

# Application of biological medicinal products and tyrosine kinase inhibitors in rheumatoid arthritis and COVID-19: A systematic review of scientific literature

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## Abstract

We analyzed whether commonly used biological medicinal products and/or tyrosine kinase inhibitors with indications for treatment of rheumatologic diseases can be used in patients with concurrent COVID-19 by systematically reviewing scientific articles. The articles were selected according to PRISMA by keywords in the MEDLINE and Central Medical Library - MU Sofia databases for the period January 2020–December 2023. We found 168 scientific publications, of which 9 met the set criteria. Results were evaluated using descriptive methods and the PICOS tool. We found no evidence that the use of BMPs and TKIs in patients with rheumatologic diseases leads to an increased risk of COVID-19 infection and/or a more severe course of SARS-CoV-2 infection. Several cases of prolonged or atypical COVID-19-induced pneumonia have been identified in patients treated with Rituximab. This suggests the need for caution in the use of this medicinal product in patients with COVID-19. The 2022 EULAR recommendations are in the same spirit.

## Keywords

biological medicinal products, tyrosine kinase inhibitors, COVID-19, rheumatologic diseases, systematic review

## Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammatory polyarthritis of unknown etiology leading to immune dysregulation with activation of proinflammatory cytokines such as IL-1, IL-2, IL-6, IL-10, or TNF-alpha (Hochberg et al. 2019). RA is a socially significant disease characterized by serious social,

economic, and psychological damage to individuals, their families, and society as a whole. It has a high share in the cost structure of treatment and rehabilitation and burdens public funds and social services due to prolonged incapacity and patient disability. The incidence of RA ranges from 0.5% to 1.5%. It usually manifests itself between the ages of 35 and 55. It is three times more common in women than in men. In Bulgaria, the number of people affected

by this disease is probably around 30 000–35 000 (in a population of less than 7 000 000). Etiopathogenetically, RA is a series of sequential immune disorders occurring in five phases: initial, mediatory, lymphoid, aggressive, and destructive. In the initial phase, the unknown etiologic factor is processed by antigen-presenting cells into peptide fragments in their intracellular organelles. This is followed by their cell-surface expression together with the class II molecules HLADR4, DR1, and, to a lesser extent, DP and DQ (depending on the racial and ethnic background of the affected individuals), which is recognized by C04+ T lymphocytes. In the mediator phase, the activated T-lymphocytes synthesize and secrete a number of proinflammatory cytokines into the synovial fluid and systemic circulation. During the lymphoid phase, there is marked lymphocyte infiltration of the synovium, followed by proliferation and differentiation of B-lymphocytes into antibody-producing cells that synthesize and secrete immunoglobulins, including rheumatoid factors. B-lymphocytes express Toll-like receptors, which play a role in innate and acquired immunity. Rheumatoid factors bind autoantigens to form immune complexes that activate the complement system, which is followed by an accumulation of polymorphonuclear cells in the synovial fluid and in the synovial membrane. Increased autoantibody production is associated with higher disease activity and bone destruction. Polymorphonuclear leukocytes produce proteolytic enzymes, prostaglandins, leukotrienes, and oxygen-free radicals that lead to tissue destruction in the joints. During the aggressive phase, a so-called “pannus” is formed, a granulation tissue composed of proliferating fibroblasts, small blood vessels, inflammatory cells, and collagen fibrils. This tissue “crawls” from the synovium to the articular cartilage and destroys it. In the destructive phase, the invasion of the pannus into the subchondral bone is exacerbated, followed by the development of fibrous and bony ankylosis in the affected joints (Hochberg et al. 2019). A hallmark of the clinical presentation of RA is symmetric synovial proliferation and tenderness in multiple joints, especially the small joints of the hands and feet. Most patients experience joint stiffness for more than an hour in the morning. Blood samples from approximately 80% of RA patients are found to contain rheumatoid factor (RF), which is an immunoglobulin that binds the Fc fragment of the immunoglobulin G (IgG) molecule, anti-citrullinated peptide antibodies (ACPAs), or both RF and ACPA. Rheumatoid nodules are seen in about 20% of patients. The main clinical manifestation is symmetrical, progressive erosive arthritis. Along with this, a number of other organs and systems may be affected.

