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MAJOR ARTICLE

Immune-Based Therapy for Hospitalized Patients With COVID-19 and Risk of Secondary Infections: A Systematic Review and Meta-analysis

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Background. Immune-based therapies are standard-of-care treatment for coronavirus disease 2019 (COVID-19) patients requiring hospitalization. However, safety concerns related to the potential risk of secondary infections may limit their use.

Methods. We searched OVID Medline, Ovid EMBASE, SCOPUS, Cochrane Library, clinicaltrials.gov, and PROSPERO in October 2020 and updated the search in November 2021. We included randomized controlled trials (RCTs). Pairs of reviewers screened abstracts and full studies and extracted data in an independent manner. We used RevMan to conduct a meta-analysis using random-effects models to calculate the pooled risk ratio (RR) and 95% CI for the incidence of infection. Statistical heterogeneity was determined using the I^2 statistic. We assessed risk of bias for all studies and rated the certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation methodology. We conducted a meta-regression using the R package to meta-explore whether age, sex, and invasive mechanical ventilation modified risk of infection with immune-based therapies. The protocol is registered with PROSPERO (CRD42021229406).

Results. This was a meta-analysis of 37 RCTs including 32 621 participants (mean age, 60 years; 64% male). The use of immune-based therapy for COVID-19 conferred mild protection for the occurrence of secondary infections (711/15 721, 4.5%, vs 616/16 900, 3.6%; RR, 0.82; 95% CI, 0.71–0.95; $P = .008$; $I^2 = 28\%$). A subgroup analysis did not identify any subgroup effect by type of immune-based therapies ($P = .85$). A meta-regression revealed no impact of age, sex, or mechanical ventilation on the effect of immune-based therapies on risk of infection.

Conclusions. We identified moderate-certainty evidence that the use of immune-based therapies in COVID-19 requiring hospitalization does not increase the risk of secondary infections.

Keywords. COVID-19; immunotherapy; secondary infection.

The optimal management of coronavirus disease 2019 (COVID-19) has evolved with our understanding of the disease pathophysiology. Earlier in the pandemic, treatment focused on medications with antiviral properties, with formal recommendation against the routine use of systemic corticosteroids for COVID-19. This stemmed not only from prior data demonstrating lack of benefit in terms of mortality, length of hospitalization, and intensive care unit admission, but also from increased rates of adverse effects with the use of corticosteroids for severe Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome (SARS), and COVID-19 [1, 2]. Moreover, corticosteroids increased the risk of secondary infections in hospitalized patients with influenza [3].

As the COVID-19 pandemic progressed, evidence suggested that an aberrant immune response is the key contributor to severe COVID-19. Consequently, immune-based therapies such as corticosteroids, tocilizumab (interleukin-6 inhibitor), and baricitinib (Janus Kinase inhibitor) were studied further for treatment of severe COVID-19. Furthermore, based on data showing a survival benefit of some of the immune-based therapies, their use is now supported by consensus guidelines [4].

As immune-based therapies are now the standard of care for treatment of severe COVID-19, the theoretical increased risk of hospital-acquired infections, especially in critically ill ventilated patients, is a matter of concern. The increased risk of secondary infections with the use of immune-based therapies is supported by the available evidence on their safety for the treatment of inflammatory disorders, mainly rheumatologic

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conditions, when compared with standard of care or placebo [5], but their impact in COVID-19 has not been appropriately rigorously evaluated.

The objective of this systematic review and meta-analysis was to assess the risk of secondary infections with the use of immune-based therapies in patients hospitalized with COVID-19.

METHODS

We registered the protocol for this systematic review and meta-analysis on the PROSPERO database (CRD42021229406), and the report was made following the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; checklist included in Supplementary Data B) [6].

Eligibility Criteria

We included peer-reviewed randomized controlled trials (RCTs) published between January 2020 and November 2021 and excluded nonrandomized studies (NRS) and non-peer-reviewed manuscripts (eg, published in preprint servers), meeting abstracts, and thesis dissertations. RCTs including adult participants (≥18 years of age), diagnosed with reverse transcription polymerase chain reaction or antigen testing, and hospitalized with COVID-19 were included if they received immune-based therapy and were compared with participants who did not receive these treatments (received either placebo, standard of care, or antiviral therapy). We excluded studies evaluating interventions with no effect on the immune system such as antivirals, vaccines, passive antibodies, and traditional Chinese herbal remedies without immune-based therapies. Studies allowing co-treatment with other immune-based therapies were included if these co-treatments were administered in both experimental and control arms. The primary outcome of interest was the rate of secondary infections, defined as infections occurring after initiation of interventions for the management of COVID-19.

Information Sources

A search was executed by an expert searcher/librarian (S.C.) on OVID Medline, Ovid EMBASE, SCOPUS, Cochrane Library, and PROSPERO using controlled vocabulary (eg, MeSH, Emtree, etc.) and keywords representing the concepts "COVID-19" and "immunotherapies" and "outcomes including secondary infections." Prognostic hedges from the McMaster Health Information Research Unit were applied to the EMBASE and Medline searches [7]. Searches were adjusted appropriately for different databases. Searches were conducted in October 2020 and updated on November 9, 2021. Update searches were limited to randomized controlled trials using RCT filters [8, 9]. No other limits were applied. Results (10 576) were exported to the COVIDence systematic review system. Duplicates (3413) were removed in COVIDence. Detailed search strategies are available in Appendix 1 in Supplementary Data C.

Study Selection

Using the web-based systematic review software COVIDence, pairs of reviewers (D.K., A.S., K.L., B.W.) independently screened all titles and abstracts, followed by full texts of potentially eligible articles. A third reviewer (C.C.) resolved conflicts. We performed training and a calibration exercise before each step.

