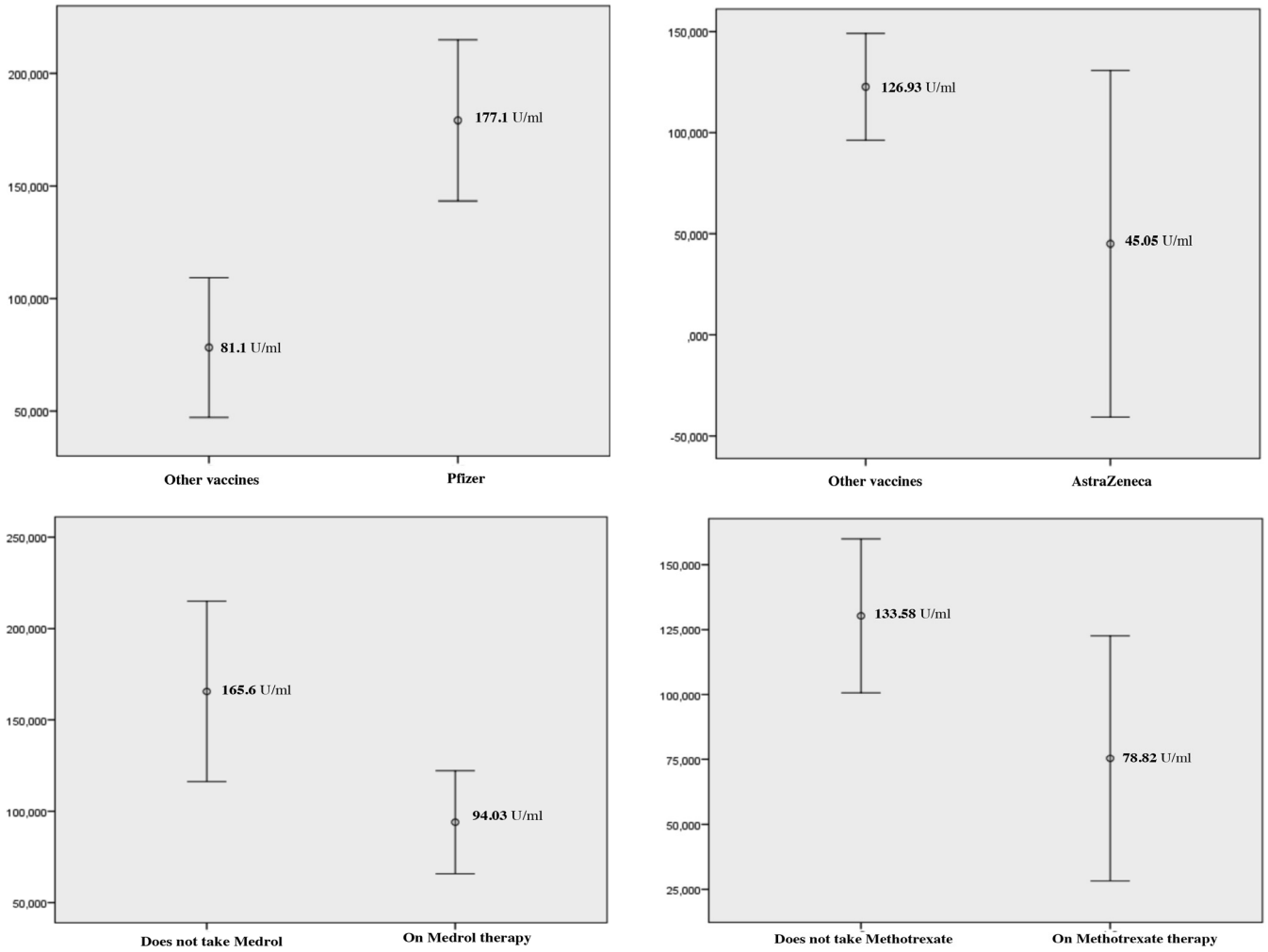

Fig. 2. Mean values and 95% confidence interval of anti-spike protein titres after Pfizer (p <0.001) and AstraZeneca (p=0.054) vaccination, besides Medrol (methylprednisolone) (p=0.008) and methotrexate intake (p=0.062).

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 prednisolone or equivalent) only 1 patient got high dose treatment (>30 mg prednisolone or equivalent). All vaccinated patients were on a stable dosage for 3 months before vaccination.

Considering vaccination reactions after Pfizer-Biontec local pain (47% *vs*. 17% p=0.001) were significantly more frequent 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 complications have been observed in 2 patients after vaccination: a 66-year-old DM female 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 research excluded underlying cancer, so the association with vaccination is presumed. We still did not reach remission 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 internal organ involvement, no myositis-specific antibody positivity and did not require any immunomodulatory treatment since 2017. Two weeks after the second dosage of mRNA vaccination coughing and dyspnoea started. It was first treated as pneumonia by the local health care services, but after worsening the patient came for further diagnostic 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 active alveolitis and honeycomb changes were also found by high resolution CT and breath tests showed severely decreased diffusion capacity (FEV52%, DLCO 22%). Immunoserology revealed new anti-EJ antibody positivity in high titre in addition to anti-Ro52 positivity. The immunological findings correlated with the clinical symptoms,

based on ILD, fever, antibody positivity IIM activity was noted and high dose intravenous corticosteroid treatment started in combination with cyclosporine A. Besides a prophylactic antibiotic, antiviral therapy was also initiated followed by alprostadil and sildenafil, which resulted major improvement in clinical status.

Discussion

According to our data, this is the first study in the Eastern-European region to assess the effects of COVID-19 pandemic on IIM patient population. Limitation of the study is based on semi-retrospective and cohort design but we are a national immunology centre treating patients from all region of Hungary and also from the countries of neighbourhood.

Among individuals with IIM, infection is frequent and the leading cause of mortality, where antibody status, lymphopenia, ILD, old age, and treatment with steroids are contributing factors in the development of infections (15) Our results approved the previous findings, that the odds of COVID-19 in patients with rheumatic disease was significantly higher than in control population (16). 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 (16). In our cohort prognosis seemed better, only prolonged myositis and the presence of Jo-1 autoantibody are risk factors for hospitalisation due to COVID-19 disease. Presence of organ involvement or comorbidities did not affect hospitalisation. This cohort study also supports that primary prevention 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 (17). Early hospitalisation and antiviral therapy should be considered in elderly patients with prolonged IIM disease or anti-Jo1 positivity.

The study was organised after vaccination become available for all citizens. Frequency of vaccination among our patients is higher also than the national 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 disease were detected in our cohort. The observed minor vaccine complications were easily manageable. Rapid recognition of severe cases helps the therapeutic choice.

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 (18, 19). Some case reports are still published proving anti-SARS CoV2 vaccination induced autoimmunity (20-22). 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 (23) as part of primary immunisation and 4th vaccine should be considered based on clinical activity, therapy and comorbidities. Cessation of immunosuppressive agents also should be reconsidered in COVID-19 infection with using the principles of personalised medicine.

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

Take home messages

- Myositis patients should be considered as high-risk group considering COVID-19 disease.
- Highlighting of primary prevention (mask, disinfection, social distancing) is important for IIM patients.
- Anti-Jo1 positivity is a risk factor for hospitalisation for unvaccinated people.
- Anti-SARS-CoV2 vaccines are safe, tolerable and could prevent complicated COVID-19 disease in IIM population.
- Further investigation is required to assess clinical significance of post-vaccination autoimmunity and disease flare

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