The aim of treatment is to achieve remission, or low disease activity. Remission is a major therapeutic goal, especially in early RA, whereas low disease activity may be an appropriate alternative in patients with long-standing RA. The treatment goal should be reached within 3 to 6 months. According to the European Alliance of Associations for Rheumatology (EULAR) consensus (Smolen et al. 2016), treatment should be initiated with disease-mod-

ifying antirheumatic drugs (DMARDs) (*methotrexate*) as soon as possible after RA diagnosis. This is a significant difference compared to disease therapy in the 1990s, when NSAIDs were used as first-line treatments (Ramiro et al. 2015). If the treatment goal is not achieved by therapy with two conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (with one necessarily being *methotrexate*) in adequate doses within 6 months, the addition of biologic disease-modifying antirheumatic drugs (bDMARDs) or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) should be considered. The occurrence of adverse drug reactions is also essential when choosing a therapeutic strategy (Parvova et al. 2016).

Drug therapy with biological medicinal products containing monoclonal antibodies (Smolen 2017) includes: *Adalimumab*, a recombinant fully human IgG1 monoclonal antibody directed against tumor necrosis factor alpha (TNF- $\alpha$ ) that binds and neutralizes the soluble and membrane-bound form of TNF- $\alpha$  (EMA 2009b); *Certolizumab pegol*, a pegylated Fab fragment of a humanized recombinant monoclonal antibody without transplacental transfer, has high affinity for human TNF- $\alpha$  in both soluble and transmembrane-bound forms and contains no Fc fragment (EMA 2010); *Golimumab*, a recombinant fully human IgG1 monoclonal antibody targeting TNF- $\alpha$ , monoclonal antibodies bind in a stable complex both the soluble and transmembrane forms of TNF $\alpha$  (EMA 2009c); *Infliximab*, a chimeric monoclonal antibody containing human and murine components, binds specifically to the soluble and transmembrane forms of TNF- $\alpha$ ; *Tocilizumab*, a humanized IgG1 monoclonal antibody against the human IL-6 receptor, produced by recombinant DNA technology (EMA 2009d); *Rituximab*, a chimeric mouse/human monoclonal antibody directed against the CD 20 antigen located on B-lymphocytes (EMA 2009a), by binding to the CD 20 membrane protein, Rituximab induces cell death via apoptosis. Rituximab in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who are insufficiently responsive or intolerant to other DMARDs, including one or more types of tumor necrosis factor (TNF) inhibitor therapy. Rituximab has been shown to reduce the rate of progression of joint damage as measured by radiography and improve physical function when administered in combination with methotrexate.

The treatment of rheumatological diseases with medicinal products containing tyrosine kinase inhibitors includes Tofacitinib, Baricitinib, and Upadacitinib.

*Tofacitinib* is a potent, selective inhibitor of the Janus kinase inhibitor (JAK) family. In enzymatic assays, tofacitinib inhibits JAK1, JAK2, JAK3, and, to a lesser extent, TyK2 (EMA 2017a). In contrast, tofacitinib has a high degree of selectivity against other kinases in the human genome. In human cells, tofacitinib preferentially inhibits signaling by heterodimeric cytokine receptors that associate with JAK3 and/or JAK1 with functional selectivity over cytokine receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib attenuates signaling of in-

terleukins (IL-2, -4, -6, -7, -9, -15, -21) and type I and type II interferons, which will result in modulation of the immune and inflammatory response. *Baricitinib* is a selective and reversible inhibitor of Janus kinase 1 and JAK2. In isolated enzyme assays, baricitinib inhibited the activities of JAK1, JAK2, Tyrosine Kinase 2, and JAK3, with IC<sub>50</sub> values of 5.9, 5.7, 53, and >400 nM, respectively. Janus kinases (JAKs) are enzymes that transduce intracellular signals from cell surface receptors for a number of cytokines and growth factors involved in haematopoiesis, inflammation, and immune function (EMA 2017b). Within the intracellular signaling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs), which activate gene expression within the cell. Baricitinib modulates these signaling pathways by partially inhibiting JAK1 and JAK2 enzymatic activity, thereby reducing the phosphorylation and activation of STATs.

