Efficacy and safety of nitazoxanide in treating SARS-CoV-2 infection. A rapid and living systematic review and meta-analysis of blinded, placebo-controlled, randomized clinical trials.

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Abstract

Introduction Nitazoxanide is a broad-spectrum antiparasitic that has been tested for COVID-19 due to the anti-inflammatory effects and in vitro anti-viral activity and promising clinical benefits against influenza and other viruses. The aim of this study was to synthesize the best evidence on the efficacy and safety of nitazoxanide as treatment for patients with COVID-19. Methods Searches for studies were performed in peer-reviewed and gray literature. The following elements were used to define eligibility criteria: (1) Population, individuals with laboratory-confirmed SARS-CoV-2 infection; (2) Intervention, nitazoxanide; (3) Comparison, placebo; (4) Outcomes: positive RT-PCR status, composite measure of disease progression (severe COVID-19, ICU admission or invasive mechanical ventilation), death, serum biomarkers of inflammation (C-reactive protein, IL-6, and IL-8), and any adverse events; (5) Study type: blinded, placebo-controlled, randomized clinical trials (RCT). Treatment effects were reported as relative risk (RR) and mean difference (MD) with 95% confidence intervals (CI). Results Four blinded, placebo-controlled RCT were included in the meta-analysis and enrolled individuals with mild or moderate SARS-CoV-2 infection. We found no difference between nitazoxanide and placebo in the frequency of positive RTP-PCR results (RR = 0.83; 95% CI 0.58 to 1.17) and there was no decreased risk for disease progression (severe COVID-19, ICU admission or invasive mechanical ventilation) (RR = 0.40; 95% CI 0.08 to 2.13) and deaths (RR = 0.55; 95% CI 0.18 to 1.68) among patients receiving nitazoxanide. There were no differences for patients treated with nitazoxanide and placebo in the levels of inflammatory markers. Conclusions In this study, we found no current evidence from blinded, placebo-controlled, RCT on the efficacy of nitazoxanide in treating patients with COVID-19. This living systematic review should be updated as soon as the results of ongoing RCT are published.

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ABSTRACT

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Methods

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Conclusions

In this study, we found no current evidence from blinded, placebo-controlled, RCT on the efficacy of nitazoxanide in treating patients with COVID-19. This living systematic review should be updated as soon as the results of ongoing RCT are published.

Key words: COVID-19; SARS-CoV-2 infection; nitazoxanide.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel single-stranded RNA virus associated with an acute pulmonary disease known as COVID-19. The binding between SARS-CoV-2 spike (S) protein and human receptor cells may lead to a dysregulated immune response with increased release of pro-inflammatory cytokines implicated in multi-organ damage and risk of death. Given the lack of effective and safe anti-viral agents against SARS-CoV-2, drug repurposing has played a critical role in the identification of rapidly available therapeutic solutions in treating patients with COVID-19 [1].

To date, only remdesivir and tocilizumab were approved by the US Food and Drug Administration (FDA) and other healthy agencies for the treatment of certain hospitalized patients with COVID-19. Other promising drugs including anti-malarial agents have also been tested in controlled clinical settings, but no benefits were found in preventing or treating patients with SARS-CoV-2 infection [2].After a comprehensive review by Sanders and colleagues [3] in April 2020 and a letter to the editor published by our research group in July 2020 in the American Journal of Physiology-Lung Cellular and Molecular Physiology [4] calling attention for the potential anti-viral effects of nitazoxanide and the need of high-quality trial evidence of nitazoxanide in the treatment of SARS-CoV-2 infection, 28 interventional studies were registered on ClinicalTrials.gov of which 8 were completed or published by June 2021.

The best evidence synthesis to assess treatment effects can be obtained through the identification, critical appraisal, and summary of results from blinded, placebo-controlled, randomized clinical trials (RCT) considered the gold standard in clinical research. The aim of this rapid and living systematic review and meta-analysis was to synthesize the available evidence on the efficacy and safety of nitazoxanide as a treatment option in patients with COVID-19.

METHODS

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [5] and the methodology proposed in conducting a rapid and living systematic review [6].

