Increased influenza vaccination rates in patients with autoimmune rheumatic diseases during the Covid-19 pandemic: a cross-sectional study

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Abstract
To assess non-compliance and potential changes in seasonal flu vaccination coverage before and during the Covid-19 pandemic in patients with autoimmune rheumatic diseases (ARDs). Consecutive patients with ARDs followed-up in 2 tertiary hospitals were telephone-interviewed (December 12–30, 2020) regarding seasonal flu vaccination during the 2019/20 and 2020/21 time periods. Self-reported disease flares that occurred after flu vaccination, as well as reasons for non-vaccination were recorded. One thousand fifteen patients were included. The rate of flu vaccination increased from 76% before to 83% during the COVID-19 pandemic (p = 0.0001). The rate of self-reported disease flares was < 1% among vaccinated patients. Reasons for not vaccination in both periods, respectively, included: ‘was not recommended by their rheumatologists’ (35.0 vs. 12.2%, p < 0.0001), ‘did not feel that they would have any benefit’ (36.9 vs. 32.6%), felt unsafe to do so (27.5 vs. 30.2%), or other reasons (18.9 vs. 23.8%). By multivariate analysis, age [OR = 1.03 (95% CI 1.02–1.04)] vs. [1.04 (95% CI 1.02–1.05)] and treatment with biologics [OR = 1.66 (95% CI 1.22–2.24) vs. [1.68 (95% CI 1.19–2.38)] were independent factors associated with vaccination in both periods. These findings, although are temporally encouraging, emphasize the need for continuous campaigns aiming at increasing patients’ and physicians’ awareness about the benefits of vaccination.

Keywords Vaccination · Influenza · Autoimmune rheumatic diseases · Covid-19

Introduction
The higher risk for infections in patients with autoimmune rheumatic diseases (ARDs) is well established [1, 2]. In this context, vaccinations are of paramount importance in this population. As outlined in EULAR recommendations, flu vaccination should be strongly considered for the majority of patients with ARDs [3] since it has been shown that is associated with reduced mortality, hospitalizations risk and influenza-related complications [3, 4].

Vaccination rates in ARD patients vary and few studies have assessed the factors that are associated with non-compliance. Covid-19 pandemic, added another factor of complexity as it has generated some degree of uncertainty in these patients [5]. Covid-19 virus entered our lives, suddenly, in December 2019, when a cluster of patients with lower respiratory tract infection was described in the province of Wuhan, in China [6]. Covid-19 is the seventh member of the corona-viruses that can infect humans [6] and its name is derived from the spikes that are present on its surface (Fig. 1). Although its origin is not clear, a close homology to two bat-derived coronaviruses has been identified [7, 8]. Clinically, is mainly expressed with fever, headache, anosmia, fatigue and cough and not infrequently, leads to admission in the intensive care unit [9–12].

Aim of our study was to assess potential changes in influenza vaccination during the Covid-19 pandemic among ARD patients and investigate the factors associated with non-compliance.
Patients and methods

In our cross-sectional, observational study, patients with ARDs who had been examined at least once during the last year in the outpatient rheumatology clinics of two tertiary hospitals were telephone-interviewed from 12/12/2020 to 30/12/2020.

Patients were consecutively enrolled, following an alphabetical order of their surname in our files. Patients with a diagnosis of osteoarthritis, crystal arthropathies and metabolic bone diseases were excluded. The following parameters were recorded: age, sex, level of education (1st level: elementary school, 2nd level: high school, 3rd level: college/university), employment status, smoking status, follow-up time (from disease diagnosis to enrollment in the study) and type of ARD (inflammatory arthritides: rheumatoid arthritis, spondyloarthropathies; connective tissue diseases: systemic lupus erythematosus, systemic sclerosis, dermatomyositis, Sjogren’s syndrome, antiphospholipid syndrome, myositis; autoinflammatory diseases: adult-onset Still’s disease, familial mediterranean fever; vasculitides: ANCA-associated vasculitis, Behcet’s disease, giant cell arteritis), current treatment for ARDs (glucocorticoids, non-biologic immunosuppressives, targeted synthetic agents and biologics) and the presence of certain co-morbidities (hypertension, coronary heart disease, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease [COPD], history of malignancies and/or chemotherapy during the last 6 months).