Data Collection

Following training and calibration exercises, full data extraction was performed by 2 independent reviewers (D.K., A.S., K.L., B.W., M.R.). Data elements collected included: demographics and methodology for each study (country of the study, study size, year of the study, number of centers, funding source, trial registration numbers if applicable, and the study design), patient characteristics (age, sex, diabetes, body mass index, immunosuppression), setting, severity of COVID-19 (percentage requiring oxygen and mechanical ventilation), method of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection diagnosis, intervention details (immune-based therapy used, including route, dosing, treatment duration, and concomitant immune-based therapies), and all secondary infections reported in the outcomes (proportion of patients with bacteremia, pneumonia, urinary tract infection, sepsis, septic shock, invasive fungal infection, and viral infections). The definition used in each trial for secondary infection is listed in Supplementary Table 1. Time to infection was not collected as this information was missing from most studies.

Risk of Bias Assessment

To assess bias in randomized controlled trials, we used the Cochrane risk-of-bias tool for randomized trials, which includes selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Each study was individually assessed by a minimum of 2 separate investigators, with any discrepancies resolved by an experienced senior investigator. Furthermore, a collective calibration exercise and training were provided before independent assessment of study biases. We used robvis (Risk Of Bias VISualization) to create the risk-of-bias plots [10].

Data Synthesis

Due to the heterogeneity among the studies in terms of study design and comparators, we used a random-effects model when conducting the meta-analyses. The primary analysis was the incidence of secondary infection in each group. Each

outcome (including total infection, pneumonia, bacteremia, invasive fungal infection, sepsis, and septic shock) was analyzed separately. In studies that did not outline total infection in the RCT, we calculated the variable by adding different infectious syndromes with the exception of sepsis and septic shock. The unit of analysis was based on the aggregated outcome of secondary infections, as access to individual patient data was unavailable. Dichotomous data were analyzed using risk ratio (RR) with 95% CI. The weight in each trial was calculated using RevMan and represents the inverse of the variance (the square of the standard error) of the trial's summary statistic. This relates closely to the sample size and the number of events in each trial. Nonquantifiable data were narratively described. Statistical heterogeneity was determined using the I^2 statistic to assess the appropriateness of performing a meta-analysis and was categorized as (1) 0%–40%, might not be important; (2) 30%–60%, moderate heterogeneity; (3) 50%–90%, substantial heterogeneity; 75%–100%, considerable heterogeneity. The statistical software RevMan 5.31 (The Cochrane Collaboration) was used to calculate and combine each outcome.

We screened for clinical trial registration on the international clinical trials registry platform of the World Health Organization (http://apps.who.int/trialssearch). Publication biases were evaluated using a funnel plot (Figure 12 in Supplementary Data A).

Moderator and Sensitivity Analysis

To try to explain potential sources of heterogeneity, we performed subgroup analysis according to the different drugs used in these clinical trials. In addition, and although we predefined 3 subgroup analyses in our protocol (age, severity of illness, and immunosuppression), we used meta-regression to explore the potential impact of age and invasive mechanical ventilation as a surrogate of severity of illness on the (log) RR of infection with immune-based therapies. For the meta-regression, we conducted the analysis using the R package meta [11]. We could not perform a subgroup analysis on immunosuppression as most RCTs excluded these patients.

To assess the impact of potential publication-related confounding factors on the overall outcome, we used a sensitivity analysis. More specifically, we omitted studies with high rates of participant attrition, other missing data, and those judged to have high risks of bias. Furthermore, a sensitivity analysis was also conducted excluding studies where total infection was calculated or only infection leading to death was presented.

Certainty of the Evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group methodology to assess the certainty of evidence across the domains of risk of bias: consistency, directness, precision, outcome, and publication bias [12].

RESULTS

After screening 7163 titles and abstracts and 444 full texts published between January 2020 and November 8, 2021, we identified 37 RCTs that fulfilled our eligibility criteria (Figure 1). The characteristics of the RCTs are summarized in Table 1 and Table 1 in Supplementary Data A.

The immune-based therapies used in the RCTs consisted of corticosteroids in 8 studies [13–20], tocilizumab in 10 [21–30], interferon in 3 [31–33], sarilumab in 3 [21, 34, 35], baricitinib in 2 [36, 37], anakinra in 2 [38, 39], colchicine in 2 [40, 41], ruxolitinib in 1 [42], tofacinib in 1 [43], imatinib in 1 [44], levilimab in 1 [45], mavrilimumab in 1 [46], itolizumab in 1 [47], canakinumab in 1 [48], and vilobelimab in 1 [49]. Most RCT protocols were registered online (36/37, 97%). A total of 32 621 subjects were randomized (15 721 to immunotherapy and 16 900 to standard of care or placebo). The participant's mean age (SD, range) was 60 (3.9, 49–70) years, and 64% were male. In most RCTs, participants with moderate to severe COVID-19 were randomized to immune-based therapies vs placebo or standard of care, while in 11 RCTs [20, 22, 28, 30, 33, 36, 37, 40, 41, 43, 45, 50], patients who did not require oxygen supplementation were also included. At the time of randomization, 19 RCTs [13, 15, 17–24, 28–31, 35, 41, 49–51] had patients who required invasive mechanical ventilation with or without extracorporeal membrane oxygenation (ECMO). Concurrent treatment with steroids and antivirals varied between trials (Table 1).

Risk of Bias in Included Studies

The Supplementary Data contains the assessment of risk of bias for RCTs. Eleven studies were judged low risk in all domains (Aman, Dequin, Guimaraes, Jeronimo, Kalil, Lescure, Marconi, Rosas 2021a 2021b, Salama, and Stone), 13 studies were open-label and were judged high risk in the domain of blinding (Angus, Cao, Corral-Gudino, Caballero-Bermejo, Mariette 3 Recovery, REMAP CAP investigators, Salvarani, Soin, Tomazini, and Veiga), 3 had either a physician or statistician unblinded (Carchio, Kalil 2021, Tang), and 6 had high risk of bias in several domains (Davoudi-Monfared, Edalatifard, Hermine, Rahmani, Kumar, and Vlaar) (Table 2; Figure 9 in Supplementary Data A).

