DMARD TREATMENT AND COVID-19 PREVALENCE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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ABSTRACT

Introduction: *Rheumatoid arthritis (RA) has been associated with an increased risk of respiratory infections, and the Covid-19 pandemic represents a serious threat for RA patients. Considering the controversy in the scientific literature, the present study aims to investigate the prevalence and severity of Covid-19 in regard to disease-modifying anti-rheumatic drugs (DMARD) treatment in a large group of RA patients treated in a single rheumatologic center.*

Methods: *A total of 156 patients with RA on biologic or targeted synthetic DMARD (b/tsDMARD) as well as 102 patients on conventional synthetic DMARD (csDMARD) answered a standardized questionnaire focused on the development, symptoms, and complications of Covid-19 infection.*

Results: *The prevalence of confirmed or suspected Covid-19 infection did not differ between the two investigated therapeutic groups and the prevalence of hospitalization for moderate or severe Covid-19 infection was low (about 5%). No one of the investigated antirheumatic drugs was specifically associated with the Covid-19 development, symptoms or complications. In the group of female RA patients, the prevalence of confirmed (13.6% vs. 22.4%) and suspected (10.6% vs. 17.6%) Covid-19 infection was significantly lower in women on b/tsDMARD compared to csDMARD (p=0.048).*

Conclusion: *The therapy with b/tsDMARD in RA patients has not been associated with increased Covid-19 incidence, distinct clinical symptoms, or worse outcomes when compared to csDMARD therapy. Moreover, it might decrease Covid-19 incidence or increase the asymptomatic cases in women with RA. Gender and sex-specific differences in RA and Covid-19 interrelations need further evaluation.*

Keywords: *Rheumatoid arthritis, DMARD, Covid-19-SARS-Cov-2, infection.*

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with an increased risk of infections and infection-related mortality[1, 2]. Patients with RA suffer more from respiratory and skin infections and develop sepsis more often than patients with non-inflammatory rheumatic diseases[3]. The main determinants of the increased risk are the immunological disturbances typical for the active disease, immune-suppressive treatment as well as the presence of comorbidities[2, 4]. In the last two years, the Covid-19 pandemic has posed new challenges for RA patients. The prevalence of Covid-19 hospitalizations and complications has been significantly increased in individuals with RA in comparison to the general population according to most though not all studies[5-8]. The poor Covid-19 clinical outcomes have been associated with age, concomitant diseases of patients as well as with the use of high corticosteroid doses, while the role of other types of disease-modifying antirheumatic drugs (DMARD) has been rather contradictory[6, 7, 9]. Interestingly, Covid-19 and inflammatory diseases could share common pathophysiological mechanisms leading to a pro-inflammatory cytokine increase (reviewed by Dewanjee et al.)[10]. Therefore, many antirheumatic drugs have been investigated as possible modulators of the "cytokine storm" in severe Covid-19, and beneficial effects were found

for some of them[11]. However, the influence of DMARD might be different in RA patients compared to the general population in regard to Covid-19 incidence and complications. Theoretically, both the immunosuppressive features of DMARD as well as increased disease activity in case of undertreatment might potentiate infection complications in RA[12]. Thus, the expanding of knowledge about the interrelations between SARS-CoV-2 infection and different types of DMARD in distinct ethnic groups of RA patients might help to minimize Covid-19 complications.

Therefore, the present study aims to investigate the prevalence and severity of Covid-19 in regard to DMARD treatment in a large group of RA patients.

Material and methods

Participants and study protocol

Caucasian patients with seropositive rheumatoid arthritis (RA) (26-85 years) treated in a tertiary rheumatologic center were selected and sought by phone if contact data were available.

