Review

Influence of the COVID-19 Pandemic on the Treatment of immune mediated Rheumatic and Musculoskeletal Diseases during the first pandemic period: A Systematic Review

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Review

Influence of the COVID-19 Pandemic on the Treatment of Immune Mediated Rheumatic and Musculoskeletal Diseases during the First Pandemic Period: A Systematic Review

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Abstract: Background and Objectives: The COVID-19 pandemic influenced the management of patients with immune mediated rheumatic and musculoskeletal diseases (imRMDs) in various ways. The goal of our systematic review was to determine the influence of the first period of the COVID-19 pandemic on the management of imRMDs. Materials and Methods: Systematic literature search of PubMed, Cochrane and Embase databases, including studies with adult patients on the influence of the COVID-19 pandemic on management of imRMDs. There were no restrictions regarding to study-design except for systematic reviews and case reports that were excluded as well as articles on the disease outcomes in case of SARS-CoV-2 infection. Two reviewers screened the studies for inclusion, and, in case of disagreement, consensus was reached after discussion. Results: A total of 5969 potentially relevant studies were found, and, after title, abstract and full-text screening, 35 studies were included with data from 182'746 patients and 2018 rheumatologists. Non-availability of drugs, e.g., hydroxychloroquine and tocilizuab, was frequent (16–69% of patients). Further, medication non-adherence was reported among patients with different RMDs and between different drugs in 4–46% of patients. Changes to preexisting medication were reported in up to 33% of patients (e.g. reducing dose of steroids or cessation of biological disease-modifying antirheumatic drugs). Physical in-office consultations and laboratory testing decreased and as a consequence newly implemented remote consultations increased greatly with an increase of up to 80%. Conclusion: The COVID-19 pandemic influenced the management of imRMDs, especially at the beginning. Influences were wide-ranging, affecting availability of pharmacies, adherence to medication or medication changes, doctor visits and laboratory testing. New systems of care were set up, including virtual clinics and video consultations. These new forms of health care delivery should be spread and implemented worldwide to routine clinical practice to be ready for future pandemics.

Keywords: COVID-19; pandemic; influence; rheumatic diseases; treatment

1. Introduction

In 2019 the novel coronavirus SARS-CoV-2 was identified in China and spread rapidly over countries, causing a worldwide pandemic (1–5). Initially regarded as primarily affecting the lungs, corona virus disease 19 (COVID-19) is now known to be a multisystemic infectious disease that affects different organ systems (6). The course of COVID-19 ranges from mild, to severe and critical cases (depending on risk factors) often requiring intensive care (7).

Patients with immune-mediated rheumatic and musculoskeletal diseases (imRMD) are at higher risk of infections especially due to the use of immunosuppressive medication. The pandemic has therefore raised concerns amongst rheumatologists, especially regarding immunocompromised patients. Data from 2021 show that the risk for infection with SARS-CoV-2 is not increased (8) or is only slightly (9) elevated in patients with imRMDs compared to the general population, but, if infected, the risks for hospitalization or for a severe disease course are increased (7). Most

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conventional synthetic (csDMARD), biological (bDMARD) and targeted synthetic disease modifying antirheumatic drugs (tsDMARDs) do not seem to increase the risk of infection with SARS-CoV-2 or the risk of poor outcomes of COVID-19, exceptions being glucocorticoids > 10 mg/day, rituximab, mycophenolate mofetil (MMF) and, potentially, Janus kinase inhibitors (JAKi) (9).

The disease course of patients with imRMDs and SARS-CoV-2 infection has been studied widely, but systematic reviews describing the influence of the pandemic on the treatment of imRMDs are lacking.

The aim of this systematic review is to describe the influence of the COVID-19 pandemic on the management of imRMDs on adherence and changes in medications, on the access to rheumatological care and medications and on the use of other health care delivery forms.

2. Materials and Methods

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (10) . A comprehensive search was carried out in PubMed, Cochrane and Embase databases regarding publications from 01.12.2019 to 31.10. 2021. We used specific MeSH headings and additional keywords to identify studies (see search strategy in Appendix 1).

We selected articles in English or German including adult patients with imRMDs that evaluated the influence of the COVID-19 pandemic on the general management of imRMDs (Influence on adherence or changes in medications), on the access to rheumatological care and medications, and on the use of other health care delivery forms.

There were no restrictions regarding to study-design except for systematic reviews and case reports that were excluded as well as articles on the disease outcomes in case of SARS-CoV-2 infection. Studies found were screened independently by two reviewers (MS, SBa) for inclusion. In the first phase the studies were screened for title and abstract, followed by full-text screening and data extraction. In case of disagreement, consensus was reached after discussion between the two raters. Quality rating was performed according to the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (11). Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) (12) was used as the literature management program and Zotero (Corporation for Digital Scholarship, Fairfax, USA) as reference management software (13). Because no randomized controlled trials were published and data were very heterogenous no meta-analysis was performed. Out of the included studies two clusters of “influences of COVID-19 pandemic” were formed and analyzed further regarding: (i) medical management of imRMDs; (ii) health care in general regarding imRMDs.