*Upadacitinib* is a selective and reversible Janus kinase inhibitor. JAKs are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes, including inflammatory responses, hematopoiesis, and immune surveillance (EMA 2019). The JAK family of enzymes contains four members: JAK1, JAK2, JAK3, and TYK2, which work in pairs to phosphorylate and activate signal transducers and activators of transcription (STATs). This phosphorylation, in turn, modulates gene expression and cellular function. JAK1 is important for inflammatory cytokine signals, while JAK2 is important for red blood cell maturation, and JAK3 signals play a role in immune surveillance and lymphocyte function. In human cellular assays, upadacitinib preferentially inhibits signaling by JAK1 or JAK1/3, with functional selectivity over cytokine receptors that signal via pairs of JAK2. Atopic dermatitis is driven by pro-inflammatory cytokines (including IL-4, IL-13, IL-22, TSLP, IL-31, and IFN- $\gamma$ ) that transduce signals via the JAK1 pathway. Inhibiting JAK1 with upadacitinib reduces the signaling of many mediators that drive the signs and symptoms of atopic dermatitis, such as eczematous skin lesions and pruritus. Pro-inflammatory cytokines (primarily IL-6, IL-7, IL-15, and IFN $\gamma$ ) transduce signals via the JAK1 pathway and are involved in the pathology of inflammatory bowel diseases. JAK1 inhibition with upadacitinib modulates the signaling of the JAK-dependent cytokines underlying the inflammatory burden and signs and symptoms of inflammatory bowel diseases.

COVID-19 is a disease caused by a virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a newly emerging strain of coronavirus. As is well known, the first report of the disease was published on December 31, 2019. The main symptoms of COVID-19 are fever, cough, general weakness or fatigue, change or loss of taste or smell, sore throat, headache, muscle pain, and diarrhea. The severity of the illness varies widely from person to person. In severe clinical cases, symptoms may include difficulty breathing or shortness of breath, confusion, and chest pain. People with acute symptomatology may need specialized medical care. SARS-CoV-2 is included in the

Baltimore Classification Group IV of RNA viruses, which includes Dengue virus, hepatitis C virus, rhinoviruses, West Nile virus, and others, but on the other hand, it is very similar to MERS-CoV and SARS-CoV (Baltimore 1971). SARS-CoV-2 has 80% sequence identity to SARS-CoV RNA and 50% sequence identity to MERS-CoV, which is a member of the beta coronavirus genus (Lu et al. 2020; Morse et al. 2020). Although the transmission and mortality rates between MERS-CoV, SARS-CoV, and SARS-CoV-2 differ, there are significant similarities in the genetic composition, pathogenesis, and clinical characteristics of infections caused by these viruses (Katsiki et al. 2020).

The disruption of immune regulation appears to be a major component of the pathophysiology of COVID-19. SARS-CoV-2 infection can cause a wide spectrum of pathogenic phenotypic manifestations, from asymptomatic to severe manifestations with the development of ARDS or MAS-like manifestations, also known as secondary hemophagocytic lymphohistiocytosis (sHLH). Such “cytokine storm” type syndromes are associated with elevation of serum ferritin and D-dimer, lymphopenia (decreased NK and CD8+ count), elevated levels of IL-1, IL-6, TNF $\alpha$ , and IL-8, liver dysfunction, and the development of DIC. COVID-19 appears to have a unique hyper-inflammatory profile. Severe forms of the disease are likely due to immune system dysfunction and the uncontrolled release of certain cytokines and chemokines. Elevated levels of IL-1, IL-6, IL-10, TNF $\alpha$ , and GM-CSF have been found in patients with severe COVID-19. One explanation for the uncontrolled release of inflammatory cytokines is the rate of viral replication, which may cause pyroptosis, an inflammatory death of epithelial and endothelial cells, which may, as a trigger mechanism, lead to the release of cytokines and chemokines. The process involves macrophages and lymphocytes. In SARS-CoV and MERS-CoV, the INF-1 response to the virus is suppressed or defective, resulting in incomplete viral clearance as well as prolonged immune deviations. CD8+ T cells secrete perforin, granzyme, and INF $\gamma$  for viral eradication from host cells, whereas CD4+ T cells assist CD8+ and B cells in cytokine production and lead to T cell-dependent B cell activation. SARS-CoV-2 directly induces IL-6 production through the rapid activation and differentiation of CD4+ T lymphocytes, which differentiate into pathogen-releasing INF $\gamma$  and GM-CSF; these in turn activate monocytes and thereby induce IL-6 release. There are also non-immune cells, such as stromal and epithelial cells, that can induce a strong immune response when IL-6 and its soluble receptor attach to the cell membrane together with the gp30 co-receptor, after which an amplification of the immune response occurs. Treatment is symptomatic; active vaccination is necessary, which is already known not to provide durable immunity, and no definite immune correlates of protection are found.