Risk of Total Infections With Immune-Based Therapy

Out of the 37 RCTs included in this systematic review, 22 collected total infection as a secondary outcome or adverse effect (Cao, Caricchio, Caballero-Bermejo, Davoudi-Monfared, Dequin, Edalatifard, Guimaraes, Kalil 2020, Kyriazopoulou, Kumar, Lescure, Marconi, Rahmani, Rosas 2021a, 2021b, Salama, Salvarini, Stone, Soin, Tomazini, Veiga, and Vlaar). In the RECOVERY trials, infection was included as a cause of death. Hermine et al. presented infection outcomes as bacterial

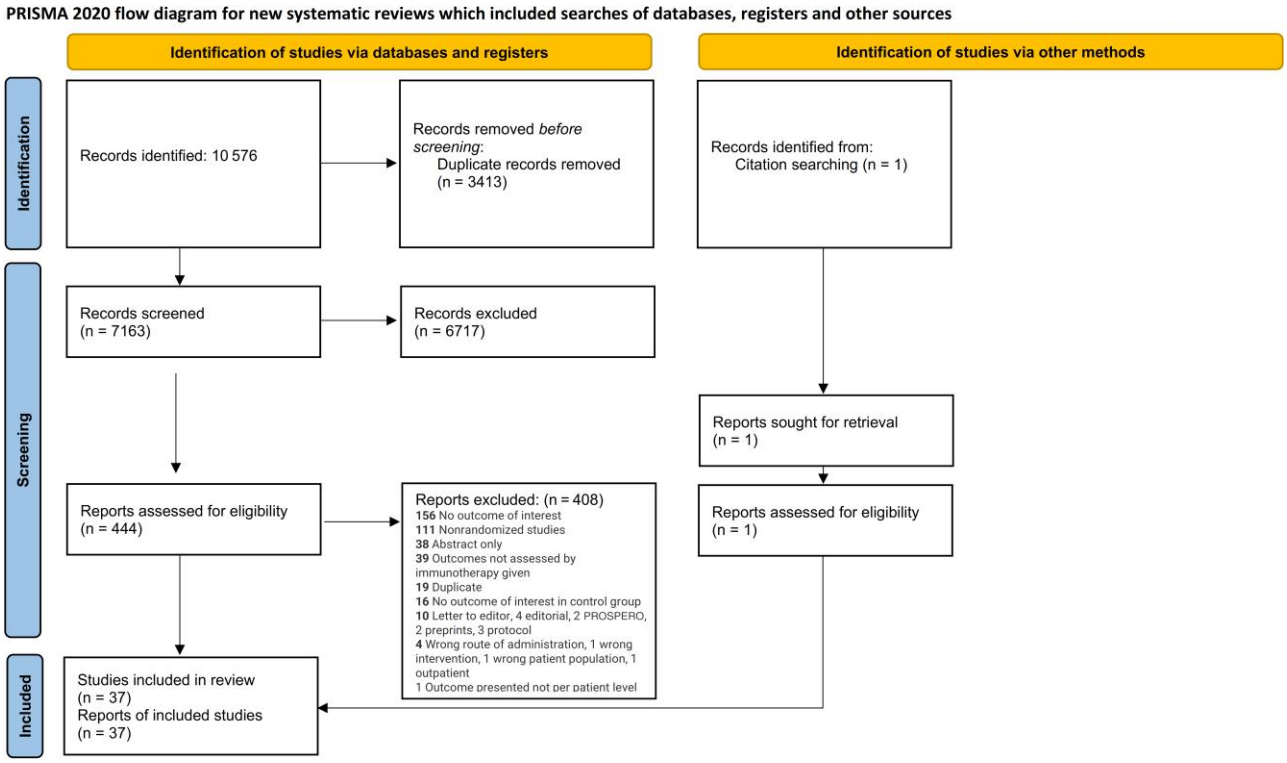

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

sepsis, fungal sepsis, and viral sepsis, and Mariette et al. presented infection outcomes as bacterial and fungal sepsis, which we combined to get total infection. Angus et al. presented only invasive fungal infection, which we included as total infection. Cremer et al., Lopes et al., and Tang et al. presented only pneumonia, which we included as total infection. The REMAP-CAP investigators presented bacterial infection, which we included as total infection. Lomakin presented opportunistic infection, which we included as total infection. In the trial by Aman et al., we included lip infection, lung infection, and other as total infection and analyzed sepsis separately. In the trial Khalil et al. (2021), we included cellulitis, bacterial pneumonia, and *Aspergillus* as total infection and analyzed sepsis and septic shock separately. In the trial by Jerenimo et al., we included bacteremia as total infection and analyzed sepsis separately. Finally, for the trial by Corral-Gudino et al., we combined pneumonia and invasive fungal infections as total infection.

There were 711 infections identified in 15 721 patients receiving immune-based therapy (4.5%) and 616 infections in 16 900 patients receiving placebo or standard of care (3.6%). Based on a random-effects meta-analysis, the summary RR was 0.82 (95% CI, 0.71–0.95; $P = .008$). There was little inconsistency between the trial results ($I^2 = 28\%$; $P_{\text{heterogeneity}} = .06$) (Figure 2).

We performed a subgroup analysis using immunotherapy mostly used in clinical practice in the management of COVID-19 including only steroids, tocilizumab, and baricitinib. There were 550 infections identified in 11 389 patients receiving immune-based therapy (4.8%) and 464 infections in 10 854 patients receiving placebo or standard of care (4.3%). Based on a random-effects meta-analysis, the summary RR was 0.85 (95% CI, 0.72–0.99; $P = .04$). There was little inconsistency between the trial results ($I^2 = 26\%$; $P_{\text{heterogeneity}} = .03$).

Influence of Drug Type, Age, Sex, and Need for Invasive Mechanical Ventilation in RCTs

We explored subgroup analysis by immune-based drugs and found no significant difference ($P = .85$; $I^2 = 0\%$) (Figure 3). Meta-regression revealed no impact of age, percentage of female sex, or percentage of participants on mechanical ventilation on the effect of immune-based therapies on the risk of infection (Figures 6, 7, and 8 in Supplementary Data A).