3. Results

Study Selection

The search strategy identified 5969 potentially relevant studies. Based on title and abstract and after removal of duplicates, 155 studies were assessed in full-text screening. A final total of 35 studies with data from 182’746 patients and from 2018 rheumatologists were included in the systematic review. Figure 1 shows the study flow.

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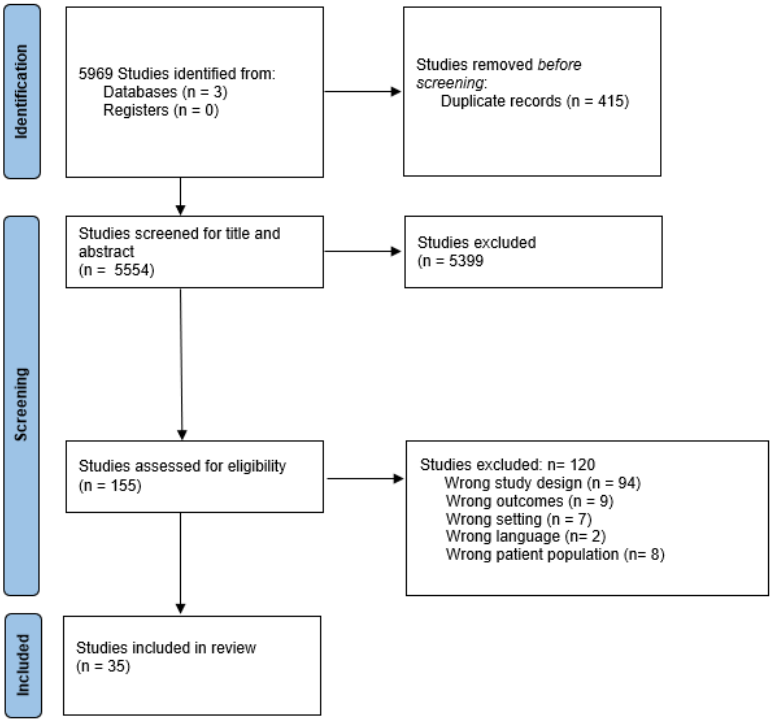

Figure 1. Study flow diagram according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 [15].

Study characteristics and levels of evidence

The majority of included studies were surveys or questionnaires (14–47), which are evidence grade IV according to the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (11). One was a cohort study, graded level III (48). Seventeen studies were from Europe (15,16,18,19,21,22,24,28–31,37,39,41,42,46,47), three from Africa (14,17,34) , ten from North America (23,25–27,33,35,36,38,45,48,49) and five from Asia (20,32,40,43,44). Details of the included studies are shown in Table 1.

Outcomes

1) Influence on the medical management of imRMDs

Non-availability of rheumatic medication was a prevalent issue, important examples being hydroxychloroquine (HCQ) and tocilizumab. Shortages or difficulties in the availability of HCQ was an issue in 16–69% of patients (14,15,17,20,23,30,47), with the highest level reported from India (20). Shortages of tocilizumab was reported in 14% of patients (45,47).

Non-adherence to prescribed drugs was another issue. Non-adherence was defined in the different studies very heterogeneously as changing of medication, adaptation of dose or interval without professional health advice or as stopping of medication or irregular intake of medication without professional health advice. The overall non-adherence rate among all included studies was 4–46% of patients (16,26,29–32,43). High rates of non-adherence were reported by four studies (20,21,24,33), with the highest level (46% of patients) reported from India (20). The second highest level of non-adherence (almost 40% of patients) was reported from North America (33). A Swiss study (16) comparing medication adherence of patients with different imRMDs before and during the pandemic found only slight adherence reductions. A significant increase in non-adherence was only seen in patients with axial spondyloarthritis (axSpA) (13% medication non-adherence in pre-COVID-19 period versus 20% during the first wave, P = 0.003). The lowest level of medication non-adherence was reported from Denmark (21). In this study, compliance with medication was compared between

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the start of the first lockdown to three months later, when society was gradually reopened. Low levels of non-adherence were reported (4-6% at the start of the lockdown versus 2-4% three months later).

The drugs mostly changed or stopped were bDMARDs and JAKi (28,32). Low-dose prednisolone and csDMARDs were the least likely medications to be stopped. Longer disease duration of the underlying rheumatic disease and higher disease activity were significantly associated with medication discontinuation (19). Disease flares were described in high proportions of the patients (63-74 %), who had stopped their DMARDS (15,18).

Regarding different rheumatologic diseases, a study from India (43) found that 43% of patients with inflammatory arthritis, 31% with systemic lupus erythematodes (SLE), and 13% with inflammatory myositis and scleroderma ($P < 0.05$) stopped their treatment. Further detailed information regarding non-adherence to, or non-availability of medication is shown in Table 2.

Many studies reported reasons for changes in medication-taking. The following factors were significantly associated with change in at least one medication due to patients' fear of COVID-19 (21): male sex (odds ratio (OR) 1.51, 95% confidence interval (95% CI) 1.21–1.89), age >80 years compared to <39 years (OR 0.11, 95% CI 0.006–0.52), lower education (OR 0.56, 95% CI 0.45–0.69), being employed (OR 1.52, 95% CI 1.16–1.99), and use of bDMARDs (OR 1.86, 95% CI 1.02–3.81). Further, there was a direct correlation of incidence of SARS-CoV-2 infections in the general population and medication non-adherence: the higher the incidence of COVID-19, the lower the medication adherence (24).