Patients who were reached by phone and who consented to participate were included in the present study. RA diagnosis was previously made in accordance with the 1987 American College of Rheumatology criteria[13]. A total of 258 patients with rheumatoid arthritis agreed to answer a standardized questionnaire focused on the development of Covid-19. Clinical information about symptoms of the infection (anosmia, ageusia, fever, cough, dyspnea, headache, gastrointestinal symptoms, and presence of lung infiltrate by imaging studies), the severity of the disease, laboratory nasopharyngeal swabs performed, the need for hospitalization, and Covid-19 vaccination status was collected retrospectively. The Covid-19 disease was considered "confirmed" in the case of laboratory-confirmed positive SARS-CoV-2 nasopharyngeal swabs. The presence of presumptive Covid-19 symptoms and/or SARS-CoV-2 antibodies was registered as a "suspected" Covid-19 infection. The Covid-19 infection was considered severe in case of hospitalization or lung involvement. Additionally, the patients were asked to estimate the infection severity subjectively, irrespective of the aforementioned criteria. Additional personal data such as age, sex, height, weight, smoking habits, concomitant diseases as well as therapy were also collected. Information about close contacts with infected people and strict isolation during pandemics was obtained as in other studies[14]. The patients were divided into two different categories according to the antirheumatic therapy they received during the investigated period: patients on conventional synthetic disease-modifying antirheumatic drugs (csDMARD) such as antimalarials, methotrexate, sulfasalazine, and leflunomide were included in group 1, while patients on biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARD) with or without csDMARD were included in group 2. Biologic therapy included treatment with tumor-necrotic factor (TNF) inhibitors (etanercept, adalimumab, golimumab, certolizumab, and infliximab), interleukin-6 (IL-6) (tocilizumab) and CD20 (rituximab) inhibitors. Targeted synthetic disease-modifying antirheumatic drugs used were baricitinib, tofacitinib, and upadacitinib.

Patients with RA on b/tsDMARD were 156 (24 men and 132 women), while patients on csDMARD only were 102 (17 men and 85 women). Treatment with corticosteroids (CS) was also registered and the specific dose was calculated as a methylprednisolone equivalent. Anthropometric characteristics and data about concomitant diseases such as obesity, hypertension, diabetes mellitus type 2 (T2DM), cardiovascular, neurologic, renal, gastroenterological diseases were collected. Verbal informed consent was obtained by the patients. The study was approved by the local ethics committee and carried out in accordance with the ethical principles of the Declaration of Helsinki.

Statistical analysis

The results were presented as frequency (%) and number /n/ for categorical variables and as mean with standard deviation (median) for continuous variables. The data were analyzed through the χ^2 test or Fisher's exact test. Differences between groups were estimated through independent sample t-test or Mann-Whitney test according to the normality of the distribution after a Kolmogorov-Smirnov test. Logistic regression analysis was used where appropriate. All results were considered significant at the 0.05 level. Calculations were made through the software package MedCalc® Statistical Software version 20.027 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022).

Results

The main characteristics of the patients on csDMARD and b/tsDMARD are presented in Table 1. Considering the b/tsDMARD therapy most of

the patients were on anti-IL6 inhibitor (50.6% /79/), while 34.0% /53/ were on an anti-TNF-based treatment, 13.5% /21/ received JAK-kinase inhibitors and only 1.9% /3/ were on rituximab. The two groups of patients did not differ in terms of concomitant cardiovascular, neurological, pulmonary, gastrointestinal, nephrological, or other diseases (p>0.05 for all). The two groups included also a similar percentage of patients attempting strict isolation during pandemics (41.6% vs. 48.1%, p=0.369) as well as a similar percentage of patients who had had close contact with Covid-19 infected individuals (31.7% vs. 25.6%, p=0.321). Patients on b/tsDMARD had more often at least one concomitant disease in comparison to patients on csDMARD (53.9% /83/ vs. 38.2% /39/, p=0.015). Patients on csDMARD received more often corticosteroids (37.3% /38/ vs. 19.2% /30/, p=0.002), antimalarial agents (13.7% /14/ vs. 5.1% /8/, p=0.022) as well as leflunomide (12.7% /13/ vs. 5.1% /8/, p=0.036) than patients on b/tsDMARD as expected, while no significant differences in the number of patients treated with methotrexate or sulphasalazine treatment in both groups were observed (p>0.05 for all).

The prevalence of confirmed or suspected Covid-19 infection did not differ between the two investigated therapeutic groups and the prevalence of hospitalization for moderate or severe Covid-19 infection was about 5% (Table 1) with only one patient being hospitalized in an intensive care unit who survived. The prevalence of confirmed or suspected Covid-19 infection, Covid-19 lung infiltrate as well as the prevalence of hospitalizations, did not differ amongst groups of patients treated with TNF-inhibitors, IL-6-inhibitors, or targeted synthetic disease-modifying antirheumatic drugs (p>0.05 for all). Additionally, no one of the conventional synthetic disease-modifying antirheumatic drugs showed any associations with the Covid-19 infection or Covid-19 lung infiltrate prevalence, hospitalization rate, or subjective severity score (p>0.05 for all).