There is a need to define a targeted therapy for the treatment of COVID-19. The significant interest in medicinal products used to treat rheumatologic diseases is due to the immune cascade of signaling pathways involving a

number of cytokines such as IL-1, IL-6, and TNF $\alpha$  in patients with severe COVID-19. It is well known that protein kinases are one of the most studied groups of drug targets, representing 20–30% of the drug discovery programs of big pharmaceutical companies. Numerous kinase inhibitors exert important immunomodulatory actions that may help alleviate the symptoms of COVID-19, such as cytokine suppression, anti-inflammatory effects, and anti-fibrotic effects, due to which they appear to be of interest to scientists as they are able to block cytokine cascades and immune effector signaling pathways. Several kinases have been proposed as vital mediators of various viral infections, in particular MERS-CoV, SARS-CoV, and SARS-CoV-2. Currently, kinase inhibitors with good pharmacokinetic profiles that are repurposed for COVID-19 may be beneficial by suppressing disease symptoms and reducing infection through direct viral targeting (Catanzaro et al. 2020). On the other hand, kinase inhibitors have been screened in combination with antiviral agents or other targeted therapies that have shown potential activities in clinical trials for COVID-19 to achieve higher efficacy than either agent alone (Weisberg et al. 2020).

## Objective

The aim of the present study is to determine, through an analysis and systematic review of scientific articles published in the scientific literature, whether commonly used in therapeutic practice biological medicinal products and/or tyrosine-kinase inhibitors with therapeutic indications for the treatment of rheumatological diseases can be used in rheumatological patients during active disease with COVID-19. Is there an interaction between the two diseases? Are there additional therapeutic benefits from overlapping therapeutic regimens? Is there a negative association? Should we stop rheumatology treatment? When, how, etc.?