Lastly, there was also an influence of the pandemic on the treating physician regarding medication. Rheumatologists reduced the dose of steroids in 23–36% of patients (14,47) and, in 17% of patients, steroids were stopped completely (14). In contrast, csDMARDs were stopped only rarely (in 2 % of patients) (14), whereas bDMARDs were stopped more frequently (in 33% of patients) (15). In a few cases drug application intervals of bDMARDs were extended (28). Moreover rheumatologists were hesitant to start a bDMARD in 75% (47) or a tsDMARD in 14% (14) of cases.

2) Influence on healthcare in general

Singh et al. (45) reported an increase in alternative types of visits to the rheumatologist related to COVID-19 compared to the pre-COVID-19 era, such as telephone visits (plus 53%), video-based Veterans Affairs Video Connect (VVC) visits (plus 44%) and clinical video tele-health (CVT) visits with a facilitator (plus 29%). Bos et al. (46) reported telephone visits to be the most commonly used form of remote consultation, with 80% of rheumatologists using exclusively telephone consultations. In-person visits were conducted only in special circumstances, such as for joint aspiration (46).

From the patients' perspective high levels of unwillingness to health care visits were reported (21–86%) (14,15,27,30,36). The highest levels with 86% of patients unwilling to attend the hospital were reported from Turkey (30). Inability to communicate with or to see the rheumatologist was also frequently reported by 7% (21) to 39% (20) of patients (17,20,21,25,30).

George et al. (27) and Banerjee et al. (36) reported avoidance of laboratory testing in 42% and 47% of patients, respectively. Patients with imRMDs were significantly less likely to avoid in-person visits (OR 0.79 (95% CI 0.70–0.89)) or laboratory tests compared to patients with non-autoimmune RMDs (35% versus 39%, OR 0.84 (95% CI 0.73–0.96) (26,48). Other factors associated with avoidance of in-person visits and laboratory testing were older age, low socioeconomic status, living in urban areas or in countries with higher COVID-19 activity and regarding medication receiving a bDMARD or JAKi (48).

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Table 1. Characteristics of included studies.

Study, Year, Country/World region	Study design	Reference number	Level of evidence	Research question	Population	Specific influence on the treatment/main outcome measures
Abualfadl et al. 2020 Egypt	Survey	34	IV	To determine the influence of the COVID-19 pandemic on patients with RA	1037 patients with RA aged 18 years and older	The following percentage of patients had difficulties obtaining their anti-rheumatic medication: hydroxychloroquine/ chloroquine (42%), methotrexate (6%), biologics (2%), leflunomide (1%))
Akintayo et al. 2021 Africa	Survey	14	IV	To identify changes in rheumatology service during the COVID-19 pandemic in Africa	554 questionnaires completed by rheumatologist	66% described shortage of hydroxychloroquine; 36% reduced corticoids; 16% stopped corticoids; 14% avoided start of biologics
Banerjee et al. 2020 USA	Survey	36	IV	To identify effects of COVID-19-pandemic on patients with vasculitis and especially their health related behaviour	662 patients with vasculitis	11% of all patients stopped their immunosuppressive therapy. 8% of patients temporarily discontinued rituximab. 13% reported avoiding receiving an infusion with rituximab. 6% of patients on < 10mg prednisone equivalent/ day and 11% > 10mg prednisone equivalent/ day stopped their medication. 66% of all patients avoided doctor's visits. 47% of all patients avoided laboratory tests. 46% of all patients had a telehealth visit.
Batibay et al. 2021 Turkey	Survey	15	IV	To determine how the COVID-19 pandemic affected routine care in rheumatology and if there were any changes in rheumatologic medication use	320 patients with different immune-mediated rheumatic diseases	16% had problems in getting hydroxychloroquine; 12% changed medication without advice; 33% interrupted bDMARDs with advice from their physician; 9% stopped bDMARDs on their own
Bos et al.2020 Netherlands	Survey	46	IV	To determine the influence of COVID-19 pandemic on the delivery of care using telemedicine for patients with rheumatic musculoskeletal disease from the perspective of rheumatologists in the Netherlands	75 members of the Dutch rheumatologist society were interviewed during 8–22 of May 2020	99% of the rheumatologists used telephone and 9% used video-consultations. More than 80% of the outpatient consultations were performed exclusively via telephone.