The prevalence of confirmed or suspected Covid-19 infection, hospitalization rate, and severity did not depend significantly on the presence of pre-existing obesity, hypertension, diabetes mellitus type 2 or other concomitant diseases as well as on the CS use and smoking (p>0.05 for all). However, the prevalence of Covid-19 lung infiltrate was increased (13.9% vs. 5.3%, p=0.019) in patients with at least one concomitant disease in comparison to patients without any concomitant diseases. The prevalence of confirmed Covid-19 infection (29.3% vs. 17.1%, p=0.082), as well as the prevalence of Covid-19 pneumonia (17.1% vs. 8.3%, p=0.090), tended to be higher in men than in women with RA.

	All patients With RA N=258	Group 1 (csDMARD) N=102	Group 2 (b/tsDMARD) N=156	p
Age (years)	59.55±12.48 (60.0)	57.70±12.32 (58.5)	60.77±12.48 (62.0)	0.053
BMI (kg/m^2)	26.72±5.45 (26.23)	26.77±6.21 (26.07)	26.69±4.90 (26.35)	0.913
Smoker-active; former (% /n/)	31 /80/; 2.7 /7/	35.3 /36/; 2.0 /2/	28.2 /44/; 3.2 /5/	0.434
Obesity (% /n/)	25.0 /64/	23.5 /24/	26.0 /40/	0.768
Hypertension (% /n/)	26.4 /68/	17.6 /18/	32.1 /50/	0.014
DM type 2 (%/n/)	6.6 /17/	7.8 /8/	5.8 /9/	0.610
CVD (% /n/)	7.8 /20/	6.9 /7/	8.3 /13/	0.813
Other concomitant diseases (% /n/)	7.8 /20/	7.7 /8/	7.7 /12/	1.000
CS (% /n/)	26.4 /68/	37.3 /38/	19.2 /30/	0.002
CS-dose (mg)	5.01±2.99 (4.0)	5.76±3.11 (4.0)	4.07±2.59 (4.0)	0.009
Covid-19 - confirmed (% /n/)	19.0 /49/	21.6 /22/	17.3 /27/	0.420
Covid-19 - confirmed or suspected (% /n/)	31.8 /82/	37.3 /38/	28.2 /44/	0.135
Covid-19 hospitalization (% /n/)	4.7 /12/	5 /5/	4.5 /7/	1.000
Covid-19 Vaccination (% /n/)	17.4 /45/	21.6 /22/	14.7 /23/	0.181

Table 1: Main characteristics of the investigated patients. *Group 1 (csDMARD)-patients with rheumatoid arthritis on conventional synthetic disease-modifying antirheumatic drugs only); Group 2 (b/tsDMARD)-patients with rheumatoid arthritis on biologic or targeted synthetic disease-modifying antirheumatic drugs irrespective of csDMARD treatment); CS-corticosteroids; BMI-body mass index; CVD-cardiovascular diseases.*

In the group of female RA patients, the prevalence of confirmed (13.6% vs. 22.4%) and suspected (10.6% vs. 17.6%) Covid-19 infection was significantly lower in women on b/tsDMARD compared to csDMARD (p=0.048) (Table 2). No such differences were found in the group of men with RA, though the male group was too small (n=41) to draw any definitive conclusions (p>0.05, data not shown). The prevalence of confirmed or suspected Covid-19 infection, as well as the prevalence of hospitalizations, Covid-19 lung infiltrates or Covid-19 severity, did not differ between groups of patients treated with TNF-inhibitors, IL-6-inhibitors, or targeted synthetic disease-modifying antirheumatic drugs in both sexes (p>0.05 for all).

Logistic regression analysis showed that the b/tsDMARD administration was associated with a significantly reduced odds of confirmed or suspected Covid-19 infection after adjustment for age, corticosteroid use, and presence of concomitant diseases (OR 0.513 (95%CI 0.277-0.951), p=0.034). The presence of at least one concomitant disease was

related to a double risk of Covid-19 infection (OR 2.027 (95%CI 1.071-3.839), p=0.030) in the model.

