"CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST
DOCTORAL SCHOOL
FIELD OF MEDICINE

THE COVID-19 PANDEMIC, VACCINATION, AND AUTOIMMUNE DISEASES

SUMMARY OF THE DOCTORAL THESIS

PhD Supervisor:

PROFESSOR BĂICUȘ CRISTIAN RĂSVAN, MD, PhD

PhD Student:

PINTE LARISA

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List of published scientific papers

1.**Pinte L**, Caraiola S, Balaban DV, Badea C, Mazilu D, Ionescu GD, et al. Covid-19 impact and vaccination willingness among romanian patients with autoimmune/immune-mediated diseases. Healthcare (Switzerland). 2021 Dec 1;9(12):1707.
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1. The Fundamental Problem

The COVID-19 pandemic has posed major challenges to healthcare systems worldwide, generating unprecedented scientific interest in understanding the impact of infection and vaccination among vulnerable populations. Currently, it ranks fifth among the deadliest pandemics in history, with at least 1 million deaths and an estimated global death toll ranging from 7.1 to 36.5 million by the year 2025 [1,2].

Patients with autoimmune conditions undergoing immunosuppressive treatment represent a population group for which available data at the onset of the pandemic were limited. This context served as the primary motivation for the research initiative, which aimed to conduct a multidimensional investigation into the impact of SARS-CoV-2 infection and COVID-19 vaccination on individuals with autoimmune diseases in Romania.

COVID-19 vaccines use various technologies to stimulate the immune system to recognize and combat the SARS-CoV-2 virus, targeting primarily the Spike (S) glycoprotein, which is essential for the virus's entry into host cells [3].

The European Alliance of Associations for Rheumatology (EULAR) strongly recommends vaccination for patients diagnosed with autoimmune inflammatory rheumatic diseases, with the exception of live attenuated vaccines, arguing that the risk of infection associated with the absence of vaccination significantly outweighs the risk of a potential disease flare induced by vaccination [4], a position also supported by the American College of Rheumatology (ACR) [5]. Exacerbations of autoimmune diseases following vaccination have been documented in the context of certain vaccines, such as the recombinant shingles vaccine, the influenza vaccine, and the hepatitis B vaccine, being attributed to immune mechanisms or viral reactivation [6].

The relevance and novelty of the topic stem from the fact that, prior to the initiation of the present research, no published data were available in Romania regarding the clinical course of patients with autoimmune diseases in the context of the COVID-19 pandemic. Moreover, information on the safety and effects of SARS-CoV-2 vaccines in this patient group was extremely limited worldwide. The research thus aligned with international concerns and the recommendations of prestigious scientific organizations, such as EULAR and ACR, which have emphasized the need to gather robust evidence on this topic.

Based on clinical experience and interactions with patients suffering from autoimmune diseases, the main concerns they expressed regarding COVID-19 vaccination

centered around two major aspects: the increased risk of developing post-vaccination adverse reactions due to stimulation of an already hyperactive immune system, and the possibility of triggering an autoimmune disease flare as a result of additional immune activation. Moreover, the study was integrated into the work of a medical research team with expertise in autoimmune conditions, benefiting from multicenter collaborations and the support of patient communities.

2. Working Hypothesis

At the time of initiating this doctoral work, no specific national data were available regarding the impact of the COVID-19 pandemic on patients with autoimmune diseases in Romania.

Since the onset of the pandemic, a key milestone was the launch of global vaccination campaigns, starting on December 8, 2020 [7] , followed by the national rollout in Romania on December 27, 2020. The first vaccine administered was the Pfizer-BioNTech vaccine (BNT162b2), based on mRNA technology [8].

The introduction of vaccination with a product recently authorized by the Food and Drug Administration (FDA) for emergency use, starting in December 2020 [9], raised concerns among patients with autoimmune diseases. These concerns were heightened by the fact that phase 3 clinical trials, which formed the basis for vaccine approval, excluded this patient category, leaving the potential adverse effects of vaccination on these conditions unknown.

The personal contributions section of this doctoral thesis will focus on integrating the population with autoimmune diseases in Romania into the epidemiological context generated by the COVID-19 pandemic. The study addressed two major directions: 1. The prevalence and severity of SARS-CoV-2 infection among patients with autoimmune diseases, offering insight into the direct impact of the pandemic on this vulnerable group; 2. Post-vaccination manifestations, analyzed both in terms of vaccine reactogenicity in the autoimmune population and the general population, as well as in terms of the effects on the underlying autoimmune disease activity.

3. The General Objectives Outlined in the Subchapters of the Personal Contributions Section

The first study presented the results of a multicenter research project based on the application of a questionnaire, which aimed to assess the impact of the COVID-19 pandemic on individuals with autoimmune diseases in Romania. The study highlighted access to medical services during the first year of the pandemic, the prevalence of SARS-CoV-2 infection, the severity of disease forms, and the approaches used to manage the condition.

The second and third studies focused on SARS-CoV-2 vaccination in patients with autoimmune diseases. They explored both attitudes toward vaccination and the factors associated with vaccination intent - including the level of information and the sources used - as well as the prevalence of vaccination and the types of vaccines administered within the studied cohort. The research aimed to identify post-vaccination adverse reactions reported after each dose, estimate the time interval until their onset, and correlate these findings with the patients' clinical and demographic characteristics, underlying disease, and immunosuppressive treatment. A key objective was the evaluation of the potential risk of autoimmune disease flares (increased disease activity) following COVID-19 vaccination. Patients were monitored over a median period of 6 months per patient. In addition, the studies included the description of a particular case of adult-onset Still's disease occurring in a previously healthy patient after the first dose of an mRNA vaccine, which was managed at the study center [10].

To outline future research directions regarding patients with autoimmune diseases and chronic immunosuppressive treatments, in the context of mRNA-based vaccines - a rapidly evolving and continuously refined technology - the final chapter of this thesis included a systematic analysis of the protocols of interventional clinical trials registered on the most comprehensive clinical trial databases. The objectives were: to identify the exclusion criteria applied to patients with autoimmune diseases and immunosuppressive therapy; to analyze in detail the rationale behind these decisions (including dosage, duration, and timing of immunosuppressive treatment discontinuation prior to study enrollment); and to document the types of autoimmune conditions currently being investigated in studies using mRNA-based compounds, whether non-replicating or self-amplifying. The research also included a comparison between cell-based and non-cell-based delivery systems and correlated the data on immunosuppressive treatment

discontinuation with current international guidelines regarding COVID-19 vaccination in vulnerable populations [11].

4. The General Methodology of the Research

A substantial part of this research was based on a multicenter study conducted in two phases: initially, a cross-sectional study, followed by a prospective cohort study.

The **cross-sectional study** relied exclusively on data provided by patients through the completion of a questionnaire and captured their perspective on the first year of the COVID-19 pandemic, particularly in terms of access to medical care. Additionally, a subgroup of patients infected with the SARS-CoV-2 virus was selected, and the course of infection was analyzed in the context of their underlying autoimmune condition and ongoing immunosuppressive treatment.