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Ciurea et al. 2021 Switzerland	Survey	16	IV	Adherence to anti-rheumatic drugs before and during the first COVID-19 wave	666 Patients with immune-mediated rheumatic diseases (RA, AxSpa and PsoA) compared pre-COVID and during COVID-19 wave.	20% of AxSpA patients were not adherent to anti-rheumatic drugs during the first COVID wave (versus 13% pre-COVID); regarding the other diseases only a slight non-significant increase in nonadherence was observed
Cornet et al.2021 Europe	Survey	39	IV	Availability of hydroxychloroquine during the first wave of COVID-19 pandemic	2075 patients with Lupus during the first wave of the COVID-19 pandemic registered in the Lupus Europe's patient advisory network	48% could get hydroxychloroquine from the first place they asked, 11% could get the drug by going to more than one pharmacy. 9% could not get any hydroxychloroquine during the first wave of the pandemic. During the second wave only 0.8% of patients could not get any hydroxychloroquine.
Coskun et al. 2021 Turkey	Survey	19	IV	To assess whether patients maintain their treatment for rheumatic conditions during the pandemic period (and determine the factors responsible for discontinuation)	278 patients with immune-mediated rheumatic diseases (ankylosing spondylitis (AS) and RA) from Turkey	Overall 22% of patients reduced or stopped treatment. 27% of the patients stopped bDMARDS. 5% stopped low-dose glucocorticoids, 4% stopped methotrexate.
Costantino et al. 2021 France	Survey	18	IV	Consequences of the pandemic on rheumatic disease management	655 Patients with immune mediated rheumatic diseases (AxSpA, RA, PsoA)	More than one-third of patients (34.2%) suspended or decreased the dosage of one drug. NSAIDs were the most commonly decreased medication (33.7% of patients), followed by bDMARDS (13.4%) and cDMARDS (10.1%).

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Dejaco et al. 2020 Austria	Survey	47	IV	To asses how the COVID-19 pandemic has affected decisions of rheumatologists	1286 rheumatologists have been questioned in 58 countries	82% of rheumatologists indicated cancellation or postponement of face-to-face visits of new patients. 91% indicated cancellations/ postponements in follow-up patients (with 96% offering remote consultation). 74% of rheumatologists indicated bDMARDS/tsDMARDS were less likely to be started during pandemic. 49% reported shortage of HCQ and consequently it had to be stopped in 10% of patients. 14% reported shortage of tocilizumab. 15% recommended decreasing and 2% stopping NSAID in asymptomatic patients. 23% recommended to decrease and 0.1% to stop glucocorticoids in asymptomatic patients
Ganapati et al 2021 India	Survey	20	IV	To assess the impact of COVID-19 on patients with chronic rheumatic diseases	1533 completed responses of patients with chronic rheumatic diseases (inflammatory and non inflammatory) across India	47% of patients were fully compliant to medication. 35% were partly compliant and 11% discontinued their medication. 90% of patients experienced difficulty in procuring medication. 69% of patients on hydroxychloroquine had difficulty getting it.
George et al. 2021 North America	Survey	27	IV	To learn about patient's concerns, healthcare disruption and use of telehealth as well as interruption in DMARDs.	1,517 participants with common immune-mediated rheumatic diseases (RA, PsoA, SpA, or SLE) representing all 50 states of the USA	15% of the patients without COVID-19 stopped their DMARDs, mostly on their own.

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George et al. 2021 USA	Survey	26	IV	To better understand the concerns and behaviors of patients with autoimmune rheumatic disease compared with patients without autoimmune rheumatic diseases	2319 patients with a non-autoimmune rheumatic disease and 6885 patients with an autoimmune rheumatic disease from America	10% of patients with autoimmune rheumatic disease stopped immunomodulatory medication. Patients on biologics or JAK-inhibitors were more likely to stop their medication than the other patients in the population (OR 1.53 (1.22-1.90). Patients with autoimmune disease were significantly less likely to avoid in-person visits (predicted probability 45.2% versus 51.0%, OR 0.79) and avoid laboratory tests compared to patients with non-autoimmune rheumatic diseases (34.9% versus 38.8%, OR 0.84). Patients who had a telemedicine visit were at greater risk of stopping a medication than those with an office visit (OR 1.54)
George et al. 2021 USA	Cohort study	48	III	Examination of trends in in-person versus telehealth visits versus cancelled visits during COVID-19 pandemic	126,550 patients extracted from the analytic cohort from the Columbus electronic health record data warehouse of the American Arthritis and Rheumatology Associates network during the year 2020	Overall follow-up visit volume decreased by 25% in the COVID-19 transition period but rebounded within a few months to pre-COVID-19 levels. Telehealth visits pre-COVID-19 were nearly non-existent and increased to 41% and 28% of all follow-up clinician visits in the COVID-19 transition period and after the first wave of the pandemic. 90% of telehealth visits were videobased, 7% by phone and 2% digital. Up to maximum of 60% of visits were cancelled during the COVID-19 transition period. The odds of starting a new biologic or JAKi therapy for an RA patient in the COVID-19 transition period in 2020 was substantially lower (adjusted odds ratio=0.55) compared to the corresponding 6-week period in 2019.
Glintborg et al. 2021 Denmark	Survey	21	IV	To explore self-protection and health behavior including adherence to disease-modifying anti-rheumatic treatment (DMARD) during the COVID-19 pandemic	12 789 patients with immune-mediated rheumatic diseases (RA, PsoA, AxSpA, connective tissue disorders)	With the beginning of the pandemic restrictions 4% of patients changed the dosage of csDMARDS, whereas 3 months later only 2% of patients did. With the beginning of the pandemic restrictions 6% of patients changed the dosage of bDMARDS, whereas 3 months later only 4% of patients did.

