Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Seminars in Arthritis and Rheumatism 50 (2020) 1191–1201

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Acute respiratory viral adverse events during use of antirheumatic disease therapies: A scoping review

Adam Kilian[a,*], Yu Pei Chock[b], Irvin J. Huang[c], Elizabeth R. Graef[d], Laura A. Upton[e], Aneka Khilnani[f], Sonia D. Silinsky Krupnikova[a], Ibrahim Almaghlouth[g], Laura C. Cappelli[h], Ruth Fernandez-Ruiz[i], Brittany A. Frankel[c], Jourdan Frankovich[j], Carly Harrison[k], Bharat Kumar[l], Kanika Monga[m], Jorge A. Rosario Vega[j], Namrata Singh[c], Jeffrey A. Sparks[n], Elaine Sullo[f], Kristen J. Young[o], Ali Duarte-Garcia[p], Michael Putman[q], Sindhu Johnson[r], Rebecca Grainger[s], Zachary S. Wallace[t], Jean W. Liew[c,*,#], Aruni Jayatilleke[j,*,#]

[a] *Division of Rheumatology, Department of Medicine, George Washington University School of Medicine and Health Sciences, Washington, DC*
[b] *Division of Rheumatology, Department of Medicine, Yale University School of Medicine, New Haven, CT*
[c] *Division of Rheumatology, Department of Medicine, University of Washington School of Medicine, Seattle, WA*
[d] *Division of Rheumatology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*
[e] *Georgetown University School of Medicine, Washington, DC*
[f] *George Washington University School of Medicine and Health Sciences, Washington, DC*
[g] *King Saud University College of Medicine, Riyadh, Saudi Arabia*
[h] *Division of Rheumatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD*
[i] *Division of Rheumatology, Department of Medicine, New York University Langone Health, New York, NY*
[j] *Division of Rheumatology, Department of Medicine, Lewis Katz School of Medicine, Temple University, Philadelphia, PA*
[k] *Lupus Chat*
[l] *Division of Rheumatology, Department of Medicine, University of Iowa, Iowa City, IA*
[m] *Division of Rheumatology, Department of Medicine, University of Texas Houston, Houston, TX*
[n] *Division of Rheumatology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*
[o] *Division of Rheumatology, Department of Medicine, University of Texas Southwestern Medical Center, Dallas, TX*
[p] *Division of Rheumatology and Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN*
[q] *Division of Rheumatology, Department of Medicine, Northwestern Medicine, Chicago, IL*
[r] *Division of Rheumatology, Toronto Western Hospital, Mount Sinai Hospital; Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada*
[s] *Department of Medicine, University of Otago, Wellington, New Zealand*
[t] *Clinical Epidemiology Program, Division of Rheumatology, Allergy and Immunology, Massachuse General Hospital and Harvard Medical School, Boston, MA*

ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Rheumatic disease
Adverse event
Antirheumatic medications
Immunosuppressive treatment

ABSTRACT

Introduction: COVID-19 is an acute respiratory viral infection that threatens people worldwide, including people with rheumatic disease, although it remains unclear to what extent various antirheumatic disease therapies increase susceptibility to complications of viral respiratory infections.
Objective: The present study undertakes a scoping review of available evidence regarding the frequency and severity of acute respiratory viral adverse events related to antirheumatic disease therapies.
Methods: Online databases were used to identify, since database inception, studies reporting primary data on acute respiratory viral infections in patients utilizing antirheumatic disease therapies. Independent reviewer pairs charted data from eligible studies using a standardized data abstraction tool.
Results: A total of 180 studies were eligible for qualitative analysis. While acknowledging that the extant literature has a lack of specificity in reporting of acute viral infections or complications thereof, the data suggest that use of glucocorticoids, JAK inhibitors (especially high-dose), TNF inhibitors, and anti-IL-17 agents may be associated with an increased frequency of respiratory viral events. Available data suggest no increased frequency or risk of respiratory viral events with NSAIDs, hydroxychloroquine, sulfasalazine, methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, or apremilast. One large cohort study demonstrated an association with leflunomide use and increased risk of acute viral respiratory events compared to non-use.

On behalf of The COVID-19 Global Rheumatology Alliance

* Corresponding authors.
E-mail addresses: AKilian@mfa.gwu.edu (A. Kilian), jwliew@uw.edu (J.W. Liew), arundathi.jayatilleke@tuhs.temple.edu (A. Jayatilleke).
Co-Principal Investigator

https://doi.org/10.1016/j.semarthrit.2020.07.007
0049-0172/© 2020 Elsevier Inc. All rights reserved.

Conclusion: This scoping review identified that some medication classes may confer increased risk of acute respiratory viral infections. However, definitive data are lacking and future studies should address this knowledge gap.

© 2020 Elsevier Inc. All rights reserved.

Introduction

COVID-19 is an acute respiratory viral infection that threatens the health and wellbeing of people worldwide. People with rheumatic disease, especially those who take immunosuppressive medications, may be particularly susceptible to infection or severe disease course with adverse outcomes [1,2]. Although the extent to which various antirheumatic disease therapies increase susceptibility to complications of viral respiratory infections has been explored in analyses of COVID-19 outcomes for people living with rheumatic disease [3–7], these studies have been limited by small sample sizes and biases inherent in observational data.

The aim of this scoping review is to systematically map the empiric evidence regarding the frequency and severity of acute respiratory viral adverse events (AEs) related to antirheumatic disease therapies, as well as to identify any existing gaps in knowledge. A scoping review was identified as the most appropriate method of knowledge synthesis as the reviewers anticipated substantial heterogeneity of study populations and designs as well as exposures and outcomes within the analysis. This review may be used to inform research directions to identify subpopulations at greatest risk for or from acute viral respiratory infections. Such directions may include focusing monitoring for potential COVID-19 complications, identifying possible predictors of poor outcomes in patients taking immunosuppressive treatments, and triage and counseling of patients.

Methods

A scoping review protocol was developed, guided by the methodological framework proposed by Arksey and O'Malley [8]. The protocol was developed *a priori* based on the research question, "Does the use of common antirheumatic disease therapies impact the susceptibility to acute respiratory viral infections or frequency and severity of complications thereof?" The review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) [9].

Eligibility criteria

A study was eligible for inclusion if it reported primary data on acute respiratory viral infections in patients treated with antirheumatic disease therapies. Case reports, case series with fewer than ten subjects, non-English articles, and studies featuring patients undergoing treatment for cancer, bone marrow transplantation, or solid organ transplantation were excluded.

Literature search strategy

To identify relevant studies, a systematic literature search was designed, and implemented on April 1, 2020, using both keywords and controlled vocabulary (Medical Subject Headings/MeSH and Emtree) to search the following databases from the date of database inception: MEDLINE (Ovid), Scopus, Embase (Ovid), Proquest Dissertations and Theses, Cochrane Database of Systematic Reviews, and OpenGrey (http://www.opengrey.eu/). No study type limits were applied. Search terms were included representing the exposure (antirheumatic disease therapy, non-immunosuppressive and immunosuppressive), primary outcomes (risk of acquiring a new acute respiratory viral infection; frequency and severity of upper respiratory tract infection (URTI) and lower respiratory tract infection (LRTI)), and secondary outcomes (worsening outcomes related to a new acute respiratory viral infection: oxygen requirement; mechanical ventilation; hospitalization; death; cytokine storm; and coronavirus/COVID-19-related). The full MEDLINE search strategy is available in the appendix (Supplemental Table 1). Following abstract and full text screening, we identified additional relevant clinical trials by hand search. In this search, we used PubMed to search for specific disease states and medications. Disease states were limited to Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), vasculitides, and Systemic Sclerosis (SSc), and medications to conventional synthetic, targeted synthetic, and biologic disease modifying antirheumatic drugs (csDMARDs, tsDMARDs, and bDMARDs, respectively), as these were felt to be of the potentially highest yield. References from all searches were identified by unique reference identifiers.

Identification and selection of eligible studies

The titles and abstracts of all references were screened independently by each member of a pair of reviewers. Duplicates and studies not meeting inclusion criteria were excluded from further review. Studies investigating antirheumatic disease therapies for the management of rheumatic diseases and inflammatory bowel disease (IBD) were included. Studies investigating antirheumatic disease therapies for management of stem cell transplantation, solid organ transplantation, or nonrheumatic non-IBD autoimmune disorders were excluded. In the case of multiple reference identifiers arising from the same study, we included manuscripts with the most complete information and the latest publication date and excluded others as duplicates. Full texts of included references were obtained and screened by new reviewer pairs, with discrepancies resolved by a third reviewer (AJ, AK, or JL).

Data charting process and data items

Data from eligible studies were charted using a standardized data abstraction tool by nine pairs of independent reviewers (Appendix: Supplemental Table 2). The charted data for each study included meta data (author, date, year of publication), demographic information of study participants (age, sex), study design (randomized controlled trials (RCTs), pooled safety analyses, cohort studies, and other observational studies (case-control, cross-sectional, case series), participants, exposures (treatments, duration of treatment exposure, comparator), and key findings relevant to our defined primary and secondary outcome measures.

Synthesis of results

Studies were grouped into medication categories, including acute anti-inflammatory drugs, csDMARDs, tsDMARDs, and bDMARDs. We summarized study characteristics and synthesized acute viral respiratory outcomes of interest relative to medication classes and subclasses. All findings and statements regarding acute respiratory viral AEs of antirheumatic disease therapies are based on published information as listed in the references.