The **prospective cohort study** was conducted using the same group of patients with autoimmune diseases who agreed to be contacted for a maximum period of 6 months, in order to allow for subsequent monitoring of their underlying disease activity. Based on their SARS-CoV-2 vaccination status, the cohort was divided into two groups (vaccinated and unvaccinated). Patients were contacted by phone every two months over a median follow-up period of 6 months per patient, to enable a comparative assessment of the incidence of disease flares.

Both types of studies used a questionnaire as the main data collection tool, which was internally developed and validated at the center where the study was initiated (Colentina Clinical Hospital, Bucharest), with additional data obtained through follow-up telephone interviews with the patients.

Given the epidemiological context at that time, the questionnaire was distributed in a hybrid format - online (using the Survey Monkey platform [12]) and in physical form.

The enrollment process was carried out over a period of 3 months, between **February 5 and May 7, 2021**, with patients being enrolled consecutively, regardless of the method of questionnaire distribution (hospital setting or online).

The following criteria were used for the selection of participants for study enrollment:

Inclusion criteria:

-Patients with autoimmune diseases, regardless of the type of condition or associations between conditions, and regardless of disease activity;

-Age ≥ 18 years;

-Patients who agreed to participate in the study by signing the informed consent form (for the paper-based version), or who checked and validated their consent prior to accessing the questionnaire content (for the online version).

Exclusion criteria:

-Refusal to sign the informed consent form (regardless of the method of questionnaire distribution);

-Failure to complete the field corresponding to the name of the autoimmune disease;

-Duplicate entries (applicable to questionnaires distributed online).

For the online questionnaires, in cases where more than 50% of the required information was missing, additional exclusion criteria included the absence of contact details or an incorrect phone number. If more than 50% of the questions had at least one recorded response, patients were excluded only if age or gender data were missing.

An additional exclusion criterion was applied for enrollment in the prospective cohort study, excluding participants receiving immunosuppression for oncological conditions or post-transplant care.

At the time of completing the questionnaire, participants were asked to provide their personal phone number, which was used both as an identification number (ID) in the study database and as a means of contact for follow-up throughout the duration of the study.

The online questionnaire was distributed within closed groups of patients affiliated with autoimmune/immuno-mediated disease associations, where membership typically required a verification mechanism imposed by the group administrator. However, to further ensure the authenticity of respondents, each individual who completed the online survey was contacted by phone after submitting their responses. Participants who could not confirm the autoimmune condition reported in the questionnaire or who provided answers considered suspicious during the call were classified as not having autoimmune/immuno-mediated diseases and were excluded from the study.

Given the hybrid system of questionnaire dissemination, the study was conducted in accordance with the recommendations outlined in the 'Checklist for Reporting Results of Internet E-Surveys' (CHERRIES) [13].

Additionally, we adhered to the reporting guidelines for observational studies, given the study’s prospective observational component: the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [14].

Ethical considerations for study enrollment

The study was conducted in accordance with the General Data Protection Regulation (GDPR) of the European Union, in effect since May 25, 2018, and was approved by the Ethics Committee of Colentina Clinical Hospital (the coordinating center of the study) – Decision No. 3/08.02.2021.

Informed consent was obtained from all subjects enrolled in the study.

Data collection for study development and participant group allocation

The questionnaire items were structured into four sections (one section for general data and three sections addressing targeted topics A–C). Initially, questions were used to collect data on demographic characteristics, as well as the history and treatment of the underlying autoimmune disease. Subsequently, the focus shifted to the participants' attitudes toward vaccination (both seasonal influenza and SARS-CoV-2), as well as their SARS-CoV-2 immunization status at the time of enrollment.

For patients who had received at least one dose of the vaccine prior to enrollment, in addition to completing the questionnaire and confirming their vaccination status, respondents were given access to an additional section (Section D). This section was designed to collect general information about the vaccination process, as well as data regarding post-vaccination adverse reactions and their impact on the activity of the underlying autoimmune disease.

Patients were divided into two groups (vaccinated and unvaccinated) and were monitored by telephone at two-month intervals to identify post-vaccination adverse reactions, the timing of their onset, and correlations with the clinical profile, treatment regimen, and the initial attitude toward vaccination [15].

The primary variable analyzed was the time interval until the occurrence of an autoimmune disease flare. In addition, the analysis included an assessment of the incidence of flares within the two study groups - vaccinated and unvaccinated patients [16].

Given the subjectivity of patients' perception of their general condition and the fact that disease activity monitoring was conducted exclusively through telephone interviews, without direct clinical evaluation in a hospital setting, the flare of the underlying autoimmune disease was defined as a combination of clinical and/or paraclinical events, in order to increase diagnostic accuracy in the absence of physical examination. Thus, any flare was defined as typical symptoms indicating increased disease activity accompanied

by at least one of the following criteria: a) hospitalization; b) systemic inflammation and biological markers specific to the underlying disease (documented through laboratory tests); and/or c) adjustments to treatment (increase in dosage or frequency of baseline therapy, change to a more potent immunosuppressive agent, or addition of another immunosuppressive drug) [16].

Patients were considered lost to follow-up if: a) they withdrew their consent to participate in the study; or b) they did not respond to two consecutive phone follow-up calls, including the final scheduled call.

Questionnaire Validation Methodology

The validation of the questionnaire was carried out through successive stages, including face validity assessment, pilot testing on a sample of patients, question adjustment, evaluation of repeatability, and calculation of the intraclass correlation coefficient (ICC) [17]. The resulting reliability ranged from moderate to high (ICC between 0.64 and 1), which was considered appropriate for the pandemic context.

Sample Size Calculation

Assuming an estimated flare incidence of 5% in the control group, we calculated a required sample size of 868 patients to detect at least a twofold increase in incidence in the vaccinated group, with an alpha error of 5% and a beta error of 20%. [16].

Data Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA) and Microsoft Excel 2018 (Microsoft Corporation, USA).

Categorical variables were presented as number and percentage, and correlations between them were analyzed using the Chi-square test. Numerical variables that did not follow a Gaussian distribution were expressed as median (minimum, maximum) and compared using the Mann-Whitney U test.

A p-value < 0.05 was considered statistically significant.

Variables associated with a p-value ≤ 0.1 were included in multivariable models using binary logistic regression to identify associated factors.

Time to flare in the two groups was compared using the Log-Rank test in the bivariate analysis and the Cox proportional hazards model in the multivariable analysis [16].

In the multivariable model, variables associated with flares at a p-value ≤ 0.10 were included, and regression was performed using the backward stepwise selection method to identify potential suppressor factors [16, 18].

Materials and methods employed in the systematic synthesis

Protocol development, search strategy, and selection process for relevant Clinical Trials

The protocol for the systematic review was developed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [19] and Cochrane [20] guidelines. It was registered on the PROSPERO platform (CRD42024544811).