A specific questionnaire, constructed by the investigators of this study specifically for this purpose, was used and included the following: Firstly, patients were asked if they had the influenza vaccine in the periods 2019/20 and 2020/21 and if so, whether they had a disease flare that could be linked to vaccination. If they haven’t been vaccinated, they were asked why that occurred; the following options were given: (a) believe that flu-vaccination is not helpful, (b) do not feel safe to have the vaccination, (c) was not suggested by their doctor (d) was not their priority, due to the covid pandemic (for 2020/21), (e) other reasons (including forgot to take the vaccine, previously allergic on vaccination etc.).

Comparisons were made between patients who were vaccinated and those who did not, in the two different time periods (2019/20 and 2020/21). Also, patients who did not take the vaccine in 2019/20, but decided to get vaccinated in 2020/21, were compared with those who did not change their vaccination behaviour.

The current study was conducted according to the Declaration of Helsinki and was approved by the Scientific Council of the hospital (No: 2020/14/4).

Statistics

Fisher’s exact and Mann–Whitney tests were used for categorical and continuous characteristics, respectively. Normality of data distribution was evaluated with Kolmogorov–Smirnov test. For parameters not normally distributed, results were expressed as median (range). Logistic regression analysis were performed using “vaccinated in the period 2019/20”, “vaccinated in the period 2020/21”, “vaccinated in both periods” as dependent variables, in three different models. Age, sex and parameters that demonstrated statistical significance in the univariate analyses served as independent variables. Statistical package SPSS 21.0 was used.

Results

Patient characteristics

In total, 1046 patients were called. From those, 1015 (97%) patients responded. They were 75% females, with a median (range) age of 58 (18–82) years and a mean disease duration of 7 (0.5–50) years (Table 1). The majority had inflammatory arthritides (59.6%) or connective tissue diseases (29.9%). Half of them were current or previous smokers. Their treatments and comorbidities are also shown in Table 1.

Vaccination rates, reported disease flares and reasons for non-vaccination

In the 2019–20 period, 76.0% (771/1015) of ARD patients were vaccinated against the flu while the respective figure climbed to 83.1% (843/1015) during the COVID-19 pandemic period (2020/21, \( p = 0.0001 \)). The respective rates
of self-reported disease flares after vaccination were < 1% (2019/20: 0.3%, 2/771, 2020/21: 0.7%, 6/843).

The main reasons for non-vaccination in these 2 time periods were the belief that this would not be helpful (2019–20: 36.9%, 2020–21: 32.6%, p = 0.41), the fear of side effects (2019/20: 27.5%, 2020/21: 30.2%, p = 0.58), the absence of a recommendation from the treating physician (2019/20: 35%, 2020/21: 12%, p = 0.0001) and other reasons including forgetfulness about the vaccination (2019/20: 18.9%, 2020/21: 23.8%, p = 0.22).

Comparison of patients’ characteristics between those who did and those who did not vaccinate

During the two consecutive time periods (2019/20 and 2020/21), older patients, those on biologics and those with certain comorbidities such as hypertension and diabetes mellitus were most likely to get vaccinated (Table 2). Similarly, comparing patients who were vaccinated in both time periods (2019/2021) (n = 774) with those who were never vaccinated (n = 145), it was recorded that the former were older, more commonly on biologics or had comorbidities like hypertension, diabetes and COPD (Table 3).

By multivariate analysis, it was found that vaccination was associated for both periods, assessed individually or combined, with age [2019/20: OR = 1.03 (95% CI 1.02–1.04), 2020/21: OR = 1.04 (95% CI 1.02–1.05), 2019/21: OR = 1.04 (1.02–1.05)] and treatment with biologics [2019–20: OR = 1.66 (95% CI 1.22–2.24), 2020/21: OR = 1.68. (95% CI 1.19–2.38), 2019/21: OR = 1.90 (1.30–2.77)].