	All female patients with RA N=217	Group 1 (csDMARD) N=85	Group 2 (b/tsDMARD) N=132	p
Age (years)	59.55±12.66 (60.0)	57.27±12.28 (58.0)	61.03±12.73 (62.0)	0.033
BMI (kg/m^2)	26.55±5.72 (26.03)	26.56±6.63 (25.71)	26.54±5.07 (26.23)	0.978
Smoker-active; former (% /n/)	29.0 /63/; 2.3 /5/	34.1 /29/; 1.2 /1/	25.8 /34/; 3.0 /4/	0.311
Obesity (%)	25.6 /55/	23.5 /20/	26.9 /35/	0.633
Hypertension (%)	25.8 /56/	17.6 /15/	31.1 /41/	0.038
DM type 2 (%)	6 /13/	5.9 /5/	6.1 /8/	1.000
CVD (%)	6.9 /15/	5.9 /5/	7.6 /10/	0.786
Other concomitant diseases	7.4 /16/	8.2 /7/	6.8 /9/	0.792
CS (%/n/)	26.3 /57/	36.5 /31/	19.7 /26/	0.007
CS-dose (mg)	4.86±2.97 (4.0)	5.71±3.09 (4.0)	3.85±2.50 (4.0)	0.006
Covid-19 – confirmed (%)	17.1 /37/	22.4 /19/	13.6 /18/	0.100
Covid-19 - confirmed or suspected (%)	30.4 /66/	40 /34/	24.2 /32/	0.016
Covid-19 hospitalization (%)	4.6 /10/	6 /5/	3.8 /5/	0.516
Covid-19 Vaccination (%)	16.1 /35/	21.2 /18/	12.9 /17/	0.130

Table 2: Main characteristics of the investigated women. Group 1 (csDMARD) - patients with rheumatoid arthritis on conventional synthetic DMARD only; Group 2 (b/ts DMARD)-patients with rheumatoid arthritis on biologic or targeted treatment. CS - corticosteroids; BMI - body mass index; CVD - cardiovascular diseases.

Covid-19 symptoms	All female patients with RA N=217	Group 1 (csDMARD) N=85	Group 2 (b/tsDMARD) N=132	p
Anosmia (% /n/)	14.4 /31/	17.9 /15/	12.1 /16/	0.319
Ageusia (% /n/)	11.1 /24/	15.3 /13/	8.5 /11/	0.122
Fieber (% /n/)	18.1 /39/	22.6 /19/	15.2 /20/	0.204
Cough (% /n/)	6.0 /13/	9.5 /8/	3.8 /5/	0.139
Dyspnea (% /n/)	7.9 /17/	8.3 /7/	7.6 /10/	1.000
Headache (% /n/)	1.4 /3/	2.4 /2/	0.8 /1/	0.561
Gastrointestinal symptoms (% /n/)	1.4 /3/	2.4 /2/	0.8 /1/	0.561
Pneumonia (% /n/)	8.3 /18/	7.1 /6/	9.1 /12/	0.801
Severe infection (% /n/)	6.0 /13/	6.0 /5/	6.1 /8/	0.331
Hospitalization (% /n/)	4.6 /10/	6.0 /5/	3.8 /5/	0.516

Table 3: Main Covid-19 symptoms of the investigated female patients.
Group 1 (csDMARD)-patients with rheumatoid arthritis on conventional synthetic disease-modifying antirheumatic drugs only; Group 2 (b/tsDMARD)-patients with rheumatoid arthritis on biologic or targeted synthetic disease-modifying antirheumatic drugs irrespective of csDMARD treatment.

The b/tsDMARD use was not related to any specific Covid-19 symptom in women with RA (Table 3).

Discussion

Our results showed that the prevalence of Covid-19 infection was lower in women with RA treated with b/tsDMARD than in those treated with csDMARD. The differences were significant, though the female patients on b/ts DMARD were older and with an increased prevalence of hypertension in comparison to women receiving csDMARD. In opposite, men with RA did not benefit significantly from b/ts DMARD treatment in regard to Covid-19 infection. The present results support the findings from several large registry-based studies.

The COVID-19 Global Rheumatology Alliance physician-reported registry showed that treatment with b/ts DMARD was associated with a reduced risk of Covid-19 hospitalization in patients with rheumatic diseases[9]. Similarly, the hospitalized German patients with inflammatory rheumatic diseases tended to receive less frequent bDMARDs in comparison to individuals not admitted to Covid-19 hospital treatment[15]. Other studies also assume a positive influence of b/ts DMARD on Covid-19 morbidity, but their conclusions are limited because of the very few proven Covid-19 cases included[16, 17]. However, other studies did not find such protective but rather neutral effects of b/tsDMARD treatment[18,19]. The use of b/tsDMARD was neither protective nor harmful in respect to Covid-19 hospitalization and mortality according to a large Italian study[18]. Similarly, the BIOBADASER study group suggested that treatment b/tsDMARD was not associated with a different Covid-19 hospitalization rate or mortality in comparison to the general Spain population[19]. Recently, a large multicenter study in the USA also did not find differences in regard to Covid-19 complications between b/tsDMARD and csDMARD users[20]. Unlike most b/tsDMARD medications, several Covid-19 fatal cases in RA patients treated with rituximab have been described[21,22]. Moreover, patients on rituximab had shown an increased prevalence of Covid-19 hospitalization and mortality in comparison to individuals treated with TNF-inhibitors[20, 23].