To identify relevant clinical trial protocols, a systematic search was conducted without restrictions on language or recruitment status, using the International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov (CTG), the Cochrane Central Register of Controlled Trials (Cochrane Library), as well as the official websites of Pfizer and Moderna. A PICO-based search strategy was adapted for each registry: '(RNA) OR (messenger RNA) OR (mRNA) OR (replicon RNA) OR (repRNA) OR (dendritic cell non replicating RNA)', with the most recent update performed on May 8, 2024 [11].

For the selection of trials, the following inclusion and exclusion criteria were applied:

Inclusion criteria: protocols of clinical trials registered regardless of trial status or publication status of the results; inclusion of adult patients (aged over 18 years); administration of mRNA-based compounds (both non-replicating mRNA and self-amplifying mRNA), regardless of the delivery system used; regardless of the type of condition for which the intervention was applied.

Exclusion criteria: experimental studies without human subjects or studies that detected the presence of RNA in various biological preparations; observational study protocols; clinical trial protocols based on other types of RNA [11].

Data extraction

For each eligible protocol, the database was structured according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines [21], with detailed information extracted regarding study design, inclusion or exclusion of patients with autoimmune diseases, and use of immunosuppressive therapy. The studies were subsequently classified by type of mRNA, delivery system, purpose, and targeted condition, and their current status was updated to enable a relevant interpretation of the results [11].

Strategy for synthesizing extracted data and statistical analysis

A descriptive synthesis of the extracted data (as previously mentioned) was performed. The data were grouped according to the type of mRNA and the delivery and administration system, as well as by the targeted pathology and the purpose of the intervention.

Results were reported as absolute numbers and percentages, and to determine the statistical significance of comparisons, p-values were calculated using the Chi-square test for two and three variables (MedCalc software) [22].

5. Synthesis of the Results

5.1 The Impact of the COVID-19 Pandemic on the Population with Autoimmune Diseases in Romania

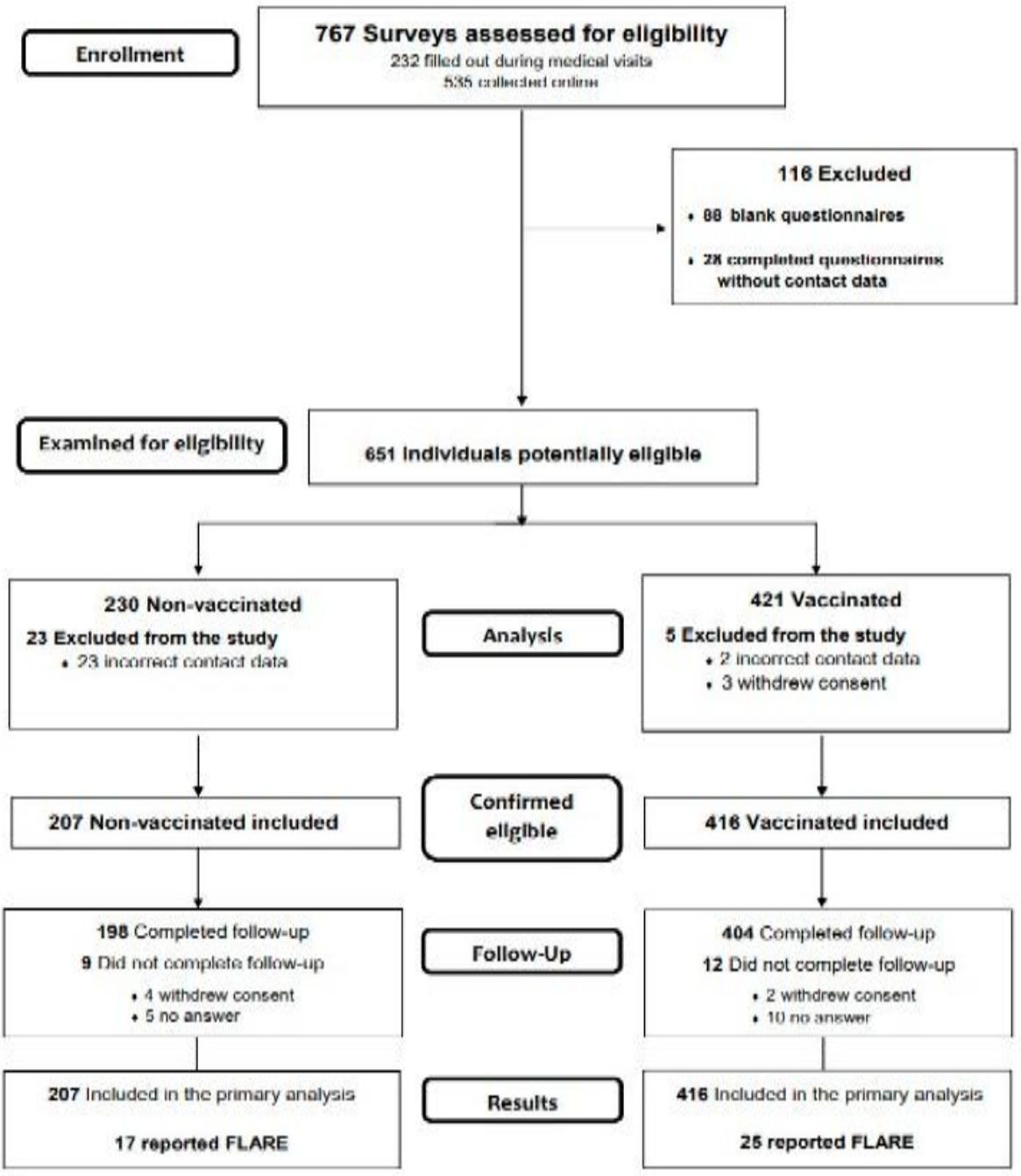

Figure 5.1. Flowchart of the study describing the methods: participant recruitment, inclusion and exclusion criteria, vaccination status, and disease flares [15]

Respondent Characteristics

A total of 767 questionnaires were collected, of which 232 were completed during medical visits at the study centers, and 535 were completed online. After excluding patients according to the previously mentioned eligibility criteria, 651 patients with autoimmune diseases were enrolled in the study for analysis. The patient selection flowchart for enrollment is detailed in Figure 5.1.

The entire analyzed sample had a median age of 49 years (range 19–88), with the majority of participants being women, representing 84% (546 out of 651) of the total.

From the perspective of interaction with the healthcare system, all participants (100%) responded to this question. The majority, 79% (511 out of 651), reported no direct professional connection to the healthcare field. The remaining participants indicated either direct involvement in the medical system or a connection through their close social circle: 6% (43/651) were physicians, 5% (29/651) were nurses, and 10% (68/651) reported having contact with the healthcare system through friends or acquaintances.