Results

Characteristics of published studies

After duplicates were removed, a total of 9686 unique citations were identified from searches of electronic databases. Based on the title and abstract, 8968 citations were excluded, resulting in 718 articles reviewed for full text retrieval and eligibility assessment. Of these, 509 were excluded for the following reasons: wrong study type, irrelevant exposure, wrong study population, irrelevant outcomes, non-English language, or unavailability. The remaining 209 studies were considered eligible for data charting. Supplemental hand search identified an additional 52 studies eligible for data charting. After the charting process, studies with duplicate or redundant data from extensions and pooled analyses were excluded, as well as studies in which outcomes were not reported by the treatment group, which resulted in 180 primary studies eligible for qualitative analysis. Fig. 1 presents the article identification and screening process.

Characteristics of the 180 studies included in the scoping review qualitative analysis are listed in Table 1. A total of 480,334 patients were included in the 180 studies. Most of the studies (77.8%) were published between 2011 and 2020. Study types in the analysis included 89 (49.4%) RCTs, 32 (17.8%) case series, 15 (8.3)% pooled safety analysis/postmarketing surveillance studies, and 44 (24.4%) other observational studies. Regarding region of origin, 22.8% of the studies included were from North America, 16.7% from Europe, 15.6% from Asia, and 37.8% from multiple continents. Of the remaining studies, 7.2% were from either Oceania, South America, or unspecified. Most (168 (93.3%)) of the studies focused on populations with a single disease including 72 (40%) on RA, 27(15%) on SLE, 9 (5%) on vasculitis, 5 (2.8%) on IBD, and 12 (6.7%) of the studies focused on populations with either unspecified or heterogeneous diseases. The numbers of studies reporting various acute respiratory viral outcomes are depicted in Fig. 2.

Results are presented by medication class, with additional detail in the Supplemental Results.

Acute anti-inflammatory drugs

NSAIDs: There were two included studies in which nonsteroidal anti-inflammatory drugs (NSAIDs) were the main exposure of interest, including one placebo-controlled RCT [10] and one active comparator RCT [11]. Based on these data, use of NSAIDs does not appear to be associated with a higher frequency of URTI or LRTI compared with placebo and there was no difference in the frequency of URTI between medications within the NSAID class.

Glucocorticoids: Although many included studies incorporated concomitant glucocorticoid (GC) exposure, there were eleven studies included in which GCs were a main exposure of interest. These included one active comparator RCT [12], seven cohort studies [13–19], one case-control study [20], one cross-sectional study [21], and one case series [22]. Based on data from these primarily observational cohort studies, the use of GCs was associated with a higher frequency of URTI, viral infection, and pneumonia.

Conventional synthetic DMARDs (Non-Immunosuppressive)

Antimalarials: There were three included studies in which hydroxychloroquine (HCQ) was the exposure of interest, including two cohort studies [17, 18] and one nested case-control study [20]. Based on the data from these observational studies, the use of HCQ was not identified as an independent risk factor for infection and/or infection-related mortality. One study noted that HCQ use was protective against infection-related mortality [17].

Sulfasalazine: There were two included studies in which sulfasalazine (SSZ) was the exposure of interest, including one cohort study [19] and one cross-sectional study [21], both of which included subjects from the same database (National Data Bank for Rheumatic Diseases). Based on the data from these two studies, the use of SSZ may be associated with a minimal protective effect for sinus infections and LRTI (pneumonia) among individuals with RA. Given the limited number of studies cautious interpretation of the results is warranted.

Dapsone, Doxycycline, Minocycline: There were no studies with primary data on the incidence of acute respiratory viral infection that met the inclusion criteria in which these therapies were the main exposure of interest.

Conventional synthetic DMARDs (Immunosuppressive)

Methotrexate: There were nineteen included studies in which methotrexate (MTX) was the exposure of interest. There were eight placebo-controlled RCTs using MTX, usually as an active comparator against a bDMARD [23–30]. There were two active comparator RCTs in which MTX was the active comparator [31,32]. Finally, there was one open-label extension (OLE) of an RCT [33] of iguramotid with MTX. Most of these trials were conducted in patients with RA. Additionally, we identified six cohort studies [34–39], one cross-sectional analysis of a prospective cohort [21], and one case series [40]. In general, the use of MTX for the treatment of inflammatory conditions does not appear to be associated with an increase in viral respiratory infections.

Leflunomide: There were five included studies in which leflunomide (LEF) was the exposure of interest, including one cohort study [19], one case-control study [41], two cross-sectional studies [21,42], and one case series [43]. In the prospective cohort study of 16,788 RA patients, the use of LEF was significantly associated with an increased risk of LRTI requiring hospitalization after adjustment for important confounders [19]. In the remainder of the studies, however, there appeared to be a low frequency of respiratory infections with LEF.

Azathioprine: There were four included studies in which azathioprine (AZA) was the exposure of interest, including one RCT [44] and three cohort studies [18,45,46]. In the RCT, the incidence of pneumonia was <1% in patients treated with AZA. Data from the three cohort studies were insufficient to draw conclusions regarding the use of AZA and risk of pulmonary infections in patients with SLE or lupus nephritis (LN).

Mycophenolate: There were nine included studies in which mycophenolate mofetil (MMF) alone was the exposure of interest, including one placebo-controlled RCT [47], seven active comparator RCTs [44,48–53] and one cohort study [18]. The majority of the studies showed no evidence of increased risk of viral infection compared to other immunosuppressive agents

Tacrolimus, Cyclosporin-A: There were two included studies in which tacrolimus or cyclosporine-A (CsA) were the exposure of interest, including one active comparator RCT [12] and one case series [54]. There was insufficient evidence to assess the true risk of viral URTI or LRTI related to tacrolimus or CsA due to confounding medication co-exposures.

Cyclophosphamide: There were nine included studies in which cyclophosphamide (CYC) was the exposure of interest, including five active comparator RCTs [12,49–51,55], one cohort study [45], and three case series [56–58]. Assessment of the effect of CYC on the development of viral respiratory infections is difficult due to heterogeneous reporting of data and small trial sizes. The frequency of pneumonia events after treatment with CYC in these studies was low.

Targeted synthetic DMARDs

Apremilast: There were three included studies in which apremilast was the exposure of interest, including two placebo-controlled

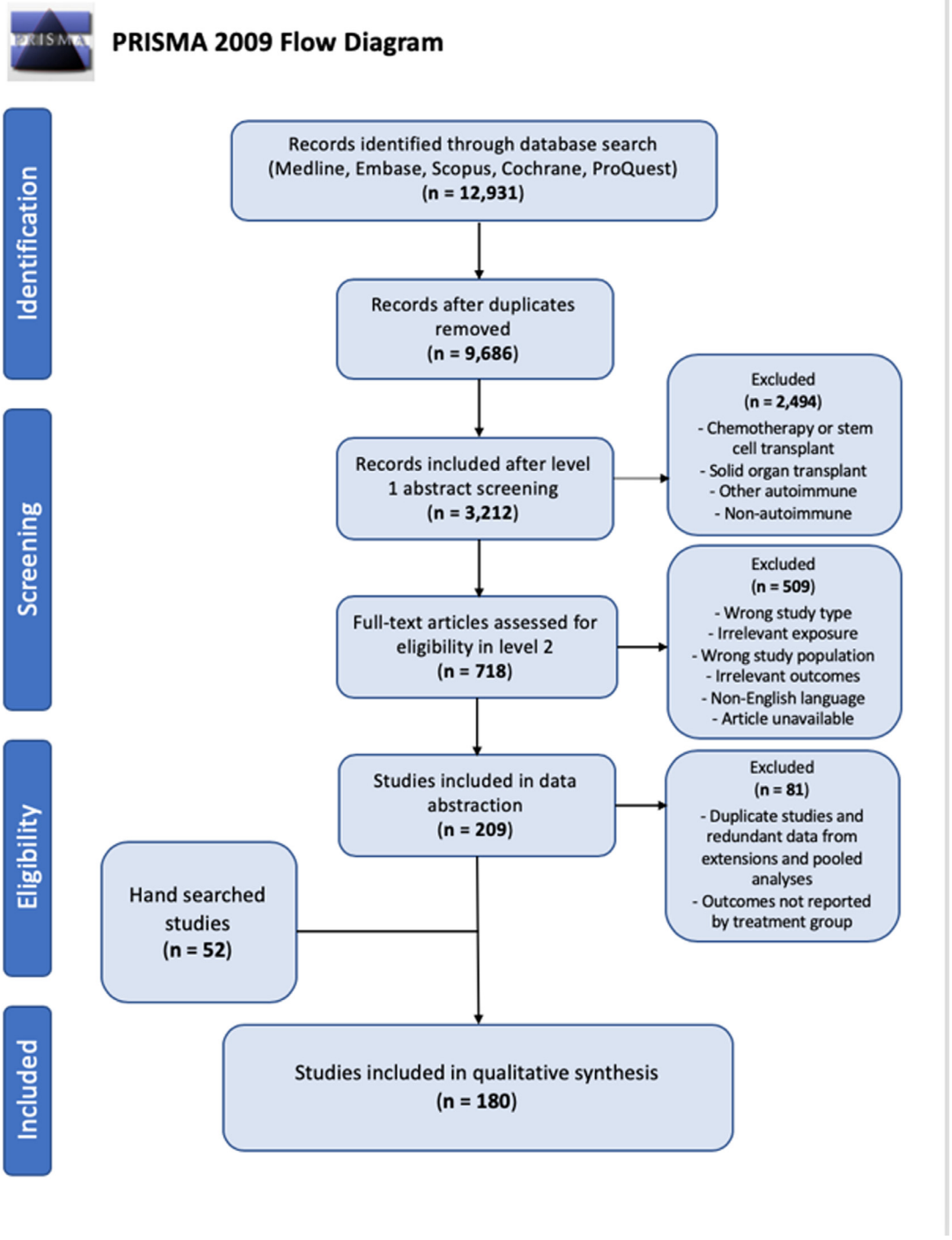

Fig. 1. PRISMA flow diagram for the scoping review process.