Sensitivity Analysis

By omitting studies with high rates of participant attrition or other missing data or studies that were judged to be at high risk of bias (Davoudi-Monfared, Edalatifard, Hermine, Rahmani, Kumar, and Vlaar), the summary RR remained in favor of immune-based therapy (RR, 0.84; 95% CI, 0.74–0.95; $P = .0040$) (Figure 10 in Supplementary Data A). Moreover, when omitting studies where the total number of infections was calculated or only infections leading to death were included (Angus, Aman, Corral-Gudino, Cremer, Hermine, Jeronimo,

Table 1. Characteristics of Patients and Interventions Used in Randomized Clinical Trials

Author-Year Trial Name	Design and Setting	Participants	Intervention Dose/Route and Duration	SOC	Co-intervention (%)	Outcomes
Salama 2021 EMPACTA	Double-blind Multicenter	I: 249, C: 128	Tocilizumab IV 8 mg/kg 1–2 doses	Antiviral RDV: I: 131 (52.6), C: 75 (58.6)	Steroids I: 200 (80.3), C: 112 (87.5)	Total infection: I: 25/250, C: 16/127
Stone 2020 BACC Bay Tocilizumab	Double-blind Multicenter	I: 161, C: 81	Tocilizumab IV 8 mg/kg (max 800 mg), 1 dose	Antiviral, HCQ RDV: I: 53 (33), C: 24 (29)	Steroids: I: 18 (11%), C: 5 (6%)	Total infection: I: 13/161, C: 14/82
Veiga 2021	Open-label Multicentre	I: 65, C: 64	Tocilizumab IV 8 mg/kg (max 800 mg), 1 dose	HCQ, AZM, antibiotics	Steroids: I: 45 (69), C: 47 (73)	Total infection: I: 10/65, C: 10/64
Salvarani 2021	Open-label Multicenter	I: 60, C: 66	Tocilizumab IV 8 mg/kg (max 800 mg), 2 doses	Varied as per treatment protocol of each center	Steroids: I: 7 (11.7), C: 5 (8.3)	Total infection: I: 1/6°C: 2/63
Hermine 2021 CORIMUNO-TOCI1	Open-label Multicenter	I: 63, C: 67	Tocilizumab 8 mg/kg (1st dose); 400 mg (2nd dose), 1 or 2 doses	AZM, HCQ, LPV/r, LPV, RDV, oseltamivir	Steroids: I: 21 (33), C: 41 (61) Anakinra: I: 1 (2), C: 3 (4.4) Eculizimab: I: 0, C: 1 (1.6)	Total infection: I: 2/63, C: 14/67
Dequin 2020 CAPE-COD	Double-blind Multicenter	I: 76, C: 73	Hydrocortisone IV 200 mg/d × 7 d, 100 mg/d × 4 d, 50 mg/d × 3 d	HCQ, AZM, LPV/r, RDV	Tocilizumab: I: 1 (1.3), C: 2 (2.7) Eculizumab: I: 3 (3.9), C: 2 (2.7)	Total infection: I: 28/76, C: 30/73
Angus 2020 REMAP-CAP	Open-label Multicenter	I: 278, C: 101	Hydrocortisone IV 50 mg q6 h, 7 d or shock resolved, vasopressors off 24 h, max 28 d	…	…	Total infection: I: 1/278, C: 0/101
Edalatifard 2020	Single-blind Multicenter	I: 34, C: 24	Methylprednisolone IV 250 mg/d × 3 d (3 doses)	HCQ, LPV, naproxen	…	Total infection: I: 1/34, C: 0/28
Tomazini 2020 Codex	Open-label Multicentre	I: 151, C: 148	Dexamethasone IV 20 mg × 5 d; then 10 mg × 5 d 10 doses	AZM, antibiotics, HCQ	Steroids: C: 52 (35.1)	Total infection: I: 33/151, C: 43/148
Jeronimo 2020 MetCOVID	Double-blind Single-center	I: 199, C: 194	Methylprednisolone IV: 0.5 mg/kg BID × 5 d 10 doses	Antibiotics	…	Total infection: I: 9/108, C: 7/88
Corral-Gudino 2021 GLUCOCOVID	Open-label Multicentre	I: 35, C: 29	Methylprednisolone IV 40 mg BID × 3 d, then 20 mg BID × 3 d 12 doses	Antibiotics, AZM, HCQ, LPV/r	…	Total infection: I: 5/35, C: 1/29
Vlaar 2020 PANAMO	Open-label Multicentre	I: 15, C: 15	Anti-C5a Ab (IFX-1) IV 800 mg up to 7 doses	HCQ	…	Total infection: I: 3/15, C: 4/15
Rahmani 2020	Open-label Single-center	I: 33, C: 33	Interferon SQ B-1b 250 mcg every 2nd day for 2 wk	LPV/r or ATV/r, HCQ	Steroids: I: 5 (15.15), C: 9 (27.27)	Total infection: I: 1/33, C: 5/33
Davoudi-Monfared 2020	Open-label Single-center	I: 42, C: 39	Interferon B-1a 44 mcg/mL SQ (12 MIU/mL) 3x/wk for 2 wk	HCQ, LPV/r, ATV/r	Steroids: I: 26 (61.9), C: 17 (43.58)	Total infection: I: 11/42, C: 5/39
Kalil 2020 ACTT-2	Double-blind Multicenter	I: 515, C: 518	Barcitinib: PO 4 mg/d × 14 d or until d/c, RDV IV 200 mg × 1 d, then 100 mg × 9d or until d/c	RDV: 200 mg × 1 d, then 100 mg × 9 d or until discharge	Steroids: I: 87 (16.9), C: 104 (20)	Total infection: I: 30/515, C: 57/518
Cao 2020	Single-blind Multicenter	I: 20, C: 21	Ruxolitinib PO 5 mg BID 56 doses	Antivirals, antibiotics Placebo: Vit C PO BID 56 doses	Steroids: I: 14 (70), C: 15 (71.4)	Total infection: I: 0/2°C: 2/21