However, it should be considered that rituximab is used as second-line therapy for RA patients with contra-indications or therapeutic failure on other biologics, thus the patients on rituximab are probably patients with more severe RA than others,

and the latter could influence the Covid-19 infection outcomes[24]. In our study, only 3 patients were on rituximab, so no conclusions considering its effects could be drawn. The protective effects of b/tsDMARD in regard to Covid-19 infection onset in our female group did not depend on the b/tsDMARD type (TNF-inhibitors, IL-6-inhibitors, or JAK-kinase inhibitors). Recent large studies identified TNF-inhibitors as a safe biological drug class in RA patients in regard to Covid-19 infection[20, 23, 25]. Additionally, a recent meta-analysis showed significant protective effects of TNF inhibitors against severe Covid-19 infection in patients with different inflammatory diseases[26]. On the opposite, the use of TNF-inhibitors was associated with increased Covid-19 incidence according to the analysis of the World Health Organization pharmacovigilance database[27].

The proper role of TNF-signalling in patients with Covid-19 and inflammatory disorders has not been revealed so far. Both increased TNFα levels, as well as elevated soluble TNF-receptor 1 concentration, have been associated with pronounced Covid-19 severity and increased mortality[28, 29]. Additionally, the elevated concentration of a disintegrin and metalloprotease 17 (ADAM17) was also a strong predictor of severe infection course[29]. ADAM17 is a shedding enzyme that could modulate the release of soluble TNFα as well as many other membrane-bound proteins including angiotensin-converting enzyme 2 (ACE2)[30, 31]. The latter is crucial for the SARS-CoV-2 entry in the targeted cells, but it also exerts important tissue-protective effects by precluding the angiotensin II-induced inflammation, vasoconstriction, and fibrosis[32]. Thus, the blockade of TNF-signalling might influence the ADAM17 expression and probably the Covid-19 infection rate and clinical complications[30, 33].

The precise role of IL-6 inhibitors in RA patients with Covid-19 is also poorly investigated. IL-6 inhibitors reduced Covid-19 mortality in the general population[34]. Moreover, they represent the only class of biologic medication that could be continued during active Covid-19 infection in RA patients in selected circumstances according to the recommendation of the American College of Rheumatology[35]. According to the COVID-19 Global Rheumatology Alliance physician registry, IL-6 inhibitors and TNF-inhibitors exert a similar influence on Covid-19 severity[23]. On the opposite, patients with RA on IL-6 inhibitors showed an increased prevalence of Covid-19 hospitalizations in comparison to individuals with RA on TNF-inhibitors according to a large multicentre USA study, though no differences in ICU admission frequency or mortality were observed[20]. Similarly, the aforementioned studies have obtained contradictory results about the role of JAK-kinase inhibitors for the Covid-19 progression. JAK-kinase inhibitors have been shown to exert both neutral and unfavorable effects on Covid-19 severity when compared to TNF-inhibitors according to different authors[20, 23, 36]. On the other hand, they might be related to a decreased Covid-19 incidence in patients with inflammatory rheumatic diseases[27].

The chronic treatment with b/ts DMARD irrespective of the type was not related to increased prevalence, different clinical symptoms, or a more severe form of Covid-19 infection compared to other treatment protocols in our RA patients. According to our data, male patients with RA tended to have increased Covid-19 prevalence, with increased frequency of pulmonary involvement as in other studies[20, 37]. The glucocorticoid use was not a significant risk factor for increased Covid-19 prevalence or severity in opposite to other studies[9, 20], however, the mean corticosteroid dose used by our patients was very low, with only 7.36% of individuals being on more than 10 mg prednisolone equivalent, which could explain discrepancies. Our data showed sex-dependent differences in the association between the b/tsDMARD or csDMARD treatment and Covid-19 infection prevalence. Rheumatoid arthritis is a disease with a pronounced female preponderance possibly associated with X-chromosome-related genetic or hormonal factors[38,39]. Similarly, important sex and gender differences have been observed in Covid-19 patients considering the disease incidence and clinical severity, which could be attributed to distinct endocrine, immunological and psychological factors[40]. More clinical studies are needed to shed light on sex and gender differences that could influence the therapeutic approach in patients with inflammatory diseases and Covid-19 infection. Though our study encompasses a large number of RA patients it has several important limitations. The prevalence of Covid-19 symptoms was self-reported, thus some of the patients might have had an asymptomatic infection. Additionally, the prevalence of severe Covid-19 infection was very low, and only 5% of patients were hospitalized. Thus, our conclusions might be referred to mild or moderate Covid-19 infection only.