RCTs [59,60] and one pooled analysis of active comparator RCTs [61]. Overall, the frequency of URTI or nasopharyngitis in patients taking apremilast for psoriasis (PsO) or PsA was comparable to placebo.

JAK inhibitors: There were seventeen included studies in which a JAK inhibitor (JAKi) was the exposure of interest, including eleven placebo-controlled RCTs [24,25,62–70], one OLE [71], two pooled safety analyses [72,73], one postmarketing study [74], one cohort study [75], and one case series [76]. JAKi, especially at higher doses, may be associated with a higher frequency of mild viral respiratory infections. However, most studies had a short follow-up period and small sample sizes, which may limit the statistical power to detect significant differences between these groups. Within these constraints, JAKi do not seem to increase the frequency of severe viral respiratory AEs.

T-cell-directed biological DMARDs

CTLA4-Ig: There were a total of ten included studies in which abatacept (ABT) was the exposure of interest, including two placebo-controlled RCTs [77,78], one active comparator RCT [79], three pooled analyses of RCTs [80–82], and four cohort studies [75,83–85]. Based on pooled RCT results, ABT appears to have a similar incidence of viral outcomes compared to placebo. However, cohort studies

Table 1
Summary of general characteristics of included studies

Characteristics	Number of studies (Total 180)	Number of patients (Total 480,344)	%Studies	%Patients
Publication Year				
1991–2000	3	498	1.67%	0.10%
2001–2010	37	111,403	20.56%	23.19%
2011–2020	140	368,443	77.78%	76.70%
Publication Type				
Case series	32	4485	17.78%	0.93%
Other observational studies	44	395,486	24.44%	82.33%
Randomized controlled trial	89	39,041	49.44%	8.13%
Pooled safety analysis/postmarketing surveillance	15	41,332	8.33%	8.60%
Continent				
Multiple	68	55,621	37.78%	11.58%
North America	41	379,488	22.78%	79.00%
Europe	30	19,078	16.67%	3.97%
Asia	28	17,105	15.56%	3.56%
Oceania	3	999	1.67%	0.21%
South America	1	60	0.56%	0.01%
Not specified	9	7993	5.00%	1.66%
Condition Studied				
Antiphospholipid Syndrome	1	19	0.56%	0.00%
Autoinflammatory	2	115	1.11%	0.02%
Axial spondyloarthritis	10	4081	5.56%	0.85%
Gout	1	312	0.56%	0.06%
Inflammatory bowel disease	5	1322	2.78%	0.28%
Juvenile idiopathic arthritis	8	891	4.44%	0.19%
Myositis	1	18	0.56%	0.00%
Neuromyelitis optica	2	181	1.11%	0.04%
Osteoarthritis	3	2636	1.67%	0.55%
Psoriasis	6	2587	3.33%	0.54%
Psoriatic arthritis	18	9678	10.00%	2.01%
Rheumatoid arthritis	72	391,014	40.00%	81.40%
Systemic lupus erythematosus	27	51,149	15.00%	10.65%
Systemic sclerosis	3	235	1.67%	0.05%
Vasculitis	9	1348	5.00%	0.28%
Multiple/Unspecified	12	14,758	6.67%	3.07%
Drug Studied				
Acute Anti-inflammatory Drugs	13	112,124	7.22%	23.34%
Conventional DMARDs (Non-Immunosuppressive)	5	26,494	2.78%	5.52%
Conventional DMARDs (Immunosuppressive)	48	89,328	26.67%	18.60%
Targeted Synthetic DMARDs	20	59,597	11.11%	12.41%
T-cell Directed Biological DMARDs	10	94,969	5.56%	19.77%
B-cell Directed Biological DMARDs	29	34,832	16.11%	7.25%
Cytokine Directed Biological DMARDs	94	425,104	52.22%	88.50%
Other	3	813	1.67%	0.17%

demonstrated that ABT was associated with decreased incidence of respiratory AEs compared to JAKi [75] and other DMARDs [84].

B-cell-directed biological DMARDs

Anti-CD20: There were 24 included studies in which anti-CD20 medications were the exposure of interest, including three placebo-controlled RCTs [47,86,87], one pooled safety study of placebo-controlled RCTs [88], five cohort studies [84–91], and fifteen case series [92–106]. Overall, there were limited data for the outcomes of interest in studies that evaluated anti-CD20 therapy. The frequency of URTI was noted to be about 30–35% in several studies of patients who received rituximab (RTX) [47,84–87,90,91] but this number varied widely and was similar to rates of URTI in patients who received placebo in two out of three studies [47,87].

Anti-BAFF: There were five included studies in which agents blocking BAFF/BLyS were the exposures of interest, including one placebo-controlled RCT [107], one placebo-controlled RCT with OLE data [108], two pooled safety studies of placebo-controlled RCTs [109,110], and one case series [111]. There was no clinically relevant difference in URTI, sinusitis, bronchitis, LRTI, or pneumonia between exposure of interest and placebo groups.

Cytokine-directed biological DMARDs

TNFi: There were 60 studies included in which TNF inhibitors (TNFi), individually or as a class, were the exposure of interest among immune-mediated systemic inflammatory diseases. These included eighteen placebo-controlled RCTs [27,28,112–127], ten active comparator RCTs [128–137], 25 cohort studies [19,34,35,38,39,75,83,–85,138–153], one pooled safety analysis [154], one case-control study [155], one cross-sectional study [21], and four case series [156–159]. In several of the placebo-controlled RCTs, TNFi exposure was associated with higher frequency of respiratory outcomes, particularly nasopharyngitis or URTI, compared to placebo. However, this finding was not universal and was not statistically significant. In general, exposure to TNFi was not associated with worse viral respiratory outcomes, including bronchitis and pneumonia, nor with complications such as hospitalization and mortality compared with antirheumatic medications such as MTX, tocilizumab (TCZ), or other bDMARD classes. In general, there were few differences for respiratory viral outcomes noted between drugs within the TNFi class.

Anti-IL-1: There were seven included studies in which anti-IL-1 therapy was the exposure of interest, including four placebo-controlled RCTs [160–163], two active comparator RCTs [131,164], and one case series [165]. Overall, frequencies of respiratory infections

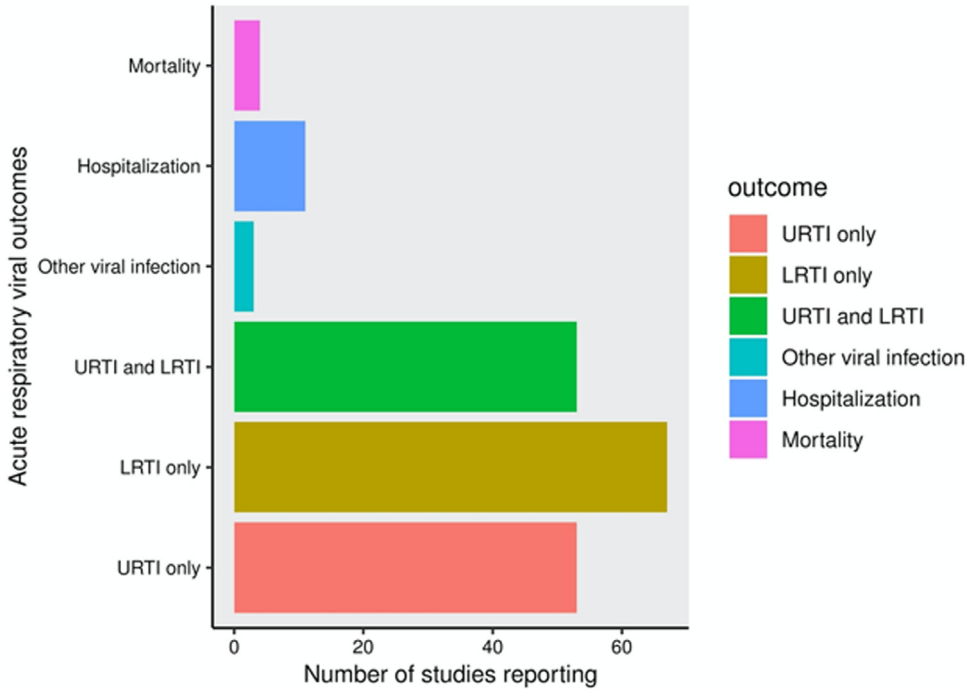

Fig. 2. Acute respiratory viral outcomes reported in included studies.

Footnote to Fig. 2: Mortality represents mortality secondary to an acute respiratory infection (including viral); Hospitalization represents hospitalization secondary to an acute respiratory infection (including viral); URTI, upper respiratory tract infection, includes sinusitis, nasopharyngitis, pharyngitis; LRTI, lower respiratory tract infection, includes bronchitis, pneumonia.

were low in studies examining anti-IL-1 therapy; no meaningful differences in outcomes of interest were seen between patients treated with anti-IL-1 therapy and placebo, triamcinolone, or TNFi.

Anti-IL-5: There were no studies that met the inclusion criteria in which an anti-IL-5 monoclonal antibody was the main exposure of interest with primary data on the incidence of acute respiratory viral infection.