Of the 651 patients included in the study, 411 (63.13%) were diagnosed with systemic rheumatologic autoimmune diseases [15].

Within the studied sample, the most common autoimmune condition identified was autoimmune thyroiditis, affecting 140 patients (22%), followed by rheumatoid arthritis, present in 104 patients (16%), and systemic lupus erythematosus (SLE), diagnosed in 99 patients (15%). Sjögren's syndrome was identified in 80 patients (12%), and ankylosing spondylitis in 69 patients (11%). Other frequently reported conditions included psoriatic arthritis (55 patients, 8%), inflammatory bowel disease (IBD) (44 patients, 7%), systemic sclerosis (SSc)/CREST (31 patients, 5%), and myasthenia gravis (30 patients, 5%).

Antiphospholipid syndrome (APS) was reported in 26 patients (4%), multiple sclerosis in 25 patients (4%), and autoimmune liver diseases in 21 patients (3%). Systemic vasculitides—including Behçet's disease (3/20), granulomatosis with polyangiitis (5/20), microscopic polyangiitis (3/20), giant cell arteritis (5/20), Takayasu arteritis (1/20), polyarteritis nodosa (1/20), Henoch-Schönlein purpura (1/20), and cryoglobulinemia (1/20)—and celiac disease each affected 20 patients (3%). Dermatomyositis/polymyositis was diagnosed in 12 patients (2%) [15]. Other rarer autoimmune conditions reported by the participants are graphically represented in Figure 5.2.

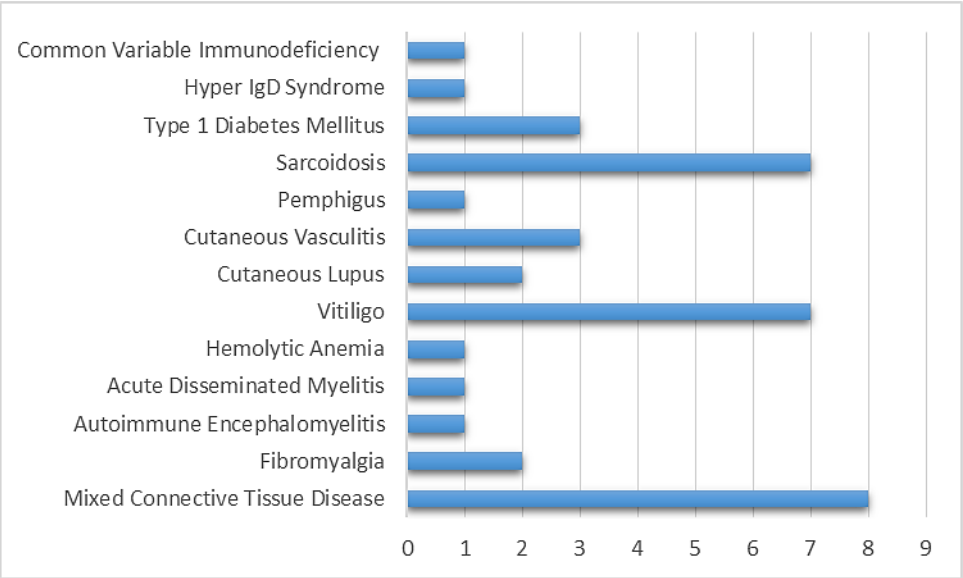

Figure 5.2. Number of patients with low-prevalence autoimmune diseases in the analyzed cohort.

Most patients enrolled in the study reported a single autoimmune disease, accounting for 79% (513 out of 651) of the total. The remaining patients reported having two autoimmune diseases in 17% (109/651) of cases, while 4% (29/651) reported three or more concurrent autoimmune diseases [15].

Regarding baseline treatment, 22% of participants (144/651) reported corticosteroid use, while 38.09% (248/651) mentioned systemic non-biologic immunosuppressive therapies, and 21% (133/651) received biologic treatments [15]. In terms of the frequency of systemic immunosuppressive treatments used, most subjects reported chronic treatment with hydroxychloroquine (HCQ), used by 21% of patients (137/651), followed by methotrexate, administered to 11% (72/651), sulfasalazine (8%, 50/651), and leflunomide (3%, 21/651) [15]. Less frequently used immunosuppressive treatments included azathioprine, administered to 7% of patients (46/651), mycophenolate mofetil (3%, 18/651), and cyclophosphamide at 0.3% (used as induction therapy by 2 participants) [15].

Regarding the question about the time interval between the diagnosis of the autoimmune disease and the moment of study enrollment, the response rate was 97.85% (637/651). Among the respondents, nearly one-third (31%, 195/637) reported being diagnosed with an autoimmune disease within the last 5 years, and 4% (27/637) were diagnosed during the previous year (2020) [15]. Within the analyzed cohort, 43% of patients (275/637) had a history of autoimmune disease lasting more than 10 years.

From the perspective of associated comorbidities, 50% of the patients included in the study (324/651) presented at least one concomitant non-autoimmune condition. The most common comorbidities identified were: mild liver diseases in 51 patients (7.83%), uncomplicated diabetes mellitus in 42 patients (6.45%), chronic respiratory disease in 40 patients (6.14%), and heart failure in 35 patients (5.38%) [15]. The numerical distribution of comorbidities is presented in Figure 5.3.

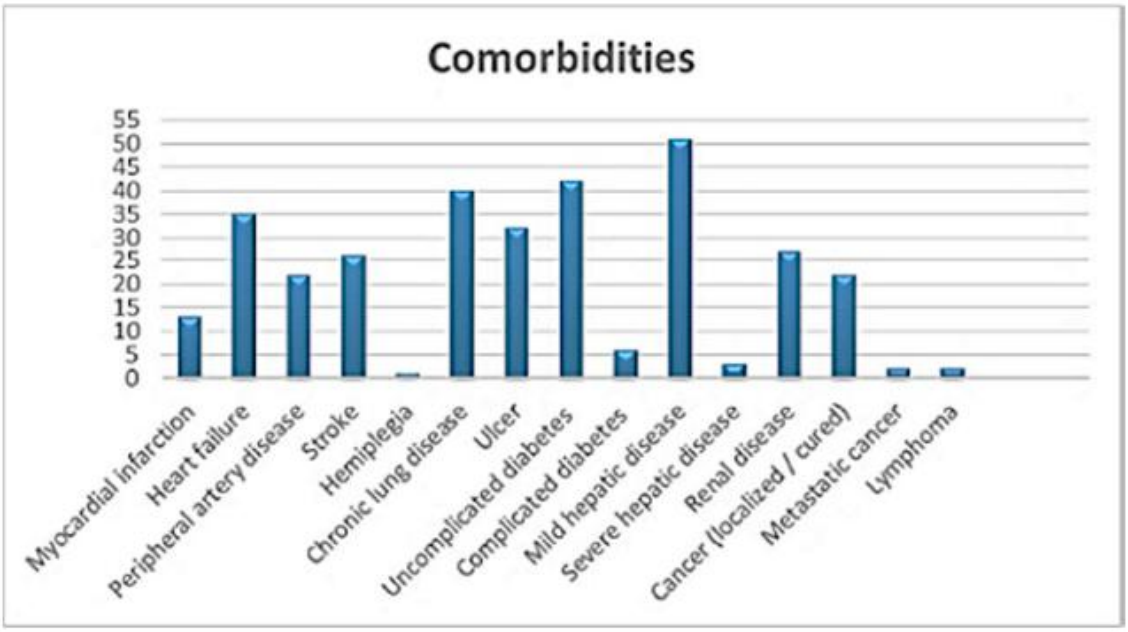

Figure 5.3. Comorbidities reported in the analyzed patient cohort.