Change in vaccination behaviour

Twenty-seven (2.7%) patients had the vaccine in 2019/20 but not during the COVID-19 period (2020/21). Only 7.4% did that because they thought that flu-vaccine was not their priority due to the COVID-19 pandemic. The most common reason was they forgot/had other reasons (63.0%) while the rest did not do it for safety concerns (18.5%), did not think that flu-vaccine was helpful (7.4%) and not recommended by their rheumatologist (3.7%).

On the other hand, 99 patients (9.8%) had their vaccine during the COVID-19 period but not in the previous year. These newly vaccinated patients compared to the patients that they did not change their vaccination behaviour (n = 889), were younger, had a shorter disease duration, were more frequently of higher education level and had less commonly hypertension (Table 4).

Discussion

Vaccination against flu is strongly recommended in patients with ARD [3]. The effect that COVID-19 could have had in flu-vaccination uptake has not been studied so far. This is the first study showing that in a real-world population with ARDs, coverage for flu vaccination has increased during the Covid-19 pandemic era. In fact, there was a statistically significant increase from 76 to 83.1%. In a recent survey of the Italian general population, the rate of those who were willing to get the flu vaccine the 2020/21 period was 44%, compared to 27% of individuals who had the vaccine in 2019/20 [13].

Table 1 Patient characteristics

| Patient characteristics | n  | SD  |
|-------------------------|----|-----|
| N                       | 1015 |     |
| Age (years), median (range) | 58 (18–82) |     |
| Females, n (%)          | 758 (74.7%) |     |
| Disease duration, years, median (range) | 7 (0.5–50) |     |
| Type of ARD, n (%)      | 605 (59.6%) |     |
| Inflammatory arthritis  | 304 (29.9%) |     |
| Connective tissue diseases | 20 (2.0%) |     |
| Auto-inflammatory diseases | 86 (8.5%) |     |
| Primary systemic vasculitides |      |     |
| Educational status, n (%) | 210 (20.7%) |     |
| 1st level               | 444 (43.7%) |     |
| 2nd level               | 361 (35.6%) |     |
| Employment status, n (%) | 176 (17.4%) |     |
| Unemployed              | 468 (46.1%) |     |
| Employed                | 371 (36.5%) |     |
| Retired                 |     |     |
| Smoking, n (%)          | 499 (49.2%) |     |
| Never                   | 268 (26.4%) |     |
| Previous                | 248 (24.4%) |     |
| Current                 |     |     |
| Therapy                 |     |     |
| Glucocorticoids, n (%)  | 371 (36.6%) |     |
| Non-biologics, n (%)    | 667 (65.7%) |     |
| Biologics, n (%)        | 575 (56.7%) |     |
| Co-morbidities          |     |     |
| Hypertension, n (%)     | 358 (35.3%) |     |
| Coronary artery disease | 64 (6.3%) |     |
| Heart failure, n (%)    | 18 (1.8%) |     |
| Diabetes mellitus, n (%) | 99 (9.7%) |     |
| Chronic Kidney Disease, n (%) | 67 (6.6%) |     |
| Chronic Obstructive Pulmonary Disease, n (%) | 44 (4.3%) |     |
| Neoplasia history, n (%) | 74 (7.3%) |     |
| Chemotherapy, n (%)     | 4 (0.4%) |     |

n number, SD standard deviation

Vaccination uptake

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The uptake of influenza vaccination varies across different countries and time periods, reflecting diversities in the studies’ design, health-system and culture differences, as well as the increasing awareness about vaccinations [14–17]. The majority of the studies, pertain RA, in which vaccination rates range from 25 to 90% [18]. In a registry-based study with RA patients a few years ago in Greece showed that the coverage for influenza vaccine was only 54% [19]. Also, recent studies investigating the vaccination rate in patients with other non-rheumatic chronic disorders showed that 40–55% were vaccinated [20, 21]. It seems, therefore, that campaigns ran by rheumatology societies about vaccinations have a significant effect in the care of ARD patients over the last years.

In concert with other studies [14–16], we found that vaccination uptake was higher by patients who have other comorbidities and by older people. Reassuringly, we found that younger people changed their behaviour for flu vaccination during the last year.