Table 1. Continued

Author-Year Trial Name	Design and Setting	Participants	Intervention Dose/Route and Duration	SOC	Co-intervention (%)	Outcomes
Lopes 2021	Double-blind Single-center	I: 38, C: 37	Colchicine 0.5 mg TID × 5 d then 0.5 mg BID × 5 d	AZM, HCQ, UHeparin	Steroids: I: 25 (69), C: 24 (67)	Total infection: I: 3/36, C: 5/36
Caballero-Bermejo 2021 SARTRE	Open-label Multicentre	I: 99, C: 102	Sarilumab 200 mg IV × 1 or 400 mg IV × 1 if >75 kg	Antibiotics, antivirals, anticoagulants	Steroids: I: 99 (100), C: 102 (100)	Total infection: 1: 1/99, C: 3/102
Soin 2021 COVINTOC	Open-label Multicentre	I: 91, C: 89	Tocilizumab 6 mg/kg IV (max 480 mg) + another dose >12 h prn	RDV: I: 31 (43), C: 36 (41)	Steroids: I: 83 (91), C: 80 (91)	Total infection: I: 6/91, C: 5/89
Kyriazopoulou 2021 SAVE- MORE	Double-blind Multicentre	I: 405, C: 189	Anakinra 100 mg SC daily × 7–10 d	RDV: I: 298 (73), C: 141 (74.6) LMWH, antibiotics	Steroids: I: 342 (84.4), C: 168 (88.9)	Total infection: I: 34/405, C: 30/189
Caricchio 2021 CAN-COVID	Double-blind Multicenter	I: 224, C: 223	Canakinumab 450–750 mg IV × 1	Convalescent plasma, antivirals, anticoagulants RDV: I: 49 (22), C: 45 (20)	Steroids: I: 92 (41), C: 73 (32) Tocilizumab: I 5 (2.2), C: 20 (8.8) Anakinra: I: 2 (1)	Total infection: I: 23/225, C: 43/223
Mariette 2021 CORIMUNO-ANA-1	Open-label Mulicenter	I: 59, C: 55	Anakinra: 200 mg IV BID × 3 d then EITHER 100 mg IV BID × 1 d then 100 mg IV QD × 1 d OR if necessary 400 mg × 3 d then 200 mg × 1 d then 100 mg × 1 d	Antibiotics, antivirals, anticoagulants	Steroids: I: 30 (51), C: 29 (53) Tocilizumab: I: 1 (2) C: 0 (0)	Total infection: I: 11/59, C: 4/55
Guimaraes 2021 STOP-COVID	Double-blinded Multicentre	I: 144, C: 145	Tofacitinib: PO 10 mg BID × 14 d	Antibiotics, anticoagulants, antivirals	Steroids: I: 128 (88.9), C: 130 (89.7)	Total infection: I: 7/142, C: 8/142
Kumar 2021	Open-label Multicentre	I: 22, C: 10	Itolizumab: IV 1.6 mg/kg + if deemed necessary IV 0.8 mg/kg weekly up to total of 4 doses	Antibiotics, HCQ, antivirals, LMWH, and vitamin supplements	Hydrocortisone 100 mg + pheniramine 30 mg IV: I: 22 (100), C: 0 (0), steroids	Total infection: I: 1/22, C: 3/10
Rosas 2021	Double-blinded Multicentre	I: 434, C: 215	Tocilizumab: IV 8 mg/kg + if necessary a second 8 mg/kg	Antibiotics RDV: I: 434 (100), C: 213 (100)	Low-dose corticosteroids	Total infection: I: 131/429, C: 71/213
Aman 2021	Double-blind Multicentre	I: 197, C: 188	Imatinib PO: 800 mg × 1 d then 400 mg × 9 d	Anticoagulants, antibiotics RDV: I: 40 (20), C: 40 (21)	Steroids: I: 143 (73), C: 133 (71)	Total infection: I: 12/197, C: 16/188
Tang 2021	Single -blind Multicenter	I: 43, C: 43	Methylprednisolone 1 mg/kg	Antivirals, antibiotics, immunoglobulin	…	Total infection: I: 2/43, C: 1/43
Kalil 2021 ACTT-3	Double-blinded Multicentre	I (RDV + IFN): 487 C (RDV): 482	44 μg interferon beta-1a sc q2d × 4 doses RDV (all pts): 200 mg IV × 1, 100 mg IV × 9 d	…	Steroids	Total infection: I: 5/477, C: 3/468
REMAP-CAP Investigators 2021	Open-label Multicenter	I (toci): 353 (29% 2 doses), I (sari): 48, C: 402	Toci: 8 mg/kg IV (max 800) over 1 h, could be repeated 12–24 h later Sari: 400 mg IV once only	Immunoglobulin, antivirals, anticoagulation RDV: T: 107/341 (31.4), S: 21/48 (43.8), C: 133/389 (34.2)	Steroids: T: 252/272 (92.7), S: 46/48 (95.8), C: 293/312 (93.9)	Total infection: Toc: 1/353, Sari: 0, C: 0
Lomakin 2021	Double-blind Multicenter	I: 103, C: 103	LVL 324 mg sq + single open-label LVL 324 mg rescue therapy	Antibiotics, HCQ, anticoagulants	Steroids: I: 5/103 (4.9), C: 10/103 (9.7)	Total infection: I: 1/103, C: 1/101