Access to medical care in Romania during the pandemic

Of the 651 patients included in the study, 98.5% (641/651) provided at least one response to the question regarding access to medical care during the first year of the COVID-19 pandemic.

More than half of the respondents (53%, 339/641) reported difficulties in obtaining medical care since the onset of the pandemic, with the most common reason being the conversion of the hospital where patients were usually treated into a COVID-19 Support Center, as mentioned by 37% of them (126/339) [15].

Among the respondents who reported difficulties in obtaining medical care (339/641), 174 indicated fear of contracting the SARS-CoV-2 virus during medical visits as the main reason for avoiding or postponing access to care [15], representing a major factor of reluctance. In 35% of cases (120/339), the reported difficulties in accessing

medical services were independent of the hospital's status as a COVID-19 Support Center, suggesting the presence of complex barriers to healthcare delivery during the pandemic. Additionally, 12% of respondents (41/339) considered scheduling appointments difficult due to restrictions and overburdening of the healthcare system [15].

The remaining patients (47%, 302/641) did not report difficulties in accessing medical care during the first year of the COVID-19 pandemic [15].

Only a small percentage of patients believed that the hospital they usually attended continued its activities without changes during the pandemic, representing 12% of respondents (80/641). On the other hand, 4% of patients (24/641) reported having to change their attending physician to ensure continuity of medical care [15].

The comparative analysis between the group of patients who postponed medical visits and those who did not showed no significant difference regarding the time interval from autoimmune disease diagnosis ($p = 0.14$) or the time interval from the last disease flare to study enrollment ($p = 0.48$).

SARS-CoV-2 infection in subjects with autoimmune diseases – Prevalence and clinical course

Half of the respondents (331/651, 51%) voluntarily underwent at least one test for SARS-CoV-2 detection. Only 26% (167/651) of the study participants reported symptoms that could have suggested COVID-19. Additionally, despite being symptomatic, 4% (23/651) of participants avoided testing due to fear of mandatory hospitalization if they tested positive [15].

By the time of study enrollment, 135 respondents (135/651, 21%) had been diagnosed with COVID-19 at least once. The group of patients who tested positive consisted of 114 women and 21 men, with a median age of 47 years and an age range between 19 and 84 years [15].

The only significant correlation between the type of immunosuppressive treatment and a positive SARS-CoV-2 infection diagnosis was observed in patients treated with leflunomide (42.9% vs. 20%, $p = 0.017$). Patients receiving leflunomide as baseline therapy exhibited a higher infection rate with SARS-CoV-2 compared to those on other treatments, with a relative risk of 2.14 (95% CI: 1.28–3.60).

Only 19% (26/135) of patients diagnosed with COVID-19 were hospitalized. During hospitalization, 11 out of 26 required oxygen therapy, of whom four were transferred to the

intensive care unit. A significant proportion of hospitalized patients (6/26, 23%) believed that their COVID-19 course did not warrant hospitalization [15].

In the analyzed cohort, hospitalization for COVID-19 was significantly associated with a history of stroke (16% vs. 0%, p = 0.001), leflunomide treatment (19.2% vs. 3.7%, p = 0.013), and diagnoses of autoimmune diseases such as rheumatoid arthritis (26.9% vs. 8.3%, p = 0.015) and antiphospholipid syndrome (15.4% vs. 1.8%, p = 0.013).

5.2. COVID-19 vaccination among the population with autoimmune diseases

Compared to women, men were more willing to get vaccinated (OR: 1.8, 95% CI: 1.1–3, p = 0.015) [15]. Patients who completed the questionnaire during evaluations conducted at the participating hospitals exhibited significantly greater vaccine hesitancy (OR: 0.5; 95% CI: 0.36–0.71; p < 0.001) compared to those who responded to the questionnaire electronically [15]. Although a significant difference was observed in the sex distribution of patients based on the method of questionnaire completion—with men predominantly completing the form during hospital evaluations (OR: 3; 95% CI: 1.9–4.44; p < 0.001) [15]—no significant differences were found regarding age (p = 0.09) or Charlson comorbidity index (p = 0.066) in relation to their vaccination intent. Vaccination intent was significantly lower among patients with systemic lupus erythematosus (13.3% vs. 19.4%, p = 0.031) and systemic sclerosis (3.6% vs. 7.3%, p = 0.036), but significantly higher in those with autoimmune thyroiditis (24.7% vs. 14.1%, p = 0.001). Additionally, systemic corticosteroid use was associated with reduced vaccination intent (17.9% vs. 30.1%, p < 0.001).

In logistic regression, factors associated with an increased likelihood of vaccination were male gender (OR: 2.01, 95% CI: 1.2–3.7, p = 0.001), the patient's belief that they were well-informed (OR: 3.2, 95% CI: 2.1–6.01, p < 0.001), advice from the attending physician to get vaccinated (OR: 2.1, 95% CI: 1.3–3.5, p < 0.001), and a positive attitude toward influenza vaccination (OR: 1.5, 95% CI: 1.1–2.3, p < 0.001) [15]. Factors associated with a decreased likelihood of vaccination included completing the survey during hospital evaluations (OR: 0.44, 95% CI: 0.31–0.67, p < 0.001), a history of COVID-19 (OR: 0.7, 95% CI: 0.34–0.95, p = 0.02), and the opinion that patients with autoimmune diseases have a higher risk of post-vaccination adverse reactions (OR: 0.7, 95% CI: 0.53–0.89, p = 0.001) [15].

Half of the respondents (51%, 320/631) considered themselves at increased risk compared to the general population, while the rest either did not take into account the risk of adverse reactions or disease flare (23%, 144/631), or felt they could not self-assess their risk (26%, 167/631) [15].

However, more than half (58%, 184/320) of those who believed the vaccine could impact the activity of their autoimmune disease were willing to take the risk and get vaccinated [15].

Regarding influenza vaccination history, the response rate to this question was 95.85%. Of the 624 respondents, 59% (366/624) had never been vaccinated against influenza, 15% (93/624) vaccinated annually, 14% (84/624) vaccinated generally but not annually, while 5% (31/624) reported frequent vaccination. Additionally, 42 patients who had not opted for influenza vaccination before the pandemic decided to receive the influenza vaccine prior to COVID-19 vaccination [15].