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Glintborg et al. 2021 Denmark	Survey	22	IV	To investigate if the pandemic affected the treat-to-target strategy as evaluated by disease activity and to evaluate access to physical consultations during the COVID-19 pandemic	7836 patients with immune-mediated rheumatic diseases (RA, PsoA or AxSpA) from Denmark	Glucocorticoid-injections decreased relatively by 16% in patients with rheumatoid arthritis and by 10% in patients with psoriasis arthritis. DMARDS had been altered in dose in 13% of patients compared to before the pandemic.
Guaracha -Basanez et al 2021 Mexico	Survey	33	IV	To determine the influence of the pandemic on health care interruption on the clinical status of the underlying rheumatic disease	670 patients with rheumatic diseases (mainly SLE and RA) in Mexico City	60% of patients were found to be compliant with the prescribed treatment. 51% experienced health care interruptions.
Gupta et al. 2020 England	Survey	42	IV	To determine the influence of the COVID19-pandemic on the health care of patients with myositis	608 patients with myositis from all over the world (mostly USA and England)	26% of patients faced hurdles in procuring medicines. 25% of the included patients were due for infusions, 22% of which had to delay treatment and 7% were still searching for an alternative. Of the patients who faced difficulty in getting their medication 10% were forced to stop treatment due to the situation. Scheduled physiotherapy sessions were disrupted in 35%. 26% experienced difficulty in contacting their specialist, and 5% were unable to do so.
Gupta et al. 2021 England	Survey	41	IV	To determine the influence of the COVID-19 pandemic on the health-care of systemic scleroderma patients	291 patients with scleroderma from all over the world	15.1% of the patients on steroids required an increase in dose in the current situation. 38.1% of respondents faced hurdles in procuring medicines. Of the 14.4% that were on infusions, 45% had to delay it. Physiotherapy sessions were disrupted in 25%. 7% could not contact their specialist, another 24% experienced difficulty contacting their specialist.
Hasseli et al. 2021 Germany	Survey	24	IV	The goal was to determine the influence of the SARS-CoV-2 lockdown on patients with immune-mediated rheumatic diseases on their adherence to immunomodulatory medication	4252 patients with immune-mediated rheumatic disease from Germany	Before the national lockdown 4% of the patients discontinued their medication. During and after the national lockdown reported discontinuations decreased to 2%.

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Hassen et al 2020 Saudi Arabia	Survey	32	IV	To understand the influence of the COVID-19 pandemic on health care behaviour of patients with immune-mediated rheumatic diseases	637 patients with immune-mediated rheumatic disease from Saudi Arabia	Worsening disease activity perception was significantly associated with poor medication adherence. 86% were adherent and 14% were not adherent to their anti-rheumatic medication. 30% altered their prescribed medication(s) either by decreasing, increasing, or interrupting the dosage. 48% had trouble obtaining their medication during COVID-19 outbreak.
Hausmann et al 2021 USA (survey was worldwide)	Survey	25	IV	To determine the influence of the COVID-19 pandemic on health care behaviour of patients with immune-mediated rheumatic diseases	9300 patients with inflammatory rheumatic diseases originating from 90 countries, mostly USA and Europe	82% continued their anti-rheumatic medications as prescribed. The remaining 18% of participants treated with anti-rheumatic medications discontinued at least 1 of their medications.
Ince et al. 2021 Turkey	Survey	37	IV	To determine the influence of COVID-19 pandemic on disease activity and medical treatment of patients with vasculitis	103 patients with vasculitis living in Turkey.	32% of patients missed at least 1 outpatient appointment. Attendance rate for appointments was higher among patients who used parenteral treatment in comparison to oral treatment. 5% of patients were non-compliant to their medication.
Kalyoncu et al. 2021 Turkey	Survey	28	IV	The goal was to determine the treatment adherence of patients with immune-mediated arthritis receiving b/s DMARDs	1394 patients with immune-mediated rheumatic diseases receiving either biologic- or synthetic DMARDS in Turkey	18% of all patients discontinued their bDMARDs, 32% of them on recommendation of the physician, 45% on their own demand. 14% of the RA patients and 21% of the SpA patients discontinued their bDMARDs. Among patients with RA etanercept was the least frequently discontinued bDMARD (5.4% of the patients), whereas tocilizumab was the most frequently discontinued (20.5% of the patients). In the SpA patient group, those who discontinued their bDMARDs were younger than those who did not (median age, 40 years versus median age, 44 years. 57% of the communications between doctor and patient were by phone. 77% of the patients, who were communicating with their physician, were recommended to continue bDMARD therapy.