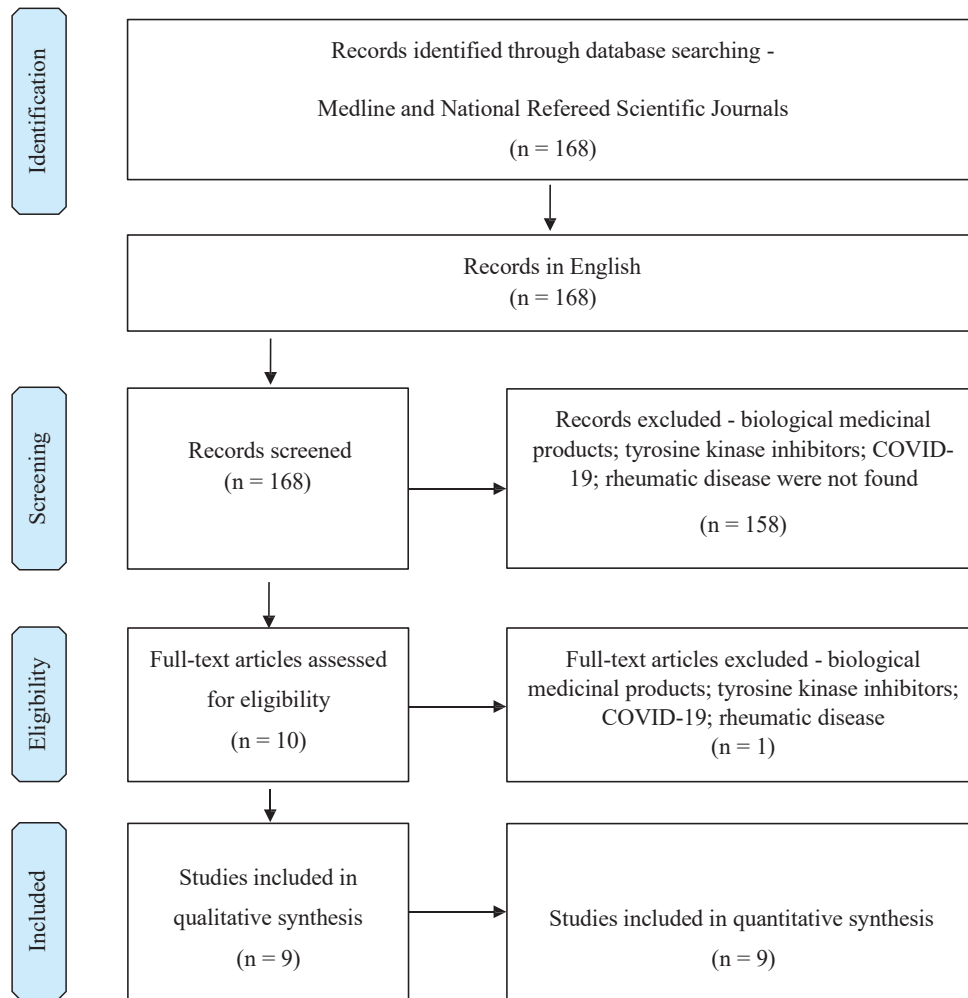
## Materials and methods

The main method applied in the present study is the so-called documentary method, which involves the analysis of data from a systematic review of specialized medical scientific literature. The systematic review (Harris et al. 2014) was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2009; Shamseer et al. 2015). PRISMA is an evidence-based minimum package of reporting elements for systematic reviews and meta-analyses. It was developed primarily for reporting reviews evaluating randomized trials, but can also be used as a basis for reporting systematic reviews in other research areas, evaluating interventions and health technologies, including medicinal products, research articles, programs, etc. The package has been modified for use in conducting and reporting preliminary reviews. We developed a study protocol in accordance with the PRIS-

MA 2009 Checklist (Hutton et al. 2015), with predefined topics: topic, design, search strategy, inclusion and exclusion criteria, data collection methods, data analysis and statistical evaluation, and conclusions. The protocol was not pre-registered in the PROSPERO system (International prospective register of systematic reviews) because the study was limited to a systematic review of scientific publications only, without conducting a meta-analysis. **The subject of** this systematic review was the study of the application of biological medicinal products and tyrosine kinase inhibitors to concomitant rheumatic diseases in patients also infected with SARS-CoV-2. **Design:** retrospective observational study. **Search strategy:** we conducted an active search for scientific publications using the following keywords in English: biological medicinal products; tyrosine kinase inhibitors; COVID-19; rheumatic diseases. **Study period and types of databases:** the search for scientific publications was conducted in MEDLINE, the Central Medical Library, and national refereed scientific journal databases in Bulgaria for the period January 2020–December 2023. Over a 4-year period, we found 168 scientific publications that simultaneously addressed biologics (including biosimilars) and/or tyrosine kinase inhibitors and COVID-19. **Evaluated outcomes and inclusion criteria.** Only scientific publications containing information on biological medicinal products and tyrosine kinase inhibitors were analyzed. The inclusion criteria for scientific publications in the analyses were as follows: the scientific article must contain data on biological medicinal products or tyrosine kinase inhibitors; it must contain data on a drug utilization analysis conducted with biological medicinal products or tyrosine kinase inhibitors in patients with rheumatologic diseases; and COVID-19. **Data extraction.** Two of the authors extracted data from the research articles that were determined to meet the inclusion criteria independently of each other. For the present study, the following data were extracted: First author's surname, year of publication, country of origin, type of scientific communication, types of biological medicinal products, types of tyrosine kinase inhibitors, type of studies, designs, frequency of articles on specific drugs by INN, mean duration of the studies, countries in which the studies were conducted, presence of data on therapies with biological medicinal products or tyrosine kinase inhibitors in patients with rheumatologic diseases and COVID-19, etc. **Statistical analyses.** We used the open-source statistical software Jamovi and Microsoft Excel 2024. We performed descriptive analysis and analysis of variance on the data. Results are presented as absolute and relative frequencies using univariate and bivariate frequency distribution tables.

## Results

The selection of the analyzed research articles, conducted according to the search strategy, is presented as a PRISMA flow diagram (Fig. 1).