Anti-IL-6: There were fourteen included studies in which anti-IL-6 therapy was the exposure of interest, including four placebo-controlled RCTs [166–169], one active comparator RCT [32], three studies encompassing pooled safety data from active comparator RCTs and post-marketing surveillance data [170–172]], three cohort studies [84,140,145], and three case series [173–175]. In general, rates of respiratory tract infections were low in studies examining IL-6 therapy; no meaningful differences in outcomes were seen between patients treated with anti-IL-6 therapy and those treated with csDMARDs or bDMARDs.

Anti-IL-12/IL-23: There were four included studies in which anti-IL-12/23 therapy was the exposure of interest, including three placebo-controlled RCTs [176–178] and one OLE of placebo-controlled RCTs [179]. Based on these limited data, there is no evidence of a clinically relevant difference in viral respiratory infections in patients treated with IL-12/23 inhibitors compared to placebo.

Anti-IL-17: There were eight included studies in which anti-IL-17 therapy was the exposure of interest, including four placebo-controlled RCTs [26,128,180–182] and four OLEs of placebo-controlled RCTs [183–186]. Overall, there was no difference in the frequency of sinusitis, bronchitis, pneumonia, or URTI in patients receiving IL-17 inhibitors compared to placebo. There was a numerically higher frequency of nasopharyngitis and URTI in patients exposed to IL-17 inhibitors, but after adjusting for medication dose no statistically significant difference was seen.

Anti-RANKL: There was one included study in which denosumab was the exposure of interest [187]. In this observational study of RA patients, which did not adjust for potential confounders including age and comorbidities, concurrent use of denosumab with bDMARDs did not increase incidence of severe acute respiratory infections compared to use of bDMARDs alone.

Interferon-receptor-directed biological DMARDs

Anti-interferon I receptor: There was one included placebo-controlled RCT of anifrolumab in 362 subjects with SLE [188]. While there were no clinically relevant differences in the frequencies of influenza or pneumonia between treatment groups, the frequency of URTI, nasopharyngitis, and bronchitis were higher in the anifrolumab group compared to placebo. One patient died from pneumonia in the anifrolumab group and there were no other deaths in the trial.

Complement-directed biological DMARDs

Anti-C5: There was one included study in which anti-C5 therapy was the exposure of interest. Based on this placebo-controlled RCT, there was an increased frequency of URTI and viral respiratory infection, specifically influenza, in patients with AQP4-IgG– positive neuromyelitis optica spectrum disorder (NMOSD) treated with eculizumab compared with patients receiving placebo [189], though 76% of patients received concomitant immunosuppressive therapy during the trial.

Discussion

To the best of our knowledge, this scoping review is the most up-to-date review of published evidence regarding the frequency and severity of acute viral respiratory AEs related to antirheumatic disease therapies. Our review complements the statements of the recent ACR COVID-19 Clinical Guidance Task Force regarding COVID-19 Clinical Guidance for Adult Patients with Rheumatic Diseases [190].

Trends in primary and secondary outcomes among drug classes

Acute anti-inflammatory drugs: Our review found that GC use was associated with a higher frequency of acute upper and lower respiratory viral events. The use of NSAIDs was not associated with a higher frequency of respiratory tract infections compared with placebo; however, data were limited to two RCTs in osteoarthritis (OA).

csDMARDs: The use of non-immunosuppressive csDMARDs, namely HCQ and SSZ, did not appear to increase the frequency of acute respiratory viral AEs. There was insufficient evidence to assess differences in the frequency of acute respiratory viral AEs related to calcineurin inhibitors (tacrolimus or CsA). For studies with MTX, AZA, MMF, and CYC overall, there was no signal for increased frequency of respiratory events. Of note, our findings were consistent with one of the largest placebo-controlled RCTs of MTX in a non-rheumatic disease population, which was adequately powered for safety, and did not show an increased risk for acute respiratory infections with MTX use [191]. One large prospective cohort study with LEF suggested an increased risk of pneumonia requiring hospitalization with LEF use compared to non-use [19], though we did not find other studies of LEF use that demonstrated similar findings.

tsDMARDs and bDMARDs: The use of apremilast was not found to be associated with a higher frequency of URTI or LRTI compared with placebo. In general, mild viral respiratory infections such as URTI, nasopharyngitis, and pharyngitis occurred more frequently in several studies in which patients were treated with JAKi, most notably at higher doses. Both TNFi and IL-17 inhibitors seemed to be associated with higher frequency of mild viral respiratory infections such as URTI and nasopharyngitis. Whether these findings represent a unique characteristic of these medication classes or reflect variation in AE reporting by more recent clinical trials cannot be determined by this review.

Strengths and limitations of the review

We conducted a rapid and comprehensive review of the available scientific literature to provide context for the management of antirheumatic disease therapies in people with autoimmune or inflammatory disease during the COVID-19 pandemic. The strengths of our review include the use of broad and detailed search terms, reference screening and data charting that were independently conducted by multiple reviewers, involvement of patient partners in all stages of the review process, and identification of outcomes that would be important to report in future studies. Nonetheless, this review has several limitations which should be acknowledged.

To manage this expansive undertaking, our database search focused on medications and outcomes rather than including medications for the treatment of all immune-mediated diseases. While this strategy did not capture all RCTs that reported our outcomes of interest, a broader search would have hindered our ability to rapidly synthesize the available literature and would have delayed dissemination of knowledge of potential respiratory viral AEs associated with antirheumatic therapy. Such a delay would diminish the utility of our review within the context of the COVID-19 pandemic. We attempted to mitigate the issue of potentially missing relevant studies by hand searching but acknowledge that this approach may still not capture all pertinent studies.

Several characteristics of the studies included in this review complicated analysis of possible associations between antirheumatic therapy and viral respiratory outcomes. Many did not have a comparator group, limiting the ability to assess differences in the frequency or risk of developing new respiratory viral Aes. Interpretation was also limited by exposure to multiple immunomodulatory medications without stratification of outcomes by medication. Many studies were insufficiently powered to identify a clinically relevant or statistically significant difference in viral respiratory event rates between different treatment groups. Furthermore, we cannot determine whether changes in incidence or risk of negative outcomes were caused by the treatment in question or potential confounders such as underlying rheumatic disease or the concomitant use of other medications.

In addition, safety assessments of many studies did not specify outcomes of viral respiratory complications, which may have led to selection bias. Studies that did report respiratory complications, moreover, often did not differentiate between pathogens; many studies did not specify etiologies of respiratory infections and thus reported outcomes non-specifically as URTI or LRTI. Safety assessments of many studies were limited to severe Aes or serious infections reported in aggregate without specifying organ system or severity which is in large part due to the standardized AE reporting systems used in large prospective clinical trials.

Conclusions and future research opportunities

This scoping review has identified gaps in our understanding of the impact of antirheumatic disease therapies on acute respiratory viral infections. This review identified a particularly large number of studies with data pertaining to the association of TNFi with acute respiratory viral infections, including nineteen placebo-controlled RCTs. While none of these were powered for safety, this body of evidence may be amenable to meta-analysis to determine whether TNFi use increases risk for acute respiratory viral infections. These limitations also represent an important finding of this review with implications for future study designs regarding the inclusion of frequency, severity, etiology, and complications of acute respiratory viral infection in safety assessments. Reporting viral respiratory AEs in future study designs would be of interest to rheumatology patients and practitioners in understanding the risks of medications. In future studies, patients desire improved reporting of mortality and hospitalizations related to viral respiratory AEs as these are a marker of severity of illness. In addition, with increased widespread respiratory viral PCR testing in the COVID-19 pandemic, immediate research opportunities exist to clarify the safety of antirheumatic therapies in terms of viral respiratory complications.

Disclaimers

Attestation: This work is original and is not being considered for publication elsewhere. This work has not been published previously. All authors have contributed significantly, and all authors are in agreement with the content of the manuscript. The authors declare that they have no conflicts of interest with his publication.

Author contribution

Each author has made substantial contributions to conception and design of the article, drafting the article, and revising it critically for important intellectual content. All authors read and approved the final manuscript. Views expressed are those of the authors and not necessarily those of their affiliations.

Funding

The COVID-19 Global Rheumatology Alliance receives financial support from Amgen and Janssen (Johnson & Johnson). This project was planned and completed prior to receipt of any funding.

Declaration of Competing Interest

The views expressed here are those of the authors and participating members of the COVID-19 Global Rheumatology Alliance and do not necessarily represent the views of the American College of

Rheumatology, the European League Against Rheumatism (EULAR), or any other organization.

Acknowledgments

The authors would like to acknowledge Keshini Devakandran for support with obtaining article PDFs included in the scoping review and for creating a citation library, Rachelle Buchbinder MBBS MSc and Kevin Winthrop MD MPH for consultation regarding the scoping review protocol, Regina Parker for support with *DistillerSR* software, and Amy Turner for support with team coordination. Patient representatives (Carly Harrison and Kristen Young DO MEd) were invited to participate in the review process by the COVID-19 Global Rheumatology Alliance Steering Committee and conducted abstract and full-text review, data charting, and manuscript preparation as part of the literature review teams.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2020.07.007.