In addition, we found that only a small percentage of the patients (0.26–0.7%) experienced a flare of their disease after vaccination. This is consistent with most studies which have shown that although transient autoantibody development can be observed, flu vaccination did not alter disease activity in ARD patients [3, 22–25].

Regarding the reasons for non-vaccination in our study, the fear of adverse effects and the notion that the flu vaccine is not helpful were equally important. Noteworthy, one third of the patients, before the Covid-19 pandemic, were not vaccinated because this was not suggested by their doctor. This, however, has dramatically changed the last year. Lack of awareness and fear for flu vaccinations have been identified by other studies, focused in inflammatory arthritis, as major causes of non-vaccination in similar percentages (i.e. 20–30%, each) [16, 26].

Our study has certain advantages and limitations. It is a large, real-world study covering the whole spectrum of ARDs in contrast to other studies [14, 16]. Having that in mind, the high percentage of females (75%) in our cohort can be explained. In fact, the majority of patients with

| Table 2 | Comparison of patients’ characteristics between those who were vaccinated and those who did not, during the 2 vaccination periods (2019–20 and 2020–21) |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Age (years), median (range)                   | Yes (n=771)                                   | No (n=244)                                    |
| Female gender, n (%)                          | 60 (18–82)                                    | 50 (19–80)                                    |
| Disease duration (years), median (range)      | 571 (74.1)                                    | 187 (87.4)                                    |
| Type of ARD                                    | 7 (0.5–50)                                    | 6 (0.5–48)                                    |
| Vasculitis                                     |                                                |                                              |
| Higher Educational status, n (%)              | 253 (32.8)                                    | 108 (44.3)                                    |
| Unemployed, n (%)                             | 131 (17.0)                                    | 45 (18.4)                                     |
| Current smokers, n (%)                        | 186 (24.1)                                    | 62 (25.4)                                     |
| Therapy                                       |                                                |                                              |
| Glucocorticoids, n (%)                        | 287 (37.2)                                    | 84 (34.4)                                     |
| Non-biologics, n (%)                          | 514 (66.7)                                    | 153 (62.7)                                    |
| Biologics, n (%)                              | 450 (58.4)                                    | 115 (47.1)                                    |
| Co-morbidities                                |                                                |                                              |
| Hypertension, n (%)                           | 305 (39.6)                                    | 53 (21.7)                                     |
| Coronary artery disease, n (%)                | 55 (7.1)                                      | 9 (3.7)                                       |
| Heart failure, n (%)                          | 15 (1.9)                                      | 3 (1.2)                                       |
| Diabetes mellitus, n (%)                      | 85 (11.0)                                     | 14 (5.7)                                      |
| Chronic Kidney Disease, n (%)                 | 58 (7.5)                                      | 9 (3.7)                                       |
| Chronic Obstructive Pulmonary Disease, n (%)  | 40 (5.2)                                      | 4 (1.6)                                       |
| Neoplasia history, n (%)                      | 59 (7.7)                                      | 15 (6.1)                                      |
| Chemotherapy, n (%)                           | 4 (0.5)                                       | 0 (0.0)                                       |

Significant values (p < 0.05) are marked with bold.

n number, SD standard deviation
inflammatory arthritis and connective tissue diseases in our cohort, suffered from rheumatoid arthritis and systemic lupus erythematosus or scleroderma, respectively. In these diseases, female population predominates. Second, it is not registry-based but data were obtained from telephone-interviews. Said that it should be stressed that our questionnaire, was not externally validated, but it was specifically designed for this purpose by the investigators of this study. We acknowledge that our patients were followed in tertiary academic rheumatology clinics and therefore their adherence to national and international guidelines (including those for vaccinations) might be higher compared to the rest of the patient population. Finally, data for 2019/20 were retrospectively collected while there was no physician documented diagnosis of a disease flare.

In conclusion, we show that the flu vaccination rate increased significantly during the COVID-19 pandemic in a large, real-life cohort of patients with ARDs. This could have been in part due to the higher recommendation rate by their caring rheumatologists. These findings, although are temporally encouraging, emphasize the need for continuous campaigns aiming at increasing patients’ and physicians’ awareness about the benefits of vaccination.