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Kant et al. 2021 USA	Survey	38	IV	To determine the influence of the COVID-19 pandemic on the treatment and disease course of patients with ANCA-associated vasculitis	206 patients with ANCA-associated vasculitis from 2 centres (Baltimore (USA) and Lancashire (UK)	7% reduced medication dosage. 10% postponed maintenance rituximab infusion. 0% had regular in-person visit with physician. 69% had video visits with physician. 13% rescheduled clinic visits. 16% decreased blood collection frequency.
Kavadichanda et al. 2020 India	Survey	43	IV	To evaluate the feasibility of having teleconsultation among the socioeconomically marginalized sections of the society in India and the influence on medical treatment.	373 patients from India with rheumatologic musculoskeletal diseases	69% of patients continued the drugs based on previous prescriptions, 31% stopped them abruptly. 43% of patients with immune-mediated arthritis stopped their treatment abruptly compared to 31% of patients with SLE (31%) and 13% of patients with Inflammatory myositis or scleroderma. 90% found tele-rheumatology consultation easy to follow. 76% considered that tele-rheumatology was better than in-person consultation in circumstances of the pandemic. 16% felt that tele-rheumatology was not as good as in-person consultation.
Kavadichanda et al. 2021 India	Survey	44	IV	To evaluate the influence of COVID-19 Pandemic on access to healthcare of systemic sclerosis patients in India	336 patients with systemic sclerosis from India	Scheduled outpatient visit was missed by 92% of the patients. 22% skipped drugs. 53% missed laboratory testing. 24% faced problems with availability of medicines.
Mancuso et al 2021 USA	Survey	23	IV	To obtain detailed information about patients' experiences with their medications during the COVID-19 Pandemic	112 Patients with immune-mediated rheumatic diseases in New York City	11–14% of respondents reported self-imposed or physician-directed changes to medications. 61% of the patients treated with HCQ had difficulties obtaining it.

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Michaud et al. 2020 USA	Survey	35	IV	To assess the influence of COVID-19 pandemic on medical treatment of patients with RA in the USA	734 patients with RA in the USA	30% of patients reported medication changes. Changers more commonly used glucocorticoids (33% versus 18%) and less commonly used non-hydroxychloroquine-conventional DMARDs (49% versus 62%) pre-COVID. While JAK inhibitor use was associated with change (OR 1.9), only pre-COVID glucocorticoids remained a strong predictor (OR 3.0). bDMARDs (irrespective of mechanism of action) and JAK-inhibitor users reported stopping or delaying the intake of that DMARD more often than users of csDMARDs or hydroxychloroquine (16–18% versus 4–8%). Overall 4–7% could not obtain their medication. 10% of hydroxychloroquine users could not obtain it. Percentage of respondents who cancelled or postponed appointments was between 28% and 35%. 42% and 47% respectively of patients on non-TNF bDMARD or JAK-inhibitors reported switching to telehealth appointments. 34–36% of patients on hydroxychloroquine and other csDMARDs reported switching to telehealth. 31% of patients in the TNF bDMARD group reported switching to telehealth.
Murray et al. 2021 Ireland	Survey	29	IV	The goal of the survey was to assess COVID-19 status, rheumatic musculoskeletal disease diagnoses and adherence to rheumatologic medication	1381 patients with immune-mediated musculoskeletal diseases from Ireland	Adherence to anti-rheumatic medications was 84% and 57% were using health authorities guidelines for information on medication use. Adherence rates were higher amongst those who followed guidelines (89.3% versus 79.9%) and lower in those with COVID-19 symptoms (64.0% versus 85.1%).

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Rathi et al. 2021 India	Survey	40	IV	To assess the influence of COVID-19-pandemic on the treatment of SLE	1040 patients with SLE	36% of patients reported problems in getting their prescribed medicines due to lockdown. Of these 40% of patients needed to change their medication schedule due to this non-availability. 1% of patients had missed their scheduled cyclophosphamide dose due to either non-availability of drug or facility to provide intravenous infusion. 22% of patients faced difficulty in the availability of hydroxychloroquine. 54% of patients missed their scheduled follow-up visits during the lockdown period. 37% of patients were unable to get their investigations done due to closure of laboratories and hospitals.
Seyahi et al. 2020 Turkey	Survey	30	IV	The goal was to learn about the healthcare behaviour of rheumatic disease patients during COVID-19 pandemic	771 patients with rheumatic disease and as a control group 535 hospital workers, and 917 teachers/academic staff.	Overall 22% of the patients discontinued their medications. In patients with SpA 54% discontinued their medication. Biological DMARDS were the most frequent drugs whose doses were skipped or stopped: anti-IL-1 agents: in 40%, anti-TNF agents in 35%, interferon in 33%, tocilizumab in 29%, rituximab in 7% of the patients. Prednisolone (low dose), azathioprine, methotrexate, leflunomide, colchicine, and sulfasalazine were least likely (≤ 10% for each drug) to be skipped or stopped. 11% of the patients on hydroxychloroquine had to skip or stop the drug due to shortage or failure of prescription renewal. 86% of patients with rheumatic diseases were unwilling to go to the hospital. Only 14% of patients visited the outpatient clinic "as it was before", 43% "did not want to come", 28% "were advised to postpone their visits".
Singh et al. 2020 USA	Survey	45	IV	To assess the experience, views and opinions of rheumatology providers during the COVID-19 pandemic.	103 rheumatologists answering a survey	32% of responders reported a medication shortage. Shortage of hydroxychloroquine was reported in 45%, of IL-6 inhibitors in 15%, non-TNF biologics in 1%; Janus-inhibitors in 1%. An increase in 50% or more in the following types of visits related to COVID-19 were reported: (1) telephone visits, 53%; (2) video-based VA video connect (VVC) visits, 44%; and (3) clinical video tele-health (CVT) visits with a facilitator, 29%.