Table 1. Continued

Author-Year Trial Name	Design and Setting	Participants	Intervention Dose/Route and Duration	SOC	Co-intervention (%)	Outcomes
Cremer 2021 MASH-COVID	Double-blind Multicenter	I: 21, C: 19	Mavrilimumab 6 mg/kg	Antivirals, antimicrobials, convalescent plasma RDV: I: 18 (85), C: 15 (79)	Steroids: I: 16 (76), C: 15 (79)	Total infection: I: 2/21, C: 1/19
Marconi 2021 COV-BARRIER	Double-blind Multicenter	I: 764, C: 761	4 mg/d oral baricitinib × 14 d or until discharge, 2 mg if GFR <30	RDV: I: 18% (140/762), C: 19% (147/756)	Steroids: I: 612/762 (80), C: 592/756 (78)	Total infection: I: 119/750, C: 123/752
Recovery 2	Open-label Multicenter	I: 5610, C: 5730	Colchicine 1 mg, then 500 µg 12 h later, then 500 µg po/NG q12h × 10 d or until d/c dose adjusted for wt and GFR	RDV: I: 1235/5610 (22), C: 1251/5730 (22)	Steroids: I: 5243/5610 (93), C: 5360 (94)	Infection as cause of death: I: 6/5610, C: 2/5730
Recovery 1	Open-label Multicenter	I: 2104, C: 4321	Dexamethasone: 6 mg oral or IV daily × 10 d (or until d/c)	Antibiotics, LPV/RTV <1% HCQ: I: 1 (16), C: 1 (24) RDV: I: <1 (2), C: 0	Steroids: I: 95, C: 8 IL-6 inhibitors: I: 2 (45), C: 3 (132)	Infection as cause of death: I: 6/2104, C: 9/4321
Lescure 2021	Double-blind Placebo-controlled Multicenter	I: 173 + 159, C: 84	Sarilumab IV 400 mg or Sarilumab IV 200 mg second dose could be given	Antivirals, antibacterials, HCQ, CQ	Steroids: I: 200 mg 25 (16), I: 400 mg 42 (24), C: 16 (19)	Total infection: I: 40/332 (12), C: 10/84 (12)
Rosas 2021 COVACTA	Double-blind Placebo-controlled Multicenter	I: 294, C: 144	Tocilizumab IV 8 mg/kg × 1 and second dose could be given 8–24 h after	Antiviral treatment, low-dose glucocorticoids, convalescent plasma	Steroids: I: 57 (19.4), C: 41 (28.5)	Total infection: I: 126/295 (42.7), C: 62/143 (43.4)
Recovery 3	Open-label Multicenter	I: 2022, C: 2094	Tocilizumab IV 400–800 mg; a second dose could be given 12–24 h later	SOC evolved over the study	Steroids: I: 82%, C: 82%	Infections as cause of death: I: 2022, C: 6/2094

Abbreviations: ATV/r, atazanavir/ritonavir; AZM, azithromycin; C, control; CQ, Chloroquine; GFR, glomerular filtration rate; HCQ, hydroxychloroquine; I, intervention; IV, intravenous; LPV/r, lopinavir/ritonavir; LVL, levilimab; RDV, remdesivir; RTV, ritonavir; SOC, standard of care; wt, wild-type.

Kalil 2021, Lomakin Lopes, Mariette, RECOVERY 1, 2, 3, REMAp-CAP, Tang), the results were not altered (RR, 0.80; 95% CI, 0.69–0.92; $P = .002$) (Figure 11 in Supplementary Data A).

Risk of Pneumonia, Bacteremia, Invasive Fungal Infection, Sepsis, and Septic Shock With Immune-Based Therapy in RCTs

Twenty trials assessed the risk of secondary pneumonia in hospitalized patients with COVID-19 treated with immune-based therapy, and based on a random-effects meta-analysis, the summary RR was 0.70 (95% CI, 0.53–0.93; $P = .01$). There was little inconsistency between the trial results ($I^2 = 19\%$; $P_{\text{heterogeneity}} = .22$) (Supplementary A, Figure 1). The risk of bacteremia was assessed in 9 trials [15, 17, 18, 23, 29, 32, 36, 39, 52], and based on a random-effects meta-analysis, the summary RR was 0.80 (95% CI, 0.54–1.19; $P = .27$), with low inconsistency between the trial results ($I^2 = 0\%$; $P_{\text{heterogeneity}} = .92$) (Figure 2 in Supplementary Data A). Nine trials assessed the risk of invasive fungal infections [13, 14, 25, 33, 36–38, 47, 48], and based on a random-effects meta-analysis, the summary RR was 1.12 (95% CI, 0.46–2.74; $P = .80$), with low inconsistency between the trial results ($I^2 = 0\%$; $P_{\text{heterogeneity}} = .78$) (Figure 3 in Supplementary Data A). Fourteen trials assessed the risk of sepsis [14, 17, 23–25, 27, 30, 33, 36, 42–44, 48, 49] and 10 trials septic shock [23, 24, 26, 31–33, 36, 39, 43, 48]. Based on a random-effects meta-analysis, the summary RR for sepsis and septic shock was 0.73 (95% CI, 0.45–1.20; $P = .21$) and 0.60 (95% CI, 0.39–0.93; $P = .02$), respectively. There was low inconsistency between the trial results (sepsis: $I^2 = 29\%$; $P_{\text{heterogeneity}} = .15$; septic shock: $I^2 = 27\%$; $P_{\text{heterogeneity}} = .20$) (Figures 4 and 5 in Supplementary Data A).

Certainty of Evidence Using GRADE

In adults hospitalized with moderate to severe COVID-19, the certainty of evidence using GRADE to assess the risk of infection with immune-based therapy compared with controls was rated as moderate (Table 5 in Supplementary Data A). Although the evidence was derived from randomized

