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

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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.

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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 empirical 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 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 five 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 iguratimod 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 was insufficient to draw conclusions regarding the use of AZA and risk of pulmonary infections in patients with SLE or lupus nephritis (LN).

**Mycrepanolate:** There were nine included studies in which mycrepanolate 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.

**Tocrolimus, 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 mediation 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
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
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], 5 cohorts [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

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**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                            | 408                               | 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                        | 395,466                           | 24.44%   | 82.33%   |
| Randomized controlled trial | 89                     | 39,041                             | 49.44%   | 8.11%    |
| Pooled safety analysis/postmarketing surveillance | 15 | 41,332                           | 8.33%    | 8.66%    |
| Continent                |                              |                                   |          |          |
| Multiple                 | 68                           | 55,621                            | 37.78%   | 11.58%   |
| North America            | 41                           | 379,468                           | 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%    | 0.26%    |
| 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                            | 2987                              | 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                    | 89,228                            | 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%    |
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 URITI in patients receiving IL-17 inhibitors compared to placebo. There was a numerically higher frequency of nasopharyngitis and URITI 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 URITI, 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 URITI 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].

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); URITI, upper respiratory tract infection, includes sinusitis, nasopharyngitis, pharyngitis; LRTI, lower respiratory tract infection, includes bronchitis, pneumonia.
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).

cDMARDs: The use of non-immunosuppressive cDMARDs, 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.

tDMARDs 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 anti-rheumatic 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.

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**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
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Supplementary materials

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