References

[1] Gianfrancesco M, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2020 http://10.1136/annrheumdis-2020-217871.
[2] D'Silva KM, et al. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US 'hot spot'. Ann Rheum Dis 2020 http://10.1136/annrheumdis-2020-217888.
[3] Brito CA, et al. COVID-19 in patients with rheumatological diseases treated with anti-TNF. Ann Rheum Dis 2020. doi: 10.1136/annrheumdis-2020-218171.
[4] Favalli EG, et al. Incidence of COVID-19 in patients with rheumatic diseases treated with targeted immunosuppressive drugs: what can we learn from observational data? Arthritis Rheumatol 2020. doi: 10.1002/art.41388.
[5] Mathian A, et al. Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine. Ann Rheum Dis 2020;79(6):837–9. doi: 10.1136/annrheumdis-2020-217566.
[6] Ye C, et al. Clinical features of rheumatic patients infected with COVID-19 in Wuhan, China. Ann Rheum Dis 2020;79(8):1007–13. doi: 10.1136/annrheumdis-2020-217627.
[7] Michelena X, et al. Incidence of COVID-19 in a cohort of adult and paediatric patients with rheumatic diseases treated with targeted biologic and synthetic disease-modifying anti-rheumatic drugs. Semin Arthritis Rheum 2020;50(4):564–70. doi: 10.1016/j.semarthrit.2020.05.001.
[8] Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005;8(1):19–32. doi: 10.1080/1364557032001196l6.
[9] Tricco AC, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467–73. doi: 10.7326/M18-0850.
[10] Sheldon E, et al. Efficacy and tolerability of lumiracoxib in the treatment of osteoarthritis of the knee: a 13-week, randomized, double-blind comparison with celecoxib and placebo. Clin Ther 2005;27(1):64–77. doi: 10.1016/j.clinthera.2005.01.002.
[11] Dahlberg LE, et al. A randomized, multicentre, double-blind, parallel-group study to assess the adverse event-related discontinuation rate with celecoxib and diclofenac in elderly patients with osteoarthritis. Scand J Rheumatol 2009;38(2):133–43. doi: 10.1080/03009740802419065.
[12] Austin HA, et al. Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. J Am Soc Nephrol 2009;20(4):901–11. doi: 10.1681/ASN.2008060665.
[13] Shah M, et al. Cumulative burden of oral corticosteroid adverse effects and the economic implications of corticosteroid use in patients with systemic lupus erythematosus. Clin Ther 2013;35(4):486–97. doi: 10.1016/j.clinthera.213.03.001.
[14] Udayakumar PD, et al. Hospitalized infections in giant cell arteritis: a population-based retrospective cohort study. J Rheumatol 2014;41(12):2447–51. doi: 10.3899/jrheum.140124.
[15] Feldman CH, et al. Serious infection rates among patients with systemic lupus erythematosus receiving corticosteroids and immunosuppressants. Arthritis Rheum 2013;65:S330. (Suppl 10). doi: 10.1016/j.survophthal.2015.06.003.
[16] Best J, et al. Association between three measures of oral glucocorticoid exposure and potential adverse events among patients with rheumatoid arthritis. Arthritis Rheumatol 2015;67 (Suppl 10).
[17] Teh CL, Wan SA, Ling GR. Severe infections in systemic lupus erythematosus: disease pattern and predictors of infection-related mortality. Clin Rheumatol 2018;37(8):2081–6. doi: 10.1007/s10067-018-4102-6.
[18] Goldblatt F, et al. Serious infections in British patients with systemic lupus erythematosus: hospitalisations and mortality. Lupus 2009;18(8):682–9. doi: 10.1177//0961203308101019.
[19] Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum 2006;54(2):628–34. doi: 10.1002/art.21568.
[20] Suh C-H, et al. Serositis, hematologic involvement, and steroid dose are risk factors for serious infections in patients with systemic lupus erythematosus. Lupus Sci Med 2019;6:A22–3 (Suppl 1). doi: 10.1136/lupu-2019-lsm.29.
[21] Michaud K, Wolfe F. The association of rheumatoid arthritis and its treatment with sinus disease. J Rheumatol 2006;33(12):2412–5.
[22] Alibaz-Oner F, et al. Assessment of prognosis and damage in patients withaAdult henochsSchonlein purpura retrospective multicentered cohort study. Rheumatology (Oxford) 2017;56 (Suppl 3): p. iii85-iii86. doi: 10.1093/rheumatology/kex151.
[23] Izumi Y, et al. The 23-valent pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis: a double-blinded, randomized, placebo-controlled trial. Arthritis Res Ther 2017;19(1):15. doi: 10.1186/s13075-016-1207-7.
[24] Tanaka Y, et al. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. Arthritis Care Res (Hoboken) 2011;63(8):1150–8. doi: 10.1002/acr.20494.
[25] Kremer JM, et al. A phase IIb study of ABT-494, a selective JAK-1 inhibitor, in patients with rheumatoid arthritis and an anadequater response to anti-tumor necrosis factor therapy. Arthritis Rheumatol 2016;68(12):2867–77. doi: 10.1002/art.39801.
[26] Genovese MC, et al. One-year efficacy and safety results of secukinumab in patients with rheumatoid arthritis: phase II, dose-finding, double-blind, randomized, placebo-controlled study. J Rheumatol 2014;41(3):414–21. doi: 10.3899/jrhem.130637.
[27] Li Z, et al. Safety and efficacy of subcutaneous golimumab in chinese patients with active rheumatoid arthritis despite mtx therapy: results from a randomized, placebo-controlled, phase 3 trial. Ann Rheum Dis 2013;72:444. (Suppl 3). doi: 10.3899/jrheum.150712.
[28] Emery P, et al. Five-year safety and efficacy of golimumab in methotrexate-naïve patients with rheumatoid arthritis: final study results of the phase 3, randomized, placebo-controlled go-before trial. Ann Rheum Dis 2013;72:432. (Suppl 3).
[29] Kingsley GH, et al. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. Rheumatology (Oxford) 2012;51(8):1368–77. doi: 10.1093/rheumatology/kes001.
[30] van Dongen H, et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2007;56(5):1424–32. doi: 10.1002/art.22525.
[31] Ishiguro N, et al. Concomitant iguratimod therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate: a randomized, double-blind, placebo-controlled trial. Mod Rheumatol 2013;23(3):430–9. doi: 10.3109/s10165-012-0724-8.
[32] Bijlsma JWJ, et al. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. Lancet 2016;388(10042):343–55. doi: 10.1016/S014-6736(16)30363-4.
[33] Hara M, et al. Safety and efficacy of combination therapy of iguratimod with methotrexate for patients with active rheumatoid arthritis with an inadequate response to methotrexate: an open-label extension of a randomized, double-blind, placebo-controlled trial. Mod Rheumatol 2014;24(3):410–8. doi: 10.3109/14397595.2013.843756.
[34] Grijalva CG, et al. Initiation of rheumatoid arthritis treatments and the risk of serious infections. Rheumatology (Oxford) 2010;49(1):82–90. doi: 10.1093/rheumatology/kep325.
[35] Grijalva C, et al. Risk of serious infections among patients with rheumatoid arthritis initiating treatment with tumor necrosis alpha antagonists. Pharmacoepidemiol Drug Saf 2009;18:S105–6 (Suppl 1).
[36] Coyne P, et al. Acute lower respiratory tract infections in patients with rheumatoid arthritis. J Rheumatol 2007;34(9):1832–6.
[37] McGregor JG, et al. Adverse events and infectious burden, microbes and temporal outline from immunosuppressive therapy in antineutrophil cytoplasmic antibody-associated vasculitis with native renal function. Nephrol Dial Transplant 2015;30(1):i171–81 Suppl. doi: 10.1093/ndt/gfv045.
[38] Aygun D, et al. The frequency of infections in patients with juvenile idiopathic arthritis on biologic agents: 1-year prospective study. Clin Rheumatol 2019;38(4):1025–30. doi: 10.1007/s10067-018-4367-9.
[39] Holland-Fischer M, et al. Prognosis of pneumonia in patients with rheumatoid arthritis: the role of medication and disease activity prior to admission a population-based cohort study. RMD Open 2020;6(1):e001102. doi: 10.1136/rmdopen-2019-001102.
[40] Wei X-N, et al. Older age, hypoalbuminaemia and renal failure might be poor prognosis factors for low dose methotrexate-induced myelosuppression in patients with rheumatoid arthritis. Ann Rheum Dis 2017;76(2):279–80 Suppl. doi: 10.1136/annrhemdis-2017-eular.3723.
[41] Yoo HG, et al. Risk factors of severe infections in patients with rheumatoid arthritis treated with leflunomide. Mod Rheumatol 2013;23(4):709–15. doi: 10.3109/s10165-012-0716-8.
[42] Hansen KE, et al. The safety and efficacy of leflunomide in combination with infliximab in rheumatoid arthritis. Arthritis Rheum 2004;51(2):228–32. doi: 10.1002/art.20228.