**Figure 1.** Overview of the searching process (PRISMA flow diagram).

The literature search is limited to articles published in English only. The initial search found 168 scientific publications. We screened 168 titles and abstracts, followed by a search for the full texts of the articles. We excluded 158 articles because the abstract did not contain all the following keywords: biological medicinal products; tyrosine kinase inhibitors; COVID-19; rheumatic disease. Finally, we excluded 1 full-text article from the remaining 10 articles because it did not contain data on the effects of concomitant administration of biological medicinal products (BMPs) and tyrosine kinase inhibitors (TKIs) in patients with rheumatic diseases and COVID-19. Nine scientific publications examining the effects of concomitant administration of biologics (BMPs) and tyrosine kinase inhibitors (TKIs) in patients with rheumatologic diseases and COVID-19 remain to be analyzed. The largest number of scientific publications addressed the application of medicinal products from the bDMARDs group (over 66% of scientific publications), followed by csDMARDs and tsDMARDs, tDMARDs, glucocorticoids, and TKIs (BTK).

We used the criteria system of the PICOS tool (population, intervention, comparison, outcomes, and study design) (Methley et al. 2014) to assess outcomes. The PICO tool focuses on the population studied, the type of inter-

vention, comparison, and assessment of outcomes; it is most commonly quantified; it is commonly used to identify components of clinical evidence for systematic reviews in evidence-based medicine; and it has been adopted by the Cochrane Collaboration (Higgins and Green 2013). In the modified version of PICOS, “S” refers to study design; thus, we will limit the number of irrelevant research articles and also focus on some qualitative indicators.

Fifty percent of the studies focused on the drug utilization of bDMARDs among patients with RA and COVID-19. The total number of patients included in the studies was 9947, with a variability between 18 and 3951 patients. 77% of the studies found no association between the administered drugs and a severe COVID-19 infection. The results are presented in Table 1.

Limitations, reasonable assumptions, generalization, and extrapolation of data. The sample we observed was relatively small, and the standard risk of bias was high, mainly due to the lack of available randomized controlled clinical trials in the scientific literature we reviewed. Due to the size and heterogeneous nature of the studies we reviewed, we cannot claim that it is possible to generalize and extrapolate our results to the entire population of rheumatoid arthritis patients affected by COVID-19.

**Table 1.** Outcome measures - PICOS.

Population	Intervention	Comparison	Outcomes	Study design
820 patients	bDMARDs	Best supportive care	The Intervention does not present a high risk of severe manifestations of COVID-19	Retrospective observational study
959 patients	bDMARDs and tDMARDs	The best standard treatment	The Intervention does not present a high risk of severe manifestations of COVID-19	Cross-sectional study
1051 patients	bDMARDs or small molecules	The best standard treatment	The Intervention does not present a high risk of severe manifestations of COVID-19	Population-based study in the province of Udine, Italy
Not specified	Tocilizumab	The best standard treatment	The Intervention does not present a high risk of severe manifestations of COVID-19	Systematic literature review
3951 patients	bDMARDs or tsDMARDs	The best standard treatment	The Intervention does not present a high risk of severe manifestations of COVID-19	Observational longitudinal study
443 patients	csDMARDs and bDMARDs	The best standard treatment	The Intervention does not present a high risk of severe manifestations of COVID-19	Prospective observational study
18 patients	Rituximab	The best standard treatment	Occurrence of severe, prolonged COVID-19 pneumonia.	Case report and literature review
1525 patients	Glucocorticoids and Tocilizumab	The best standard treatment	The Intervention does not present a high risk of severe manifestations of COVID-19	Single-center observational and case-control study
Not specified	TKI - BTK	The best standard treatment	Assessment of the potential role of BTK inhibitors in the management of COVID-19	Retrospective observational study

A retrospective observational study of the incidence of COVID-19 infection in 820 patients with rheumatologic diseases treated with biologic disease-modifying antirheumatic drugs found that the use of bDMARDs was not directly associated with severe COVID-19-induced infection. The authors concluded that IL-6 inhibitors may have a protective effect (Santos et al.). Similar results were observed in a study examining the incidence of COVID-19 in a cohort of 959 adult and pediatric patients with rheumatic diseases receiving bDMARDs and target-specific disease-modifying antirheumatic drugs (Michelena et al. 2020). There was no higher risk of COVID-19 infection or more severe disease outcome compared to the general population (Zateri et al. 2021). Another team of researchers studied the prevalence of severe coronavirus infection among 1051 adult patients with chronic inflammatory rheumatic diseases treated with BMP or small molecules. The risk of COVID-19 in patients with rheumatic diseases under the influence of BMP or small molecules did not appear to be different from that observed in the general population (Quartuccio et al.). Raiteri's team analyzed the humanized interleukin-6 receptor-inhibiting monoclonal antibody Tocilizumab as a possible treatment for severe acute respiratory syndrome caused by SARS-CoV2. Although the scientific rationale supporting Tocilizumab for the treatment of COVID-19 is solid, the team found insufficient evidence to support this claim (Raiteri et al.). At the very beginning of the pandemic, back in 2020, another research team investigated the association between COVID-19 and inflammatory rheumatic diseases and evaluated the role of tDMARDs and bDMARDs in 3951 rheumatic patients ill with COVID-19. This study provides further evidence that the use of tDMARDs and bDMARDs does not significantly increase the risk of moderate-to-severe sporadic COVID-19-induced infection (Fernandez-Gutierrez et al. 2021). For the period February–December 2020, a prospective observational study of 443 patients with inflammatory arthritis and COVID-19 undergoing treatment with convention-