General data on SARS-CoV-2 vaccination in the analyzed cohort

After collecting 651 eligible questionnaires, a total of 623 patients consented to be included in the next phase of the study. Of these, by the end of the study, 416 were vaccinated and 207 were unvaccinated [16].

The vaccinated group was mainly composed of patients enrolled online (71.9%, 299/416), the majority being women (81.5%, 339/416), with a median age of 50 years (ranging from 21 to 88). The unvaccinated group largely consisted of patients enrolled during hospital evaluations, mostly women (88.4%, 183/207), with a median age of 48 years (ranging from 19 to 73) [16].

The types of COVID-19 vaccines administered were Pfizer-BioNTech (86%), Oxford/AstraZeneca (9%), Moderna (3%), and Janssen/Johnson & Johnson (2%).

No differences were observed between the two groups (vaccinated and unvaccinated) regarding age, comorbidities, number of associated autoimmune diseases, time since autoimmune disease diagnosis, or occurrence of flares in the year prior to vaccination/enrollment. The presence of autoimmune rheumatic and musculoskeletal diseases (AIRD) was associated with a lower rate of SARS-CoV-2 immunization. In terms of autoimmune disease type, vaccination rates were significantly lower among patients with systemic lupus erythematosus (11.5% vs. 23.7%, $p < 0.001$) and systemic sclerosis

(3.4% vs. 8.2%, p = 0.011), while patients with autoimmune thyroiditis had a higher vaccination rate (26.2% vs. 13.5%, p < 0.001). Regarding baseline immunosuppressive medication, systemic corticosteroids, DMARDs, and azathioprine were associated with a lower rate of COVID-19 immunization. Additionally, vaccinated patients reported a significantly lower median daily corticosteroid dose compared to unvaccinated patients (6.25 [5, 20] vs. 10 [3, 45], p < 0.001).

More than half of the participants (60.7%, 250) had already received the first vaccine dose prior to enrollment in the study [16]. Given that the majority of patients opted for mRNA-based vaccines, no correlations were performed between the type of vaccine administered and variables such as age, gender, type of autoimmune disease, baseline treatment, or type of comorbidities according to the doses administered.

Types of vaccines administered and their reactogenicity

Although the majority of patients chose to be vaccinated with Pfizer (BNT162b2), 2% of patients opted for the Johnson & Johnson vaccine. Among these, one patient had systemic lupus erythematosus, one had systemic sclerosis, one had rheumatoid arthritis, one had autoimmune thyroiditis, two patients had a history of inflammatory bowel disease, and another patient had a combination of rheumatoid arthritis and Sjögren's syndrome.

Regardless of the dose, the main symptoms reported after vaccination were pain at the injection site, fatigue, headache, chills, arthralgia, and myalgia. Except for one patient who developed an anaphylactic shock after the second dose, no other major or life-threatening adverse events were observed. The adverse reactions were self-limiting, without requiring hospitalization or modification of baseline immunosuppressive therapy [16].

Adverse effects following the administration of the first dose

Regarding the correlation between post-vaccination adverse reactions and patient gender, women reported a higher rate of adverse reactions compared to men (76.2% vs. 62.3%, p = 0.011). Significant differences were also observed between age categories and adverse reactions (p = 0.002) among patients who experienced at least one adverse reaction following the administration of the first dose.

A correlation was also observed between the mode of enrollment and the occurrence of adverse reactions, with patients enrolled online reporting a higher rate of adverse reactions (76.3% vs. 66.7%, p = 0.031).

No differences were found regarding pulmonary involvement in the context of autoimmune disease or the presence of single versus multiple autoimmune diseases and the occurrence of at least one type of adverse reaction after the administration of the first dose.

Regarding the types of adverse reactions, no significant differences were observed between the group of patients with rheumatologic autoimmune diseases and those with other types of autoimmune conditions. However, when correlating each type of autoimmune disease included in the vaccinated patient cohort with the reporting of at least one adverse reaction, the only statistically significant difference was a lower rate of adverse reactions in patients with multiple sclerosis (47.1% vs. 74.8%, p = 0.016).

The type of baseline immunosuppressive treatment demonstrated an influence on the rate of adverse reactions, with patients undergoing biologic therapy experiencing a lower incidence of adverse reactions (62.9% vs. 76.8%, p = 0.007). Additionally, no significant differences were found based on history of COVID-19 (78.7% vs. 72.5%, p = 0.171).

Adverse effects following the administration of the second dose

Of the patients who received the first vaccine dose, 97.84% (407/416) chose to complete the immunization schedule by receiving the second dose.

Patients enrolled online reported a higher incidence of adverse reactions after receiving the second dose compared to those enrolled during medical visits (71% vs. 51.3%, p < 0.001).

Regarding the correlation between gender and the occurrence of adverse reactions, women reported a higher incidence than men (68.5% vs. 51.9%, p = 0.005), and patient age was also significantly associated with the occurrence of at least one adverse reaction following the administration of the second dose (p = 0.004).

Regarding the types of adverse reactions, the only significant difference between patients with rheumatologic autoimmune diseases and those with other autoimmune conditions was a higher prevalence of local pain after the second dose in the group without rheumatologic autoimmune diseases.

A significant proportion of patients who reported at least one adverse reaction after the first dose also reported adverse reactions after the second dose (76.5% vs. 34.5%, p <

0.001), while another subset of patients experienced adverse reactions exclusively after the administration of the second dose.

5.3. Disease Flares

A total of 651 questionnaires were considered potentially eligible, and after eligibility assessment, 623 patients—416 vaccinated and 207 unvaccinated—were included in the study.

In the vaccinated patient group, 31 participants (7.5%) reported temporary discontinuation of baseline treatment prior to vaccination, aiming to optimize the immune response, as recommended by their attending physician [16]. No difference was observed in the risk of flare between patients who interrupted their treatment and those who did not (4/31 vs. 21/385, $p = 0.105$) [16].

The median follow-up was 180 days (min = 8, max = 246): 187 days (8, 246) for vaccinated patients compared to 170 days (16, 237) for unvaccinated patients, $p < 0.001$ (16).

During the monitoring period, a total of 42 flares were reported: 25/416 (6%) in the vaccinated group and 17/207 (8%) in the unvaccinated group, $p = 0.302$.

Additionally, there was no significant difference in the occurrence of flares based on the type of COVID-19 vaccine administered: Pfizer-BioNTech (19/359, 5%), AstraZeneca (4/37, 11%), or Moderna (2/12, 17%), $p = 0.43$ [16].

Three of the 25 flares were reported after receiving the first dose, while the rest occurred after the second dose. The 3 flares reported after the first dose began on days 8, 10, and 12 post-vaccination, respectively. Sixteen percent (4/25) of the flares started on day 2, 16% (4/25) between days 14–21, and 56% (14/25) occurred 21 days after administration of the second dose.