[43] Jenks KA, et al. Leflunomide-associated infections in rheumatoid arthritis. J Rheumatol 2007;34(11):2201–3.
[44] Dooley MA, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med 2011;365(20):1886–95.
[45] Chan TM, et al. Treatment of membranous lupus nephritis with nephrotic syndrome by sequential immunosuppression. Lupus 1999;8(7):545–51. doi: 10.1191/096120399678840837.
[46] Rojas-Serrano J, et al. High prevalence of infections in patients with systemic lupus erythematosus and pulmonary haemorrhage. Lupus 2008;17(4):295–9.
[47] Rovin BH, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the lupus nephritis assessment with rituximab study. Arthritis Rheum 2012;64(4):1215–26. doi: 10.1002/art.3459.
[48] Ordi-Ros J, et al. Enteric-coated mycophenolate sodium versus azathioprine in patients with active systemic lupus erythematosus: a randomised clinical trial. Ann Rheum Dis 2017;76(9):1575–82.
[49] Ginzler EM, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med 2005;353(21):2219–28.
[50] Appel GB, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol 2009;20(5):1103–12. doi: 10.1681/ASN.2008101028.
[51] Tashkin DP, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med 2016;4(9):708–19. doi: 10.1016/S2213-2600(16)30152-7.
[52] Ong LM, et al. Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. Nephrology (Carlton) 2005;10(5):504–10. doi: 10.1111/j.1440-1797.2005.00444.x.
[53] Mok CC, et al. Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up. Ann Rheum Dis 2016;75(1):30–6.
[54] Yap DY, et al. Long-term data on tacrolimus treatment in lupus nephritis. Rheumatology (Oxford) 2014;53(12):2232–7. doi: 10.1093/rheumatology/keu265.
[55] Guillevin L, et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. Arthritis Rheum 1997;40(12):2187–98. doi: 10.1002/art.1780401213.
[56] Cavallasca JA, et al. Severe infections in patients with autoimmune diseases treated with cyclophosphamide. Reumatol Clín 2015;11(4):221–3. doi: 10.1016/j.reumae.2014.11.002.
[57] Banerjee S, et al. Low incidence of opportunistic infections in lupus patients treated with cyclophosphamide and steroids in a tertiary care setting. Med Res Arch 2017;5(3). doi: 10.18103/mra.v5i3.1084.
[58] Kwon HM, et al. Efficacy and safety of long term cyclophosphamide treatment for interstitial lung disease in systemic sclerosis. Ann Rheum Dis 2014;73(2):1011. Suppl.
[59] Papp KA, et al. Efficacy and safety of apremilast in subjects with moderate to severe plaque psoriasis: results from a Phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison study. J Eur Acad Dermatol Venereol 2013;27(3):e376–83. doi: 10.1111/j.1468-3083.2012.04716.x.
[60] Papp K, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (efficacy and safety trial evaluating the effects of apremilast in psoriasis [ESTEEM] 1). J Am Acad Dermatol 2015;73(1):37–49. doi: 10.1016/j.jaad.2015.03.049.
[61] Mease PJ, et al. Long-term safety and tolerability of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis: pooled safety analysis of three Phase 3, randomized, controlled trials. Arthritis Rheum 2013;65(10):S131–2 Suppl.
[62] Burmester GR, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018;391(10139):2503–12. doi: 10.1016/S0140-6736(18)31115-2.
[63] Genovese MC, et al. VX-509 (Decernotinib), an oral selective JAK-3 inhibitor, in combination With methotrexate in patients with rheumatoid arthritis. Arthritis Rheumatol 2016;68(1):46–55. doi: 10.1002/art.39473.
[64] Genovese MC, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. Lancet 2018;391(10139):2513–24. doi: 10.1016/S0140-6736(18)31116-4.
[65] Genovese MC, et al. Effect of filgotinib vs placebo on clinical response in patients with moderate to severe rheumatoidarthritisrRefractory to disease-modifying antirheumatic drug therapy: the FINCH 2 randomized clinical trial. JAMA 2019;322(4):315–25. doi: 10.1001/jama.2019.9055.
[66] Takeuchi T, et al. A Phase 2B study of an oral JAK inhibitor ASP015K monotherapy in japanese patients with moderate to severe rheumatoid arthritis. Ann Rheum Dis 2014;73(2) Suppl117-117.
[67] Gladman D, et al. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. N Engl J Med 2017;377(16):1525–36. doi: 10.1056/NEJMoa1615977.
[68] Mease P, et al. Tofacitinib or Adalimumab versus placebo for psoriatic arthritis. N Engl J Med 2017;377(16):1537–50. doi: 10.1056/NEJMoa1615975.
[69] van der Heijde D, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis (TORTUGA): results from a randomised, placebo-controlled, phase 2 trial. Lancet 2018;392(10162):2378–87. doi: 10.1016/S0140-6736(18)32463-2.
[70] van der Heijde D, et al. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. Lancet 2019;394(10214):2108–17. doi: 10.1016/S0140-6736(19)32534-6.
[71] Genovese MC, et al. two-year safety and effectiveness of peficitinib in moderate-to-severe rheumatoid arthritis: a Phase IIb, open-label extension study. Rheumatol Ther 2019;6(4):503–20. doi: 10.1007/s40744-019-00167-6.
[72] Cohen S, et al. Analysis of infections and all-cause mortality in phase II, phase III, and long-term extension studies of tofacitinib in patients with rheumatoid arthritis. Arthritis Rheumatol 2014;66(11):2924–37. doi: 10.1002/art.38779.
[73] Smolen JS, et al. Safety profile of baricitinib in patients with active rheumatoid arthritis with over 2 years median time in treatment. J Rheumatol 2019;46(1):7–18. doi: 10.3899/jrheum.171361.
[74] Tamura N, et al. AB0495 Post-marketing surveillance of tofacitinib in japanese patients with rheumatoid arthritis: an interim report of safety data. Ann Rheum Dis 2018;77(2) Suppl1408-1408.
[75] Bates BA, et al. Oral kinase inhibitors, biologics and serious infection in rheumatoid arthritis. Pharmacoepidemiol Drug Saf 2019;28(2):482. Suppl.
[76] Boza NC, et al. Safety of JAK inhibitors in patients with rheumatoid arthritis in conditions of daily clinical practice. Ann Rheum Dis 2019;78(2):1681–2 Suppl.
[77] Mease PJ, et al. Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis. Ann Rheum Dis 2017;76(9):1550–8.
[78] Ruperto N, et al. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. Arthritis Rheum 2010;62(6):1792–802.
[79] Chandrashekara S, et al. Subcutaneous abatacept in patients with an inadequate response to methotrexate: safety and efficacy data in Indian sub-population from acquire (abatacept comparison of subcutaneous versus intravenous in inadequate responders to methotrexate) trial: a large phase IIIB non-inferiority study. Indian J Rheumatol 2013;8(1):S34. Suppl.
[80] Fleming D, et al. Incidence rates of adverse events with death as an outcome during abatacept treatment in RA: results from an integrated data analysis from 16 clinical trials. Arthritis Rheumatol 2017;69(10) Suppl.
[81] Simon TA, et al. Infections requiring hospitalization in the abatacept clinical development program: an epidemiological assessment. Arthritis Res Ther 2010;12(2):R67. doi: 10.1186/ar2984.
[82] Alten R, et al. SAT0128 prolonged exposure to subcutaneous and intravenous abatacept in patients with rheumatoid arthritis does not affect rates of infection, malignancy and autoimmune events: results from pooled clinical trial data. Ann Rheum Dis 2014;72 A624-A624.
[83] Yun H, et al. Risk of hospitalised infection in rheumatoid arthritis patients receiving biologics following a previous infection while on treatment with anti-TNF therapy. Ann Rheum Dis 2015;74(6):1065–71.
[84] Yun H, et al. comparative risk of hospitalized infection associated with biologic agents in rheumatoid arthritis patients enrolled in medicare. Arthritis Rheumatol 2016;68(1):56–66. doi: 10.1002/art.39399.
[85] Bello SL, et al. Incidence of influenza-like illness into a cohort of patients affected by chronic inflammatory rheumatism and treated with biological agents. Reumatismo 2012;64(5):299–306.
[86] Tahara M, et al. Safety and efficacy of rituximab in neuromyelitis optica spectrum disorders (RIN-1 study): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet Neurol 2020;19(4):298–306. doi: 10.1016/S1474-4422(20)30066-1.
[87] Merrill JT, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum 2010;62(1):222–33. doi: 10.1002/art.27233.
[88] Emery P, et al. Serious infections with ocrelizumab in rheumatoid arthritis: pooled results from double-blind periods of the ocrelizumab phase III ra program. Arthritis Rheum 2010;62(10):S175. Suppl.
[89] Sun YS, et al. Cytomegaloviral or pneumocystis jiroveci pneumonia increases mortality in systemic lupus erythematosus patients with pulmonary hemorrhage: evidence from bronchoalveolar lavage fluid. J Rheumatol 2019;46(3):251–8. doi: 10.3899/jrheum.180104.
[90] McCarthy EM, et al. Short-term efficacy and safety of rituximab therapy in refractory systemic lupus erythematosus: results from the British Isles Lupus Assessment Group Biologics Register. RheumatologyRheumatology 2018;57(3):470–9. doi: 10.1093/rheumatology/kex395.
[91] Erkan D, et al. A pilot open-label phase II trial of rituximab for non-criteria manifestations of antiphospholipid syndrome. Arthritis Rheum 2013;65(2):464–71. doi: 10.1002/art.37759.
[92] Cartin-Ceba R, et al. Rituximab for remission induction and maintenance in ANCA-associated vasculitis: a single-center ten-year experience in 108 patients. Arthritis Rheum 2010;62(10):680. Suppl.
[93] Matteson EL, et al. Open-label, pilot study of the safety and clinical effects of rituximab in patients with rheumatoid arthritis-associated interstitial pneumonia. Arthritis Rheum 2012;63 10 Suppl 1.
[94] Becerra E, Cambridge G, Leandro MJ. Safety and efficacy of rituximab in patients with rheumatoid arthritis and lung involvement. Arthritis Rheum 2012;64(10):S220. Suppl.
[95] Keir G, et al. Rituximab in severe, treatment refractory connective tissue disease associated interstitial lung disease. Respirology 2014;19(2):18. Suppl. doi: 10.1111/resp.12214.

[96] Pathak H, et al. Rituximab and late-onset neutropenia: a retrospective analysis of rituximab-treated adult rheumatoid arthritis patients in a teaching hospital. RheumatologyRheumatology 2017;56(2):ii131. Suppl. doi: 10.1093/rheumatology/kex062.209.