al synthetic (cs) disease-modifying antirheumatic drugs (csDMARDs) and/or bDMARDs observed that patients treated with cs and/or bDMARDs had nearly the same disease course as the general population when infected with COVID-19 (Migkos et al. 2020). Daoussis and his team reported a clinical case showing that Rituximab can lead to severe and prolonged COVID-19-induced pneumonia (Daoussis et al.). Another author team collected data from 1525 patients with rheumatic and musculoskeletal diseases affected by COVID-19 and found that in this group of patients, poor outcome from COVID-19 was associated with older age and the presence of comorbidities rather than the type of rheumatic disease or the degree of immunosuppression (Fredri et al. 2020). Kifle ZD. aimed to collect and summarize evidence on the effectiveness of Bruton tyrosine kinase inhibitors (BTK) against COVID-19. Another scientific publication from 2021 reported that BTK may be beneficial in the treatment of COVID-19, but more clinical studies are needed to elucidate all mechanisms affecting the disease (Kifle et al. 2021).

## Discussion and conclusion

The research on the topic is undoubtedly of interest, but the publication activity is not high—only nine scientific publications over a 4-year period. This is probably due to the relatively low occurrence of some of the rheumatic diseases, while others fall within the definition of rare diseases, and there is not a sufficient pool of patients for analysis. There are also insufficient reported clinical cases. Despite these suspicions, no association between severe COVID-19-induced infection and the use of the medicinal product groups studied was found in the available publications. Concomitant use of biological medicinal products and tyrosine kinase inhibitors does not result in an increased risk of COVID-19 infection in patients with rheumatologic diseases and does not affect the severity of the course of this

disease. Several cases of long-standing or atypical COVID-19-induced pneumonia have been identified in patients treated with Rituximab. Although we do not find sufficient scientific publications on the Rituximab-COVID-19 relationship, we find several specific warnings in this regard on the European Alliance of Associations for Rheumatology (EULAR 2022) website. The first warning concerns the appropriate periods for vaccination and the activity of the rheumatic disease: “Vaccinations should ideally be given when the rheumatic and musculoskeletal diseases (RMDs) are in a quiet phase (sometimes referred to as low disease activity or remission); it is also preferable to vaccinate before planned immunosuppression if this is being given intermittently. Although it is suggested that vaccination is most effective when the degree of immunosuppression is low, pausing or reducing immunosuppression may increase the risk of flare, and therefore it is generally advised not to, or only temporarily, interrupt or decrease your medication for this purpose (if you are receiving Rituximab, please consult your rheumatologist)”. The second precaution concerns the answer to the question, “Do my treatments increase the risk of severe COVID-19 infection?” The answer of EULAR is, “Most of the drugs used in RMDs have not been associated with severe infection. To date, the only treatments that have been shown to be

associated with a severe COVID-19 outcome are rituximab, cyclophosphamide, mycophenolate mofetil, or using more than 10 mg of glucocorticoids daily. Regarding other drugs used in RMDs, we do not have evidence that they are associated with severe COVID-19 infection. Importantly, more active disease is associated with severe outcomes related to infections, including COVID-19. In case you are using one of those drugs mentioned, talk to your rheumatologist about the best options for your situation.” Obviously, decisions have to be made on a “case by case” basis. This suggests the need for caution when using this medication in patients with COVID-19. Rather, the increased risk of a severe course of COVID-19 is related to comorbidity and the overall health of the patients. Our results are inconclusive. Further studies are needed to fully identify the potential impact of these groups of medicinal products on rheumatology patients affected not only by COVID-19 but also by other serious viral infections.

## Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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