The duration of flares was less than 7 days in 30% of patients, between 8 and 21 days in 22% of patients, and longer than 30 days in 48% of patients. However, there was no significant difference in the median duration of flares between the two groups: 30 days (4, 149) in vaccinated patients and 27.5 days (14, 164) in unvaccinated patients, $p = 0.803$ [16].

The incidence densities of flares in the vaccinated and unvaccinated patient groups were 1.16 and 1.72 per 100 patient-months, respectively (p = 0.245, Log-Rank test) [16].

In the bivariate analysis, flares were associated with the presence of more than one immune condition, baseline corticosteroid therapy, and a history of a flare prior to vaccination (the variable used was flare in the previous year). In the Cox model, only the occurrence of a flare during the previous year was associated with the occurrence of a flare after vaccination (OR [95% CI]: 2.64 [1.17–5.97]) [16].

5.4. Autoimmunity as an Exclusion Criterion in Clinical Trials Involving mRNA-Based Compounds

After removing duplicates and applying eligibility criteria, a total of 608 clinical trial protocols investigating the use of mRNA technology as a therapeutic intervention were included in the final analysis, out of an initial 2,818 identified protocols [11].

General Characteristics of Included Clinical Trial Protocols

Of the 608 eligible protocols analyzed, the majority (66.6%) targeted infectious diseases, with COVID-19 accounting for 51.3% of all included protocols and 77% of the protocols addressing infectious diseases. The remaining studies primarily focused on oncology (177 protocols, 29.1%), with a significant proportion addressing melanoma and solid tumors, while a smaller number of studies (26 protocols, 4.3%) were directed towards other types of conditions [11].

Autoimmune Diseases as an Exclusion Criterion in Interventional Clinical Trials

Approximately two-thirds of registered protocols (60.8%) for studies using mRNA as an intervention excluded patients with autoimmune diseases. Among those that applied this exclusion criterion, the majority of studies (75.7%) excluded patients based solely on the diagnosis of autoimmune disease, regardless of disease activity, without providing additional justification for the exclusion decision. The remaining protocols specified additional criteria (24.3%), related to disease activity (22.2%) and the time since the last

disease flare (2.2%). Only six clinical trial protocols focused specifically on autoimmune diseases were identified, all aiming to evaluate the post-vaccination immune response to mRNA-based SARS-CoV-2 vaccines in patients with such conditions [11].

Systemic Immunosuppressive Treatments as an Exclusion Criterion in Clinical Trials

Approximately 30% of the analyzed protocols excluded patients based on the duration of **systemic immunosuppressive treatment** prior to enrollment, the majority (95.7%) being studies focused on infectious diseases that excluded patients under chronic immunosuppression (>14 days). In over half of the protocols (56.5%), the main exclusion criterion was the time interval since discontinuation of immunosuppressive treatment. Additionally, preventive studies excluded immunosuppressed patients at a significantly higher rate compared to therapeutic studies (68.6% vs. 29.5%, $p < 0.001$). The most frequently reported exclusion intervals following discontinuation of immunosuppressive treatment were 6 months (63.5%), followed by 3 months (13.9%) and 1 month (9.0%) [11].

Corticosteroid therapy was mentioned as an exclusion criterion in 54.4% of the analyzed protocols, with variable dosage thresholds ranging from physiological doses (5 mg prednisone/day) to high immunosuppressive doses (1 mg/kg/day). The most commonly used limit was 10 mg/day of prednisone (45.9%). Most studies (93.3%) considered a 14-day interval as the minimum safe period for participant inclusion. Regarding treatment discontinuation intervals prior to enrollment, the most frequently encountered periods were 6 months (47.9%), 1 month (16.5%), and 3 months (15.7%). Preventive studies imposed corticosteroid restrictions significantly more often compared to therapeutic studies (87.6% vs. 57.3%, $p < 0.001$) [11].

Administration of **immunoglobulins** prior to vaccination was an exclusion criterion in 41.1% of the protocols. The most frequently used exclusion interval following immunoglobulin administration was 3 months (73.2%). Preventive studies applied this criterion significantly more often compared to therapeutic studies (61.8% vs. 1.9%, $p = 0.015$) [11].

6. Conclusions and Personal Contributions

10.1. Personal Contributions

The research began with an analysis of access to medical services during the first year of the COVID-19 pandemic, highlighting that over 50% of patients with autoimmune diseases faced difficulties, mainly due to hospitals being converted into COVID support centers. (Chapter 6.3.2, paragraphs 2–3)

The analysis of the prevalence and severity of SARS-CoV-2 infection in patients with autoimmune diseases showed a predominance of mild forms, with rare hospitalizations and favorable outcomes. A significant association was identified between treatment with leflunomide and testing positive for SARS-CoV-2. (Chapter 6.3.3, paragraphs 7–8)

Despite EULAR's recommendations regarding the vaccination of patients with autoimmune diseases, the vaccination rate in Romania remained suboptimal due to conflicting medical advice and fears of disease exacerbation after vaccination. The lack of specific studies and the innovative nature of mRNA vaccines further amplified hesitancy, while vaccine immunogenicity was not a major concern for patients. (Chapter 7.3.1, paragraphs 3–6)

Two-thirds of respondents expressed an intention to get vaccinated, and among them, more than half had already received the first dose before enrollment. The intention to vaccinate was significantly higher among participants enrolled online compared to those evaluated in hospitals. Factors that supported the intention to vaccinate included male gender, confidence in one’s own information, the recommendation of the treating physician, and a positive attitude toward flu vaccination. In contrast, hesitancy was mainly driven by fear of adverse reactions, distrust in vaccine efficacy, and a personal history of COVID-19. More than half of the patients perceived an increased risk of adverse reactions due to their autoimmune conditions, but the majority accepted this risk and chose to be vaccinated. Communication with the treating physician was frequent and had a positive influence on the vaccination decision. The history of flu vaccination was variable, with most patients not having a regular immunization background; however, the pandemic context led some to choose flu vaccination before COVID-19 vaccination. (Chapter 7.3.1, paragraphs 7–12)

The majority of patients were vaccinated against SARS-CoV-2, primarily with the Pfizer-BioNTech vaccine. The vaccination rate varied depending on the autoimmune disease, being lower in lupus and systemic sclerosis and higher in autoimmune thyroiditis. Immunosuppressants and higher doses of corticosteroids were associated with a lower rate of immunization. (Chapter 7.3.2, paragraphs 3–5)

The most common adverse reactions were local pain, fatigue, headache, chills, arthralgia, and myalgia. Only one case of anaphylactic shock was reported; otherwise, the reactions were mild and self-limiting. (Chapter 7.3.3, paragraphs 1–12)

The use of Methotrexate (for the second dose) and biological therapies (for both doses) was associated with fewer adverse reactions. Patients with rheumatoid arthritis and psoriasis reported fewer reactions, possibly due to immunosuppressive treatment. (Chapter 7.3.1, paragraphs 1–6; Chapter 7.3.2, paragraphs 1–7)

Previous studies reported the incidence of flares only in vaccinated patients, without a control group. The present study compares, for the first time, with an unvaccinated cohort and includes an average follow-up of 5.9 months.