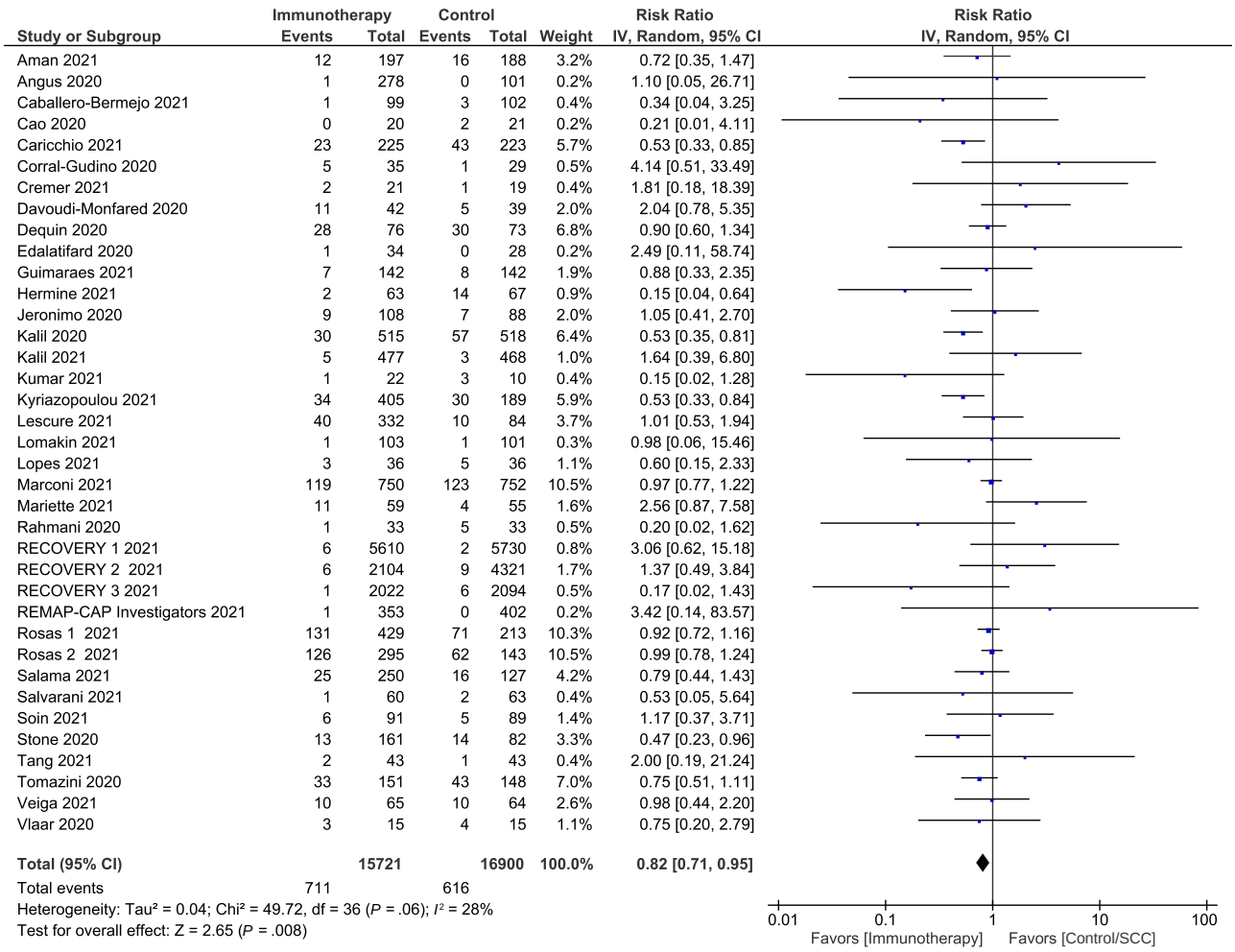

Figure 2. Risk of infection with immune-based therapy in randomized controlled trials.

controlled trials (which are considered high quality of evidence), it (the certainty of evidence) was downgraded because of the high risk of bias in 5 trials. Although we included different immune-based drug agents, we considered the indirectness to be low, as all these drugs target the aberrant immune system caused by SARS-CoV-2.

DISCUSSION

In this systematic review and meta-analysis of 37 randomized clinical trials that included 32 621 patients with COVID-19 requiring hospitalization, the use of immune-based therapies was not associated with increased risk of secondary infections from the time of randomization as compared with standard of care. We found a mild protective effect for secondary infections with the use of immunotherapy, this effect being higher for secondary pneumonia and septic shock than for other infectious syndromes. Although the percentage of infections was slightly higher in those who received immunotherapy, the adjusted analysis that considered the weight of each study showed slight protection, with an RR of 0.82. The effect of immune-based therapy on the risk of infection was not dependent on age, sex, or mechanical ventilation at inclusion.

The protective effect of immune-based therapies for secondary infections in COVID-19 seems initially counterintuitive, considering previously published data for each drug in a variety of clinical conditions. The use of short-course corticosteroids, generally prescribed for upper respiratory tract infections, acute spinal conditions, and allergies, was associated with a 5.3-fold increase in the risk of sepsis within 30 days of drug initiation in a large, population-based study in the United States [53]. A pooled analysis of 7 studies from a systematic review and meta-analysis that included 1 RCT and 29 observational studies evaluating the use of corticosteroids as adjunctive treatment for influenza requiring hospitalization showed a 2.7-fold increased risk of hospital-acquired infection [54]. In a meta-analysis including 6 RCTs from a systematic review on the use of tocilizumab for rheumatoid arthritis, the combination of tocilizumab at 8 mg/kg with