In conclusion, our study showed that b/tsDMARD therapy in RA patients was not associated

with increased Covid-19 incidence, distinct clinical symptoms, or worse outcomes when compared to csDMARD therapy. Moreover, it might decrease Covid-19 incidence or increase the asymptomatic cases in women with RA. Further studies are needed to reveal the proper pathophysiological mechanisms behind these gender-specific associations.

References

1) Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum. 2002; 46(9): 2287-2293.
2) Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. Rheumatology (Oxford). 2013; 52(1): 53-61.
3) Mehta B, Pedro S, Ozen G, Kalil A, Wolfe F, Mikuls T, Michaud K. Serious infection risk in rheumatoid arthritis compared with non-inflammatory rheumatic and musculo-skeletal diseases: a US national cohort study. RMD Open 2019; 5: e000935.
4) Widdifield J, Bernatsky S, Paterson JM, Gunraj N, Thorne JC, Pope J, Cividino A, Bombardier C. Serious infections in a population-based cohort of 86,039 seniors with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2013; 65(3): 353-361.
5) Cordtz R, Lindhardsen J, Soussi BG, Vela J, Uhrenholt L, Westermann R, Kristensen S, Nielsen H, Torp-Pedersen C, Dreyer L. Incidence and severeness of COVID-19 hospitalization in patients with inflammatory rheumatic disease: a nationwide cohort study from Denmark. Rheumatology (Oxford). 2021; 60(SI): SI59-SI67.
6) England BR, Roul P, Yang Y, Kalil AC, Michaud K, Thiele GM, Sauer BC, Baker JF, Mikuls TR. Risk of COVID-19 in Rheumatoid Arthritis: A National Veterans Affairs Matched Cohort Study in At-Risk Individuals. Arthritis Rheumatol. 2021; 73(12): 2179-2188.
7) Shin YH, Shin JI, Moon SY, Jin HY, Kim SY, Yang JM, Cho SH, Kim S, Lee M, Park Y, Kim MS, Won HH, Hong SH, Kronbichler A, Koyanagi A, Jacob L, Smith L, Lee KH, Suh DI, Lee SW, Yon DK. Autoimmune inflammatory rheumatic diseases and COVID-19 outcomes in South Korea: a nationwide cohort study. Lancet Rheumatol. 2021; 3(10): e698-e706.
8) Jung Y, Kwon M, Choi HG. Association between previous rheumatoid arthritis and COVID-19 and its severity: a nationwide cohort study in South Korea. BMJ Open. 2021;11(10): e054753.
9) Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, Izadi Z, Jacobsohn L, Katz P, Lawson-Tovey S, Mateus EF, Rush S, Schmajuk G, Simard J, Strangfeld A, Trupin L, Wysham KD, Bhana S, Costello W, Grainger R, Hausmann JS, Liew JW, Sirotich E, Sufka P, Wallace ZS, Yazdany J, Machado PM, Robinson PC; COVID-19 Global Rheumatology Alliance. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis. 2020; 79(7): 859-866.
10) Dewanjee S, Kandimalla R, Kalra RS, Valupadas C, Vallamkondu J, Kolli V, Dey Ray S, Reddy AP, Reddy PH. COVID-19 and Rheumatoid Arthritis Crosstalk: Emerging Association, Therapeutic Options and Challenges. Cells. 2021; 10(12): 3291.
11) Cavalli G, Farina N, Campochiaro C, De Luca G, Della-Torre E, Tomelleri A, Dagna L. Repurposing of Biologic and Targeted Synthetic Anti-Rheumatic Drugs in COVID-19 and Hyper-Inflammation: A Comprehensive Review of Available and Emerging Evi-dence at the Peak of the Pandemic. Front Pharmacol. 2020; 11: 598308.
12) Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: Faraway, so close! Autoimmun Rev. 2020; 19(5): 102523.
13) Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31: 315-24.
14) Carosi G, Morelli V, Del Sindaco G, Serban AL, Cremaschi A, Frigerio S, Rodari G, Profka E, Indirli R, Mungari R, Resi V, Orsi E, Ferrante E, Dolci A, Giavoli C, Arosio M, Mantovani G. Adrenal Insufficiency at the Time of COVID-19: A Retrospective Study in Patients Referring to a Tertiary Center. J Clin Endocrinol Metab. 2021; 106(3): e1354-e1361.
15) Hasseli R, Mueller-Ladner U, Schmeiser T, Hoyer BF, Krause A, Lorenz HM, Regierer AC, Richter JG, Strangfeld A, Voll RE, Pfeil A, Schulze-Koops H, Specker C. National registry for patients with inflammatory rheumatic diseases (IRD) infected with SARS-CoV-2 in Germany (ReCoVery): a valuable mean to gain rapid and reliable knowledge of the clinical course of SARS-CoV-2 infections in patients with IRD. RMD Open. 2020 Sep; 6(2): e001332.
16) Monti S, Balduzzi S, Delfino P, Bellis E, Quadrelli VS, Montecucco C. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppres-sive targeted therapies. Ann Rheum Dis. 2020; 79(5): 667-668.
17) Conticini E, Bargagli E, Bardelli M, Rana GD, Baldi C, Cameli P, Gentileschi S, Ben-nett D, Falsetti P, Lanzarone N, Bellisai F, Barreca C, D'Alessandro R, Cantarini L, Frediani B. COVID-19 pneumonia in a large cohort of patients treated with biological and targeted synthetic antirheumatic drugs. Ann Rheum Dis. 2021; 80(2): e14.
18) Salvarani C, Bajocchi G, Mancuso P, Galli E, Muratore F, Boiardi L, Catanoso M, Pip-itone N, Cassone G, Girolimetto N, Croci S, Cimino L, Gradellini F, Beltrami M, Di Lernia V, Dolci G, Massari M, Marata AM, Costantini M, Giorgi Rossi P. Susceptibility and severity of COVID-19 in patients treated with bDMARDS and tsDMARDs: a population-based study. Ann Rheum Dis. 2020; 79(7): 986-988.
19) Sanchez-Piedra C, Diaz-Torne C, Manero J, Pego-