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Sloan et al. 2021 UK	Survey	31	IV	To assess the influence of the COVID-19-pandemic on medical care and health care behaviour of patients with SLE and other autoimmune rheumatic diseases	111 patients with autoimmune rheumatic diseases	10% of patients reduced or stopped their medication and 10% increased the dose of their medication without advice of their doctor. 70% reported that their appointments, tests and treatments had been cancelled more/much more frequently since the pandemic. Between 35% and 45% felt that care from GPs, rheumatologists and other specialists had been worse/much worse during the pandemic.
Ziadé et al. 2020 Arab countries (Levant, Gulf, North Africa)	Survey	17	IV	Influence of the COVID-19 pandemic on access to rheumatology care for patients with chronic rheumatologic diseases	2190 Patients with chronic rheumatic diseases from different Arab Countries	70% reported no negative effect on medication adherence; 18% described shortage of hydroxychloroquine, thereof 15% had to stop medication due to shortage; 8% stopped medication because of fear of infections

ARD = autoimmune rheumatic disease; AxSpA = axial spondyloarthritis; bDMARDS = biological disease modifying anti-rheumatic drugs; CQ = chloroquine; csDMARDS = conventional synthetic disease modifying anti-rheumatic drugs; GP = general practitioner; HCQ = hydroxychloroquine; NSAID = non-steroidal anti-inflammatory drug; OR = odds ratio; PsoA = psoriasis arthritis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SpA = spondyloarthritis; tsDMARDS = targeted synthetic disease modifying anti-rheumatic drugs.

Table 2. Rates of non-adherence and of difficulties obtaining medication regarding different immune-mediated RMDs.

Disease	Non-adherence to or discontinuation of medication (% of patients)*	Difficulties obtaining medication (% of patients)*
Inflammatory arthritis		
Rheumatoid arthritis	14% (bDMARDS) (27) 19% (29) 22% (DMARDS) (15) 23% (17) 25% (18)	42% (hydroxychloroquine) (33) 10% (hydroxychloroquine) (34) 4-7% (34)
Vasculitis		
Vasculitis in general	5% (36) 11% (35) 20% (29)	No information
Spondyloarthritis		
Spondyloarthritis in general	19% (18) 20% (DMARDS) (15) 21% (bDMARDS) (27) 38% (17) 54% (29)	No information
Psoriasis arthritis	19% (DMARDS) (15) 31% (17)	No information
Myositis		
Myositis in general	No information	26% (41) (myositis)
Connective tissue diseases		
overall	14% (29)	No information
SLE	No information	52% (hydroxychloroquine) (38) 29% (hydroxychloroquine) (39) 36% (39)

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Systemic sclerosis	22% (43)	38% (40) 24% (43)
Periodic fever syndromes		
Familial Mediterranean fever	15% (29)	No information

*If the number relates to a specific drug it is mentioned in brackets. Otherwise the number relates to non-adherence, discontinuation or difficulties obtaining medication in general (numbers in brackets=literature reference numbers).

4. Discussion

This systematic review showed that COVID-19 influenced health care behavior in patients, as well as in rheumatologists and other doctors. In many cases patients or doctors discontinued established medication. Further, the pandemic resulted in a collapse of supply chains, causing non-availability of medication, especially in the case of HCQ and tocilizumab. Healthcare appointments took place less frequently than usual and telehealth emerged as a solution, with remote consultations with physicians or with newly established telerehabilitation services.

Medication non-adherence was a common problem among patients. A possible explanation could be the low availability of remote consultations at the beginning of the pandemic, resulting in feelings of insecurity with patients stopping their medication as a self-management strategy. The classes of medication that were discontinued most frequently were bDMARDs and JAKi (26,30), possibly because these immunosuppressive medications are considered the most dangerous regarding infections.

Between different imRMDs, relevant differences in non-adherence to medication have been reported. Low numbers of non-adherence were reported in patients with vasculitis (37,38). Patients with vasculitis are usually aware of the disease course with serious relapses in the absence of maintenance therapy, which results in adherence to treatment (38). Another factor increasing medical compliance is that parenteral treatments are often only possible in the hospital setting and are therefore not postponed by patients.

The sudden discontinuation of anti-rheumatic therapy is a relevant issue, because it can lead to disease flares. A large proportion of patients with different imRMDs reported a flare after modifying their treatment (15,18). This supports the recommendation of not stopping treatment during the pandemic in situations other than suspected or confirmed SARS-CoV2-infection, because resulting disease flares and higher requirements for glucocorticoids could increase the risk of SARS-CoV-2 infection (36).

The pandemic, and mostly the fear of infection with SARS-CoV2, had a severe influence on the medication behavior of rheumatologists. A large proportion of rheumatologists reduced the dose or frequency of steroids (14,47,51), many changed DMARDs (14,22) or stopped them (14,15) and there was hesitancy to start new DMARDs (47,51).