### Table 3

|                          | Never vaccinated (n = 145) | Vaccinated at both time periods (n = 774) | *p*     |
|--------------------------|---------------------------|----------------------------------------|---------|
| Age (years), median (range) | 49 (21–80)                | 60 (18–82)                             | 0.0001  |
| Female gender, n (%)      | 109 (75.2%)               | 551 (71.1%)                            | 0.836   |
| Disease duration(years), median (range) | 7 (0.5–48)          | 7 (0.5–50)                             | 0.516   |
| Type of ARD               |                          |                                        |         |
| Inflammatory arthritis    | 81                        | 451                                    | 0.267   |
| Connective tissue diseases | 53                        | 216                                    |         |
| Auto-inflammatory diseases | 3                        | 15                                     |         |
| Vasculitis                | 8                        | 62                                     |         |
| Higher Educational status, n (%) | 57 (39.3%)         | 240 (31.0%)                            | 0.103   |
| Unemployed, n (%)         | 25 (17.2%)                | 127 (16.4%)                            | 1.000   |
| Current smokers, n (%)    | 46 (31.7%)                | 185 (23.9%)                            | 0.09    |
| Therapy                   |                          |                                        |         |
| Glucocorticoids, n (%)    | 44 (30.3%)                | 278 (35.6%)                            | 0.110   |
| Non-biologics, n (%)      | 94 (64.8%)                | 496 (64.1%)                            | 0.701   |
| Biologics, n (%)          | 64 (44.1%)                | 440 (56.9%)                            | 0.001   |
| Co-morbidities            |                          |                                        |         |
| Hypertension, n (%)       | 35 (24.1%)                | 335 (38.8%)                            | 0.0001  |
| Coronary artery disease, n (%) | 6 (4.1%)            | 54 (7.0%)                              | 0.207   |
| Heart failure, n (%)      | 3 (2.1%)                  | 15 (1.9%)                              | 1.000   |
| Diabetes mellitus, n (%)  | 7 (4.8%)                  | 84 (10.9%)                             | 0.016   |
| Chronic Kidney Disease, n (%) | 7 (4.8%)              | 58 (7.5%)                              | 0.294   |
| Chronic Obstructive Pulmonary Disease, n (%) | 2 (1.4%)          | 39 (5.0%)                              | 0.05    |
| Neoplasia history, n (%)  | 12 (8.3%)                 | 57 (7.4%)                              | 0.737   |
| Chemotherapy, n (%)       | 0 (0%)                    | 3 (0.3%)                               | 1.000   |

Significant values (*p* < 0.05) are marked with bold

### Authors’ contributions

GEF: study design, data analysis and interpretation, drafting the manuscript. GG: study design, data analysis and interpretation, revising the manuscript. JM: data acquisition, revising the manuscript. AA: data acquisition, data analysis and interpretation, revising the manuscript. V-KB: data acquisition, data analysis and interpretation, revising the manuscript. GE: study design, data acquisition, data analysis and interpretation, drafting the manuscript. KF: data acquisition, data analysis and interpretation, revising the manuscript. AK: data acquisition, data analysis and interpretation, revising the manuscript. EK: data acquisition, data analysis and interpretation, revising the manuscript. SP: data acquisition, data analysis and interpretation, revising the manuscript. MP: data acquisition, data analysis and interpretation, revising the manuscript. KT: study design, data acquisition, data analysis and interpretation, revising the manuscript. MGT: study design, data acquisition, data analysis and interpretation, revising the manuscript. DP: study inception, study design, data acquisition, data analysis and interpretation, revising the manuscript. DV: study inception, study design, data acquisition, data analysis and interpretation, revising the manuscript. PPS: study inception, study design, data acquisition, data analysis and interpretation, revising the manuscript.

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This study has not received any funding.

### Data availability

All data are presented in the manuscript. Further details are available at reasonable request.
Declarations

Conflicts of interest  The authors declare that they have no conflicts of interest.

Ethical approval  This study was conducted according to the Declaration of Helsinki and was approved by the Scientific Council of the “Laiko” hospital (No: 2020/14/4).

Informed consent  All patients have provided informed consent to participate into the study.

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