Reigosa JM, Rúa-Figueroa Í, Gonzalez-Gay MA, Gomez-Reino J, Alvaro-Gracia JM; BIOBADASER study group. Clinical features and outcomes of COVID-19 in patients with rheumatic diseases treated with biological and synthetic targeted therapies. Ann Rheum Dis. 2020; 79(7): 988-990.

20) Raiker R, DeYoung C, Pakhchanian H, Ahmed S, Kavadichanda C, Gupta L, Kardeş S. Outcomes of COVID-19 in patients with rheumatoid arthritis: A multicenter research network study in the United States. Semin Arthritis Rheum. 2021; 51(5): 1057-1066.

21) Schulze-Koops H, Krueger K, Vallbracht I, Hasseli R, Skapenko A. Increased risk for severe COVID-19 in patients with inflammatory rheumatic diseases treated with rituximab. Ann Rheum Dis. 2021; 80(5): e67.

22) Guilpain P, Le Bihan C, Foulongne V, Taourel P, Pansu N, Maria ATJ, Jung B, Larcher R, Klouche K, Le Moing V. Rituximab for granulomatosis with polyangiitis in the pandemic of covid-19: lessons from a case with severe pneumonia. Ann Rheum Dis. 2021; 80(1): e10.

23) Sparks JA, Wallace ZS, Seet AM, Gianfrancesco MA, Izadi Z, Hyrich KL, et al.; COVID-19 Global Rheumatology Alliance. Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: Results from the COVID-19 Global Rheumatology Alliance physician registry. Ann Rheum Dis. 2021; 80(9): 1137-1146.

24) Bukhari M, Abernethy R, Deighton C, Ding T, Hyrich K, Lunt M, Luqmani R, Kiely P, Bosworth A, Ledingham J, Ostör A, Gadsby K, McKenna F, Finney D, Dixey J; BSR and BHPR Standards, Guidelines and Audit Working Group. BSR and BHPR guide-lines on the use of rituximab in rheumatoid arthritis. Rheumatology (Oxford). 2011; 50(12): 2311-2313.

25) Salesi M, Shojaie B, Farajzadegan Z, Salesi N, Mohammadi E. TNF-α Blockers Showed Prophylactic Effects in Preventing COVID-19 in Patients with Rheumatoid Arthritis and Seronegative Spondyloarthropathies: A Case-Control Study. Rheumatol Ther. 2021; 8, 1355-1370.

26) Kokkotis G, Kitson K, Xynogalas I, Spoulou V, Magiorkinis G, Trontzas I, Trontzas P, Poulakou G, Syrigos K, Bamias G. Systematic review with meta-analysis: COVID-19 outcomes in patients receiving anti-TNF treatments. Aliment Pharmacol Ther. 2022; 55(2): 154-167.