[97] Kougkas N, et al. Stabilization of rheumatoid arthritis associated interstitial lung diseaseby rituximab: a single center experience with long-term follow-up. Ann Rheum Dis 2019;78(2):1149. Suppl.

[98] Feijoo ML, Aulestia N, Rodriguez Montero, Sergio & Marenco Jose. AB0459 Treatment of systemic autoimmune diseases with rituximab: safety data. Annals of the Rheumatic Diseases, 2017;76:1211.1–1211. doi: 10.1136/annrheumdis-2017-eular.3890.

[99] Yurttas B, Egeli B, Ugurlu S. Rituximab therapy in lupus nephritis resistant to conventional therapy: a single center experience (case series). Lupus Sci Med 2019;6(1):A189–90 Suppl. doi: 10.1136/lupus-2019-lsm.255.

[100] Coffey C, et al. Rituximab therapy for systemic rheumatoid vasculitis: indications, outcomes and adverse events. Arthritis Rheumatol 2018;70(9):916. Suppl.

[101] Sharma A, et al. Efficacy and safety of biomimic rituximab in granulomatosis with polyangiitis-experience from a single tertiary care centre in india. Arthritis Rheumatol, 2018;70(9):1968–70 Suppl.

[102] Kavcic M, et al. Leveraging administrative data to monitor rituximab use in 2875 patients at 42 freestanding children's hospitals across the United States. J Pediatr 2013;162(6):1252–8 e1. doi: 10.1016/j.jpeds.2012.11.038.

[103] Duarte AC, et al. Rituximab in connective tissue disease-associated interstitial lung disease. Clin Rheumatol 2019;38(7):2001–9. doi: 10.1007/s10067-019-04557-7.

[104] Khelkovskaya A, et al. Rituximab treatment of the antisynthetase syndrome. Ann Rheum Dis 2014;73(2):701. Suppl.

[105] Holle JU, et al. Rituximab for refractory granulomatosis with polyangiitis (Wegener's granulomatosis): comparison of efficacy in granulomatous versus vasculitic manifestations. Ann Rheum Dis 2012;71(3):327–33.

[106] Chakravarty EF, et al. Pregnancy outcomes after maternal exposure to rituximab. Blood 2011;117(5):1499–506. doi: 10.1182/blood-2010-07-295444.

[107] D'Cruz D, et al. Efficacy and safety of belimumab in patients of black race with systemic lupus erythematosus: results from the EMBRACE study. Lupus Sci Med 2019;6(1):A149–50 Suppl. doi: 10.1136/lupus-2019-lsm.200.

[108] Merrill JT, et al. Long-term safety profile of belimumab plus standard therapy in patients with systemic lupus erythematosus. Arthritis Rheum 2012;64 (10):3364–73. doi: 10.1002/art.34564.

[109] Wallace DJ, et al. Safety profile of belimumab: pooled data from placebo-controlled phase 2 and 3 studies in patients with systemic lupus erythematosus. Lupus 2013;22(2) 144-54. doi: 10.1177/0961203312469259.

[110] Fraser P, Chin W, Kao A. Atacicept: integrated safety profile from phase II randomized placebo-controlled studies in autoimmune diseases. Arthritis Rheumatol 2016;68(10):1020–2 Suppl.

[111] Iaccarino L, et al. Belimumab reduces the frequency of flares and prevents damage progression in SLE patients: experience in a clinical practice setting. Arthritis Rheumatol 2015;67(10) Suppl.

[112] Cai L, et al. Efficacy and safety of adalimumab in Chinese patients with moderate-to-severe plaque psoriasis: results from a phase 3, randomized, placebo-controlled, double-blind study. J Eur Acad Dermatol Venereol 2017;31(1):89–95. doi: 10.1111/jdv.13746.

[113] Landewé R, et al. Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ABILITY-3): a multicentre, randomised, double-blind study. Lancet 2018;392(10142):134–44. doi: 10.1016/S0140-6736(18)31362-X.

[114] van der Heijde D, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2006;54(7) 2136-46.

[115] Mease PJ, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2005;52(10):3279–89. doi: 10.1002/art.21306.

[116] Keystone EC, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 2004;50(5):1400–11. doi: 10.1002/art.20217.

[117] Landewé R, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis 2014;73 (1):39–47.

[118] Reich K, et al. Maintenance of response with certolizumab pegol for the treatment of chronic plaque psoriasis: 48-week results from two ongoing Phase III, multicenter, randomized, placebocontrolled studies (CIMPASI-1 and CIMPASI-2). J Clin Aesthet Dermatol 2018;11(5 Suppl 1):S22.

[119] Weisman MH, et al. A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. Rheumatology (Oxford) 2007;46(7) 1122-5. doi: 10.1093/rheumatology/kem033.

[120] Mease PJ, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum 2004;50(7) 2264-72. doi: 10.1002/art.20335.

[121] Inman RD, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum 2008;58(11) 3402-12. doi: 10.1002/art.23969.

[122] Weinblatt ME, et al. Intravenous golimumab is effective in patients with active rheumatoid arthritis despite methotrexate therapy with responses as early as week 2: results of the phase 3, randomised, multicentre, double-blind, placebo-controlled GO-FURTHER trial. Ann Rheum Dis 2013;72(3) 381-9.

[123] Smolen JS, et al. Five-year safety and efficacy of golimumab in patients with active rheumatoid arthritis despite previous anti-tumor necrosis factor therapy: final study results of the phase 3, randomized, placebo-controlled go-after trial. Ann Rheum Dis 2013;72(3):232. Suppl.

[124] Keystone E, et al. Final 5-year safety and efficacy results of a phase 3, randomized placebo-controlled trial of golimumab in patients with active rheumatoid arthritis despite prior treatment with methotrexate. Rheumatology (Oxford) 2014;53(1):i99. Suppl.

[125] Keystone E, et al. Long-term safety and efficacy of certolizumab pegol in combination with methotrexate in the treatment of rheumatoid arthritis: 5-year results from the RAPID 1 trial and open-label extension. Ann Rheum Dis 2014;73(12) 2094-100.

[126] Antoni C, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis 2005;64(8):1150–7.

[127] Antoni CE, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum 2005;52 (4):1227–36.

[128] van der Heijde D, et al. Efficacy and safety of ixekizumab in patients with active psoriatic arthritis: 52-week results from a Phase III study (SPIRIT-P1). J Rheumatol 2018;45(3):367–77. doi: 10.3899/jrheum.170429.

[129] Alten R, et al. Efficacy and safety results of a phase iii study comparing fkb327, an adalimumab biosimilar, with the adalimumab reference product in patients with active rheumatoid arthritis. Ann Rheum Dis 2017;76(2):59. Suppl.

[130] Fleischmann RM, et al. A comparative clinical study of PF-06410293, a candidate adalimumab biosimilar, and adalimumab reference product (Humira(R)) in the treatment of active rheumatoid arthritis. Arthritis Res Ther 2018;20(1):178.

[131] Ruscitti P, et al. Anti-interleukin-1 treatment in patients with rheumatoid arthritis and type 2 diabetes (TRACK): a multicentre, open-label, randomised controlled trial. PLoS Med 2019;16(9):e1002901. doi: 10.1371/journal.pmed.1002901.

[132] Mease PJ, et al. Etanercept and methotrexate as monotherapy or in combination for psoriatic arthritis: primary results from a randomized, controlled phase iii trial. Arthritis Rheumatol 2019;71(7):1112–24. doi: 10.1002/art.40851.

[133] Lipsky PE, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study group. N Engl J Med 2000;343(22):1594–602. doi: 10.1056/NEJM200011303432202.

[134] Breedveld FC, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54(1):26–37. doi: 10.1002/art.21519.

[135] Weinblatt ME, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 2003;48 (1):35–45.

[136] Lebwohl M, et al. Certolizumab pegol for the treatment of chronic plaque psoriasis: results through 48 weeks of a phase 3, multicenter, randomized, double-blind, etanercept- and placebo-controlled study (CIMPACT). J Am Acad Dermatol 2018;79(2):266–76 e5. doi: 10.1016/j.jaad.2018.04.012.

[137] Emery P, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2008;372(9636) 375-82. doi: 10.1016/S0140-6736(08)61000-4.

[138] Chaparro M, et al. Infliximab salvage therapy after failure of ciclosporin in corticosteroid-refractory ulcerative colitis: a multicentre study. Aliment Pharmacol Ther 2012;35(2) 275-83. doi: 10.1111/j.1365-2036.2011.04934.x.

[139] Holland-Fischer M, et al. Ankylosing spondylitis and mortality following hospitalised pneumonia: a population-based cohort study. RMD Open 2020;6(1): e001140.

[140] Pawar A, et al. Risk of serious infections in tocilizumab versus other biologic drugs in patients with rheumatoid arthritis: a multidatabase cohort study. Ann Rheum Dis 2019;78(4):456–64.

[141] Sleptsova T, et al. Efficacy of infliximab treatment in patients with early and longstanding juvenile idiopathic arthritis. Clin Exp Rheumatol 2011;29(2):460–1.

[142] Nakajima A, et al. No evidence of increased mortality in rheumatoid arthritis patients treated with biologics: results from a multicenter cohort in Japan. Arthritis Rheum 2011;63(10 Suppl 1).

[143] Michaud K, et al. Infection Risk by Type and Treatment for Patients with Rheumatoid Arthritis (RA). Ann Rheum Dis 2014;73(2):126–7 Suppl.

[144] Michaud K, et al. Serious infection risk by treatments and types in patients with RA. Arthritis Rheumatol 2014;66(10):S206–7 Suppl.