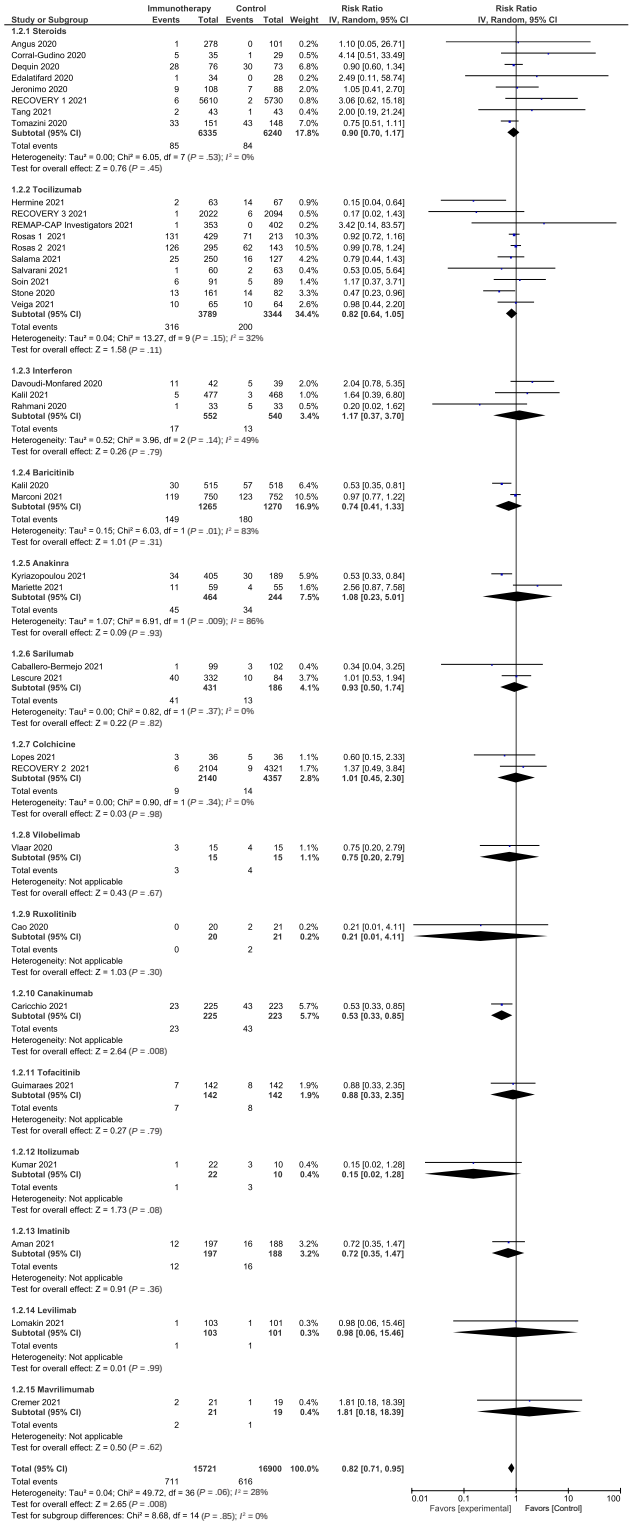

Figure 3. Risk of infection with different immune-therapeutic agents in randomized controlled trials.

methotrexate (odds ratio [OR], 1.3) mildly increased the risk of infection [55]. Baricitinib, a Janus Kinase (JAK) inhibitor, increased the risk of infections by 1.28-fold compared with placebo in patients with rheumatoid arthritis [56]. Ruxolitinib, another JAK inhibitor, increased the risk of opportunistic and nonopportunistic infections [57].

Available data from RCTs suggest that immune-based therapy for COVID-19 are not only not associated with increased risk of infections, but may also be associated with protective effect. Targeting the COVID-19-related inflammatory response with corticosteroids or tocilizumab leads to better clinical outcomes and survival [58–60]. Both corticosteroids and tocilizumab decreased the risk for mechanical ventilation (OR, 0.74 and 0.71, respectively) in a meta-analysis including 3 studies and 6873 patients treated with corticosteroids and another that included 6 studies and 771 patients treated with tocilizumab [60, 61]. As the protective effect conferred by immune-based therapy for COVID-19 is highest for secondary pneumonia, one can postulate that avoiding or decreasing the time on mechanical ventilation may decrease the occurrence of ventilator-associated pneumonia. In our meta-regression, mechanical ventilation at baseline did not influence the RR of secondary infection, indicating that preventing mechanical ventilation is not the only mechanism in decreasing hospital-acquired pneumonia. We did not have information on days of intubation in all studies, so we could not account for that in our analysis.

Patients with severe COVID-19 display either macrophage activation syndrome or very low human leucocyte antigen DR expression accompanied by a profound depletion of CD4 lymphocytes, CD19 lymphocytes, and natural killer cells that can be partially rescued with interleukin-6 blockage by tocilizumab [62]. Other drugs targeting different pathways of the inflammatory response may also partially revert the consequences of this aberrant immune response and restore optimal immune responses against other pathogens.

Immune-based therapies for severe COVID-19 have been the only treatments demonstrating survival benefit to date. The use of immune-based therapies in the most vulnerable population carries a hypothetical increased risk of secondary infections. However, our data show that this risk is absent (or even lower), and thus these treatments should not be delayed when indicated, including in older or mechanically ventilated patients.

Guidelines on the treatment of moderate to severe COVID-19 should reflect our findings and make appropriate recommendations against the routine use of preventive antibiotics and antifungals in those treated with immunomodulating drugs for severe COVID-19.

Limitations

This study has several limitations. First, the definitions and reporting of infectious adverse events were not consistent across the trials. While this lack of consistency precludes estimating the rates of infectious complications for each immune-based therapy compared with standard of care, there is no reason to

believe that this will impact the protective association measures.

Second, although there are few missing outcome data, no follow-up was done after hospital discharge in most trials, and the rates of secondary infection after hospital discharge were not evaluated. The potential immunosuppressive effects for some of the evaluated drugs may persist over time. For instance, short-term use of corticosteroids increases the rates of sepsis by 2.5-fold between 31 and 90 days after discontinuation [53], and tocilizumab has a half-life of around 10 days [63].

Third, some trials allowed combination of the study drug with other immune-based therapies. All RCTs evaluating tocilizumab allowed the concomitant use of corticosteroids ranging from 11% to 90% of all participants included in the interventional arm, and 1 participant received at least tocilizumab plus anakinra. In 1 RCT evaluating hydrocortisone, 1 participant in the interventional arm received tocilizumab and 3 eculizumab. In the 2 RCTs evaluating interferon β, 15% and 62% of the participants randomized to interferon received corticosteroids. Seventy percent of the participants assigned to ruxolitinib received concomitant treatment with corticosteroids. Finally, 17% of the participants randomized to receive baricitinib plus remdesivir received corticosteroids. Despite the obvious limitation in the accuracy of the estimations, it is important to highlight that the high frequent co-administration reinforces the hypothesis of using immune-based therapies as the first-line therapy for severe COVID-19.

Fourth, we used mechanical ventilation as a surrogate marker for the severity of the disease. However, there are reasons to use mechanical ventilation for managing COVID-19 other than the severity of the disease. As an example, early intubation has been suggested by some authors to interrupt the progressive lung deterioration mediated by tissue stress, raised pulmonary transvascular pressures, vascular flows, and fluid leakage [64]. Although mechanical ventilation may not accurately reflect the severity of COVID-19, stratifying the risk according to this variable is highly relevant as orotracheal intubation is a major risk factor for hospital-acquired pneumonia.

Finally, the protective effect of immune-based therapies may not be generalized to all populations. The RCTs included in this meta-analysis were mostly done in high-income countries, in adults, in individuals without concomitant infections (or without previous specific infections such as tuberculosis or strongyloidiasis), and in those not previously on exogenous immunosuppression. More information is required to evaluate the protective effect of immune-based therapies for secondary infections in specific populations such as children and immunocompromised patients.

This systematic review and meta-analysis provides an evidence-based review that could support future guidelines on the management of hospitalized patients with COVID-19 treated with immune-based therapy.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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