N. Rebić et al. conducted a systematic review about the adherence to medication in patients with imRMDs (51) . They described non-adherence rates of 6.5- 34.2% and discontinuation rates of 2- 31.4% which are similar rates compared to the overall non-adherence rate of 4- 46% in our systematic review. They found slightly higher numbers of physicians who reduced the dose of steroids (23- 56 % v.s. 23-36% in our review) and they also reported of a reluctance to start bDMARDS or tsDMARDS.

Different non-compliance rates to medical visits were reported between the different studies (22,30). Patients with autoimmune RMDs were significantly less likely to avoid in-person visits and laboratory tests compared to patients with non-autoimmune rheumatic diseases (26,48). These results may be explained with the fact that patients with imRMDs needed close monitoring because of their disease as well as their immunosuppressive treatment and that the fear of an infection with SARS-CoV2 was a more dominant factor determining behavior. Interestingly a study from North America (48) reported a normalization of the rates of follow-up visits a few months after the start of the pandemic, suggesting a rapid adaptation of patients and doctors to the pandemic circumstances.

The COVID-19 pandemic posed many challenges, but it also opened new opportunities for the development of health care systems. Because of the environmental risk factors for acquiring a SARS-CoV2-infection before vaccines existed, practical steps to reduce the infection risk were introduced,

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including social distancing, hand hygiene and use of face masks (9). As a consequence of social distancing patient consultations were performed remotely whenever possible, leading to an increase in telehealth care. Prior to 2019 telehealth care was very rare or non-existent, but its use grew rapidly during the COVID-19 pandemic. Nevertheless, there were huge differences between different countries in the implementation of telehealth. Data from the USA and Australia showed an increase in telehealth, whereas data from India reported that only a small proportion of patients were aware that telehealth existed, and even fewer used it. It is likely that many patients with imRMDs, especially those from non-urban parts of emerging countries, had no access to telehealth care during the COVID-19 pandemic. A major goal of telehealth was to try to avoid disruption of health care and to prevent patients from stopping their medication. In addition, telephone and video-based consultations were preferred in "stable patients" with known disease course and without the need for changing immunosuppressive medication (45).

Strengths and Limitations

This study has several strengths. Although most studies were of low evidence grade (III or IV), data from 182'746 patients and 2018 interviewed rheumatologists were included. Together with the fact that studies from four different continents and different countries were included, these large numbers paint a global picture of the influence of the pandemic on imRMDs. The influence covers a broad spectrum of issues occurring during the COVID-19 pandemic, including compliance with medication, shortage of certain medications and problems with delivery of health care. In addition, new aspects are described, such as telemedicine and telerehabilitation services, which were set up as substitutes for former in-person routine care.

The study also has limitations. First, regarding the heterogeneity of the reported outcomes and the study designs, it was not possible to carry out a meta-analysis and to evaluate the results statistically using odds ratios. Unclear and inhomogeneous reporting and extensive variation in research methods between studies creates barriers for comparison and generalization to specific patient populations. Furthermore, definitions of non-adherence with medication varied between studies, making it challenging to synthesize findings meaningfully. Most of the included studies were surveys, which leads to some typical limitations regarding the study design. Surveys may lead to inclusion biases, as patients who are more interested or worried about COVID-19 are generally more willing to participate. Responses are self-reported and cannot be verified. Survivorship bias is also probable, as very sick or deceased patients cannot participate. Further, patients with a relatively higher socioeconomic status have a greater online presence and affinity to online surveys and are therefore probably overrepresented. As many of the results were published only as case reports and congress abstracts those results were not included in the present study. Important information may therefore have been missed. Finally, this review shows only results regarding the influence on the treatment of imRMDs of the first wave of the COVID-19 pandemic lasting February 2020 to August 2020.

5. Conclusions

The COVID-19 pandemic influenced the management of patients with imRMDs, especially during first wave when no vaccine was available. The influence of the pandemic was diverse regarding adherence to medication, shortage of some medications, adherence to doctor visits or laboratory testing, and regarding governmental interventions. To preserve adherence to health care the COVID-19 pandemic was a starting point for new health care systems. Virtual clinics and remote and telehealth consultations were implemented. These new forms of health care delivery should be spread and implemented worldwide to routine clinical practice to be ready for future pandemics.

List of Abbreviations

axSpA: axial spondyloarthritis

csDMARDs, bDMARDs, tsDMARDs: conventional synthetic, biological and targeted synthetic disease modifying antirheumatic drugs csDMARDs, bDMARDs, tsDMARDs)
CVT: clinical video tele-health
HCQ: hydroxychloroquine
imRMDs: immune mediated Rheumatic and musculoskeletal diseases
JAKi: Janus kinase inhibitors
MMF: mycophenolate mofetil
NSAIDs: non-steroidal anti-inflammatory drugs
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PsoA : psoriasis arthritis RA: rheumatoid arthritis
SLE: systemic lupus erythematodes
VVC: video-based Veterans Affairs Video Connect

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