27) Dernoncourt A, Schmidt J, Duhaut P, Liabeuf S, Gras-Champel V, Masmoudi K, Ben-nis Y, Batteux B. COVID-19 in DMARD-treated patients with inflammatory rheumatic diseases: Insights from an analysis of the World Health Organization pharmacovigilance database. Fundam Clin Pharmacol. 2022; 36(1): 199-209.

28) Mortaz E, Tabarsi P, Jamaati H, Dalil Roofchayee N, Dezfuli NK, Hashemian SM, Moniri A, Marjani M, Malekmohammad M, Mansouri D, Varahram M, Folkerts G, Adcock IM. Increased Serum Levels of Soluble TNF-α Receptor Is Associated With ICU Mortality in COVID-19 Patients. Front Immunol. 2021; 12: 592727.

29) Palacios Y, Ruiz A, Ramón-Luing LA, Ocaña-Guzman R, Barreto-Rodriguez O, Sánchez-Monciváis A, Tecuatzi-Cadena B, Regalado-García AG, Pineda-Gudiño RD, García-Martínez A, Juárez-Hernández F, Farias-Contreras JP, Fricke-Galindo I, Pérez-Rubio G, Falfán-Valencia R, Buendia-Roldan I, Medina-Quero K, Chavez-Galan L. Severe COVID-19 Patients Show an Increase in Soluble TNFR1 and ADAM17, with a Relationship to Mortality. Int J Mol Sci. 2021; 22(16): 8423.

30) Palau V, Riera M, Soler MJ. ADAM17 inhibition may exert a protective effect on COVID-19. Nephrol Dial Transplant. 2020; 35(6): 1071-1072.

31) Black RA, Rauch CT, Kozlosky CJ, Peschon JJ, Slack JL, Wolfson MF, Castner BJ, Stocking KL, Reddy P, Srinivasan S, Nelson N, Boiani N, Schooley KA, Gerhart M, Davis R, Fitzner JN, Johnson RS, Paxton RJ, March CJ, Cerretti DP. A metallopro-teinase disintegrin that releases tumour-necrosis factor-alpha from cells. Nature. 1997; 385(6618): 729-33.

32) Zipeto D, Palmeira JDF, Argañaraz GA, Argañaraz ER. ACE2/ADAM17/TMPRSS2 Interplay May Be the Main Risk Factor for COVID-19. Front Immunol. 2020; 11: 576745.

33) Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: Faraway, so close! Autoimmun Rev. 2020; 19(5): 102523.

34) Belletti A, Campochiaro C, Marmiere M, Likhvantsev V, Yavorovskiy A, Dagna L, Landoni G, Zangrillo A, Hajjar LA. Efficacy and safety of IL-6 inhibitors in patients with COVID-19 pneumonia: a systematic review and meta-analysis of multicentre, randomized trials. Ann Intensive Care. 2021; 11(1): 152.

35) Mikuls TR, Johnson SR, Fraenkel L, Arasaratnam RJ, Baden LR, Bermas BL, et al. American College of Rheumatology Guidance for the Management of Rheumatic Disease in Adult Patients During the COVID- 19 Pandemic: Version 1. Arthritis Rheumatol 2020; 72: 1241-1251.

36) Bower H, Frisell T, Di Giuseppe D, Delcoigne B, Ahlenius GM, Baecklund E, et al.; ARTIS Study Group. Impact of the COVID-19 pandemic on morbidity and mortality in patients with inflammatory joint diseases and in the general population: a nationwide Swedish cohort study. Ann Rheum Dis. 2021;80(8):1086–1093.

37) Abate BB, Kassie AM, Kassaw MW, Aragie TG, Masresha SA. Sex difference in coronavirus disease (COVID-19): a systematic review and meta-analysis. BMJ Open. 2020; 10(10): e040129.

38) van Vollenhoven RF. Sex differences in rheumatoid arthritis: more than meets the eye. BMC Med. 2009; 7: 12.

39) Alpízar-Rodríguez D, Pluchino N, Canny G, Gabay C, Finckh A. The role of female hormonal factors in the development of rheumatoid arthritis. Rheumatology (Oxford). 2017; 56(8): 1254-1263.

40) Ya'qoub L, Elgendy IY, Pepine CJ. Sex and gender differences in COVID-19: More to be learned! Am Heart J Plus. 2021; 3: 100011.

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