[145] Choy EH, et al. Treatment of rheumatoid arthritis with an anti-tumor necrosis factor agent or tocilizumab as first biologic therapy in a global comparative observational study. Arthritis Rheumatol 2017;67(10) Suppl.

[145] Richter A, et al. The impact of biologic DMARD treatment on sepsis and mortality after serious infection. Arthritis Rheumatol 2015;67(10) Suppl.

[147] Colombel JF, et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. Gastroenterology 2004;126 (1):19–31. doi: 10.1053/j.gastro.2003.10.047.

[148] Zamora-Legoff JA, et al. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. Clin Rheumatol 2016;35(10) 2585-9.
[149] Selvan S, Magliano M, Hall J. safety and efficacy of certolizumab compared with other anti-tnf agents in rheumatoid arthritis patients treated at bucks healthcare trust. Rheumatology (Oxford) 2015;54(1):i102. Suppl. doi: 10.1093/rheumatology/kev089.019.
[150] Lane MA, et al. TNF-alpha antagonist use and risk of hospitalization for infection in a national cohort of veterans with rheumatoid arthritis. Medicine (Baltimore) 2011;90(2) 139-45. doi: 10.1097/.0b013e318211106a.
[151] Hashimoto A, et al. Incidence and risk factors for infections requiring hospitalization, including pneumocystis pneumonia, in japanese patients with rheumatoid arthritis. Int J Rheumatol 2017;2017. doi: 10.1155/2017/6730812.
[152] Salonen PH, et al. Decreasing trend in the incidence of serious pneumonias in Finnish children with juvenile idiopathic arthritis. Clin Rheumatol 2020;39 (3):853–60.
[153] Lawrance IC, et al. Serious infections in patients with inflammatory bowel disease receiving anti-tumor-necrosis-factor-alpha therapy: an Australian and New Zealand experience. J Gastroenterol Hepatol 2010;25(11) 1732-8. doi: 10.1111/j.1440-1746.2010.06407.x.
[154] Horneff G, et al. Safety of adalimumab in pediatric patients with polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, psoriasis, and crohn's disease. J Pediatr 2018;201:166–75 e3. doi: 10.1016/j.jpeds.2018.05.042.
[155] Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis. Rheumatology (Oxford) 2007;46(7):1157–60. doi: 10.1093/rheumatology/kem076.
[156] Philipp S, et al. Combination of adalimumab with traditional systemic antipsoriatic drugs - a report of 39 cases. J Ger Soc Dermatol 2012;10(11):821–37. doi: 10.1111/j.1610-0387.2012.07976.x.
[157] Aksoy A, et al. Efficacy of TNFα inhibitors for refractory vascular Behçet's disease: a multicenter observational study of 27 patients and a review of the literature. Int J Rheum Dis 2020;23(2):256–61. doi: 10.1111/1756-185X.13778.
[158] Calvo I, et al. Experience in the treatment with etanercept in patients with Juvenile Idiopathic Arthritis under 4 years. Clin Exp Rheumatol 2011;29(2):387.
[159] Ferrante M, et al. Infliximab for severe iv steroid-refractory ulcerative colitis: can infliximab trough levels guide our management? Gastroenterology 2011;140(5 Suppl 1):S275–6. doi: 10.1016/S0016-5085(11)61105-0.
[160] Cohen S, et al. Tofacitinib, an oral Janus kinase inhibitor: analysis of infections and all-cause mortality across Phase 3 and long-term extension studies in patients with rheumatoid arthritis. Int J Rheum Dis 2011;15(1):68. Suppl. doi: 10.1002/art.33419.
[161] Hoffman HM, et al. Rilonacept: long-term safety profile in patients with cryopyrin-associated periodic syndromes (CAPS). Arthritis Rheum 2009;60(10) Suppl.
[162] Fleischmann RM, et al. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. Ann Rheum Dis 2006;65(8):1006–12.
[163] Ilowite N, et al. Anakinra in the treatment of polyarticular-course juvenile rheumatoid arthritis: safety and preliminary efficacy results of a randomized multicenter study. Clin Rheumatol 2009;28(2):129–37. doi: 10.1007/s10067-008-0995-9.
[164] Schlesinger N, et al. Effect of canakinumab vs triamcinolone acetonide for treatment of gouty arthritis in patients who are unable to use nsaids and colchicine or with severe gouty arthritis. Ann Rheum Dis 2013;71(3):439. Suppl.
[165] Ugurlu S, et al. Anakinra treatment in refractory cases of adult-onset still disease: case series. Arthritis Rheumatol 2018;70(9):1449. Suppl.
[166] Szepietowski JC, et al. A phase 1, randomized, double-blind, placebo-controlled, multiple, intravenous, ascending-dose study of sirukumab in patients with cutaneous or systemic lupus erythematosus. Arthritis Rheum 2013;63(10 Suppl 1). doi: 10.1517/13543784.2016.1162291.
[167] Mazurov V, et al. Short-term efficacy of BCD-089, novel monoclonal Anti-IL-6 receptor antibody, in combination with methotrexate in patients with rheumatoid arthritis: 12-week results of Phase 2 aurora study. Ann Rheum Dis 2019;78 (2):721. Suppl.
[168] Khanna D, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet 2016;387(10038):2630–40. doi: 10.1016/S0140-6736(16)00232-4.
[169] Fleischmann R, et al. Sarilumab and nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis and inadequate response or intolerance to tumor necrosis factor inhibitors. Arthritis Rheumatol 2017;69(2):277–90. doi: 10.1002/art.39944.
[170] Schiff MH, et al. Integrated safety in tocilizumab clinical trials. Arthritis Res Ther 2011;13(5):R141. doi: 10.1186/ar3455.
[171] Koike T, et al. Post-marketing surveillance program of tocilizumab for RA in Japan interim analyses of 3,881 patients. Arthritis Rheum 2011;62(10):399. Suppl.
[172] Aletaha D, et al. Integrated phase 3 safety results of sirukumab, an anti-IL-6 cytokine monoclonal antibody, in patients with active rheumatoid arthritis. Arthritis Rheumatol 2017;69(10) Suppl.
[173] Uchimura T, et al. The clinical feature of 20092010 influenza virus infection during tocilizumab treatment for systemic onset juvenile idiopathic arthritis. Arthritis Rheum 2010;62(10):237. Suppl.
[174] Horneff G, et al. Safety and efficacy of tocilizumab in children with systemic juvenile idiopathic arthritis. Pediatric Rheumatology 2015;13(1):P165. Suppl. doi: 10.1186/1546-0096-13-S1-P165.
[175] Maeda K, et al. C-Reactive protein does not elevate in half of pneumonia cases for the entire observation period of pneumonia during tocilizumab treatment for rheumatoid arthritis. Ann Rheum Dis 2014;73(2):506. Suppl.
[176] Ritchlin C, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis 2014;73(6) 990-9.
[177] McInnes IB, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet 2013;382(9894):780–9. doi: 10.1016/S0140-6736(13)60594-2.
[178] Gottlieb A, et al. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet 2009;373(9664):633–40. doi: 10.1016/S0140-6736(09)60140-9.
[179] Feagan BG, et al. Risankizumab in patients with moderate to severe Crohn's disease: an open-label extension study. Lancet Gastroenterol Hepatol 2018;3 (10):671–80. doi: 10.1016/S2468-1253(18)30233-4.
[180] McInnes IB, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015;386(9999):1137–46.
[181] Mease P, et al. Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study. Ann Rheum Dis 2018;77(6):890–7.
[182] van der Heijde D, et al. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. Lancet 2018;392(10163):2441–51. doi: 10.1016/S0140-6736(18)31946-9.
[183] Deodhar A, et al. Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): a randomised, placebo-controlled trial. Lancet 2020;395 (10217):53–64. doi: 10.1016/S0140-6736(19)32971-X.
[184] Deodhar AA, et al. Safety and tolerability of secukinumab in patients with active ankylosing spondylitis: pooled safety analysis of two phase 3, randomized, controlled trials. Arthritis Rheumatol 2015;67(S10):1–4046.
[185] Combe B, et al. Safety results of ixekizumab with *1822*.2 patient-years of exposure: an integrated analysis of 3 clinical trials in adult patients with psoriatic arthritis. Arthritis Res Ther 2020;22:14. doi: 10.1186/s13075-020-2099-0.
[186] Mease P, et al. Secukinumab safety and tolerability in patients with active psoriatic arthritis: pooled safety analysis of two phase 3, randomized, controlled trials (future 1 and future 2). Ann Rheum Dis 2015;74(2):870–1 Suppl.
[187] Lau AN, et al. Occurrence of serious infection in patients with rheumatoid arthritis treated with biologics and denosumab observed in a clinical setting. J Rheumatol 2018;45(2):170–6. doi: 10.3899/jrheum.161270.
[188] Morand EF, et al. Trial of anifrolumab in active systemic lupus erythematosus. N Engl J Med 2020;382(3):211–21. doi: 10.1056/NEJMoa1912196.
[189] Pittock SJ, et al. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. N Engl J Med 2019;381(7):614–25. doi: 10.1056/NEJMoa1900866.
[190] Mikuls TR, et al. American college of rheumatology guidance for the management of rheumatic disease in adult patients during the covid-19 pandemic: version *1*. Arthritis Rheumatol 2020. doi: 10.1002/art.41301.
[191] Solomon DH, et al. Adverse effects of low-dose methotrexate: a randomized trial. Ann Intern Med 2020;172(6):369–80. doi: 10.7326/M19-3369.

Further reading

[192] Mease PJ, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum 2004;50(7):2264–72. doi: 10.1002/art.20335.1.