In the vaccinated group, 7.5% of patients temporarily discontinued background therapy prior to vaccination, with no significant impact on flare risk (4/31 vs. 21/385, $p=0.105$). The median follow-up duration was 187 days for vaccinated patients and 170 days for unvaccinated patients ($p<0.001$). A total of 42 flares were reported: 6% in the vaccinated group and 8% in the unvaccinated group ($p=0.302$). No significant differences were identified between vaccine types in terms of flare risk ($p=0.43$). The incidence densities of flares in the vaccinated and unvaccinated patient cohorts were 1.16 and 1.72 per 100 patient-months, respectively ($p=0.245$, Log-Rank test). (Chapter 8.3.1, paragraphs 1–7)

In the bivariate analysis, flares were associated with the presence of more than one immune-related condition, background corticosteroid therapy, and the existence of a flare prior to vaccination (using the variable “flare in the past year”). In the Cox model, only the occurrence of a flare in the previous year was associated with the appearance of a flare after vaccination. (Chapter 8.3.1, paragraphs 8–10)

At the time the research was conducted, approximately two-thirds (60.8%) of registered protocols for studies using mRNA-based interventions **excluded patients with autoimmune conditions**. Among those that applied this exclusion criterion, the majority of studies (75.7%) excluded patients solely based on the diagnosis, regardless of disease activity and without providing further justification for the exclusion. The remainder

specified additional criteria (24.3%), related to autoimmune disease activity (22.2%) and the latency from the last disease flare (2.2%). Only six clinical trial protocols focused specifically on autoimmune conditions were identified, all aiming to evaluate the post-vaccination immune response to anti–SARS-CoV-2 mRNA vaccines in patients with such diseases. (Chapter 9.3.5, paragraphs 1–3)

Approximately 30% of the analyzed protocols excluded patients based on the duration of prior **immunosuppressive treatment** before enrollment, with the majority (95.7%) being studies focused on infectious diseases that excluded patients under chronic immunosuppression (>14 days). In over half of the protocols (56.5%), the primary exclusion criterion was the time interval since discontinuation of immunosuppressive treatment. Additionally, preventive studies excluded immunosuppressed patients at a significantly higher rate than therapeutic studies (68.6% vs. 29.5%, $p<0.001$). The most frequently reported exclusion intervals were 6 months (63.5%), followed by 3 months (13.9%) and 1 month (9.0%). (Chapter 9.3.6, paragraphs 1–8)

Corticosteroid therapy was listed as an exclusion criterion in 54.4% of the analyzed protocols, with variable dosage thresholds ranging from physiological doses (5 mg prednisone/day) to high immunosuppressive doses (1 mg/kg/day). The most commonly used cutoff was 10 mg/day of prednisone (45.9%). The majority of studies (93.3%) considered a 14-day interval as the minimum safe period for participant inclusion. Regarding the exclusion intervals applied, the most frequently encountered were 6 months (47.9%), 1 month (16.5%), and 3 months (15.7%). Preventive studies imposed restrictions on corticosteroid therapy significantly more often than therapeutic studies (87.6% vs. 57.3%, $p<0.001$). (Chapter 9.3.6, paragraphs 9–15)

The administration of immunoglobulins prior to vaccination was an exclusion criterion in 41.1% of the protocols. The most commonly used time interval as an exclusion criterion after immunoglobulin administration was 3 months (73.2%). Preventive studies applied this criterion significantly more frequently than therapeutic studies (61.8% vs. 1.9%, $p=0.015$). (Chapter 9.3.6, paragraph 16)

Of the 608 eligible protocols analyzed, the majority (66.6%) targeted infectious diseases, with COVID-19 accounting for 51.3% of all protocols included in the analysis and 77% of those focused on infectious diseases. The remaining studies primarily addressed oncological pathology (177 protocols, 29.1%), while a smaller number of studies (26 protocols, 4.3%) focused on other types of conditions. (Chapter 9.3.1, paragraph 1)

10.2. Conclusions

The strength of the study lies in the fact that it is the first to describe the characteristics of SARS-CoV-2 infection in patients with autoimmune diseases. The number of enrolled COVID-19 cases is comparable to that reported by Romania in the EULAR and SECURE-IBD registries. Although aimed at rare pathologies, the study benefits from a large sample size, which supports the validity of the statistical analysis and allows the identification of relevant associations even for low-prevalence conditions.

A substantial limitation of the study concerns the assessment of SARS-CoV-2 infection within the analyzed cohort. Although our results may suggest that the course of COVID-19 was generally mild, only patients who survived would have been able to complete the questionnaire; therefore, we cannot draw conclusions regarding survival. We did not have access to population-based registries to accurately assess the mortality rate among COVID-19 patients with associated autoimmune diseases.

The main limitation of this study was the use of a convenience sample, which is likely not fully representative of the entire population of patients with autoimmune diseases. Except for the patients recruited directly from clinics during medical evaluations, the remaining participants had internet access and/or were members of patient associations, thus likely representing individuals with a higher level of education.

Another limitation of the study was the potential selection bias, given that the majority of enrolled respondents already had a favorable attitude toward vaccination. Consequently, the results obtained may not be generalizable to the entire population of patients with autoimmune diseases.

From the perspective of flare analysis, this study was limited by its observational design and the heterogeneous convenience sample obtained through the enrollment of patients with a wide range of autoimmune diseases. Certain systemic autoimmune conditions—such as systemic lupus erythematosus, systemic sclerosis, and autoimmune thyroiditis—were more frequently represented in the unvaccinated group, reflecting disproportionate vaccine exposure within these subgroups. However, this distribution does not affect the validity of the results, as the analysis focused on comparing the risk of flares regardless of the prevalence of autoimmune diseases in the two groups. An important limitation of the study is the lack of sufficient statistical power to draw specific conclusions for diseases with a small number of included patients. Nevertheless, the results

can be considered representative of the general population with autoimmune diseases, which was the primary objective of this research.

This chapter provides significant contributions to shaping the future outlook of mRNA technology, with applicability both in the context of COVID-19 vaccination and beyond. It represents the first original approach to the current state of ongoing research, aiming to assess the degree of representation of a vulnerable category of patients—those with autoimmune conditions and immunocompromised individuals—within clinical trials.

To further explore the complexity of the link between autoimmunity and COVID-19 vaccination, the hypothesis of de novo autoimmune reactions emerging post-vaccination is currently under investigation. For this purpose, we conducted an extensive systematic review of the international scientific literature (including both databases and "grey literature") to identify large-scale pharmacovigilance population studies evaluating the incidence of autoimmune conditions following mRNA vaccination in previously healthy individuals.

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