Search strategy

Searches for studies were performed in PubMed, Web of Science, Scopus, Embase, Google Scholar (first 100 hits), the website ClinicalTrials.gov, and the preprint server medRxiv from January 1, 2020 to June 24, 2021. The search was limited to studies published in full-text versions, without language restriction. In the ClinicalTrials.gov, only completed studies with results were analyzed. The reference lists of all eligible studies and reviews were scanned to identify additional studies for inclusion.

We used the following structured search strategy for each electronic database: (nitazoxanide) AND (COVID-19 OR "2019-nCoV Infection" OR "Coronavirus Disease-19" OR "2019-nCoV Disease" OR SARS-CoV-2). For Google Scholar, ClinicalTrials.gov and medRxiv, we used the following strategy: (nitazoxanide) AND (COVID-19 OR SARS-CoV-2). To expand the number of eligible studies, specific filters for RCTs were not used.

Study selection and eligibility criteria

Two reviewers (P.R.M.-F. and E.M.N.-J.) independently screened the search results and identified studies that were potentially relevant based on their title and abstract. Relevant studies were read in full and selected according to eligibility criteria. Disagreements between the two reviewers were resolved by consensus.

The following elements were used to define eligibility criteria: (1) Population: individuals with laboratory-confirmed SARS-CoV-2 infection; (2) Intervention: nitazoxanide; (3) Comparison: placebo; (4) Outcomes: positive RT-PCR status, composite measure of disease progression (severe COVID-19, ICU admission or invasive mechanical ventilation), death, serum biomarkers of inflammation (C-reactive protein, IL-6, and IL-8), and any adverse events; (5) Study type: blinded, placebo-controlled, RCTs. Eligible studies must report at least 1 of the outcomes of interest. Potential overlapping populations, open-label trials, and observational studies were excluded. Trials testing drug associations were also excluded.

Data extraction

Two authors (P.R.M.-F. and E.M.N.-J.) extracted the data from included studies and crosschecked them for accuracy. Using a standardized data extraction sheet, the following information were extracted from the studies: registry of study protocol, demographic characteristics of study participants, pre-existing medical conditions, treatment arms, nitazoxanide protocol, concomitant medications, follow-up duration, and outcome data.

Risk of bias assessment

Risk of bias was judged according to the Cochrane guidelines for RCTs [7]. The following domains were evaluated: sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), sample size calculation, power analysis, and early stopping for futility (operational bias), outcome measurements (information bias), and the authors' financial or non-financial conflicts of interest that could appear to affect the judgment of research team when designing, conducting, or reporting study. Studies using real-time reverse transcription polymerase chain reaction (RT-PCR) to detect SARS-CoV-2 or, if testing was limited, provided a clinical diagnosis based on COVID-19-related symptoms and epidemiological data were considered as having a low risk of bias.

Data synthesis

Treatment effects were reported as relative risk (RR) for dichotomous variables (positive RT-PCR status, composite measure of disease progression, death, and any adverse events) and standardized mean difference (SMD) for continuous variables (serum biomarkers of inflammation) with 95% confidence intervals (CI). To calculate the RR, the number of events and individuals in each treatment group were extracted. To calculate SMD, means and standard deviations (SD) were obtained for each study group. If the means and SD were not directly reported in the publication, indirect methods of extracting estimates were used [8]. A negative effect size indicated that nitazoxanide decreased levels of inflammatory biomarkers in patients with COVID-19.

We used either a fixed or random-effects model to pool the results of individual studies depending on the presence of heterogeneity. Statistical heterogeneity was quantified by the I^2index using the following interpretation: 0%, no between-study heterogeneity; <50%, low heterogeneity; 50–75%, moderate heterogeneity; > 75%, high heterogeneity [9]. In the case of heterogeneity, we used the random-effects model, otherwise, the fixed-effects model was used.

Although funnel plots may be useful tools in investigating small study effects in meta-analyses, they have limited power to detect such effects when there are few studies [10]. Therefore, because we had only a small number of included studies, we did not perform a funnel plot analysis. Forest plots were used to present the effect sizes and the 95% CI, and a 2-tailed $p < 0.05$ was used to determine significance. Analyses were conducted using Review Manager, version 5.3 (Cochrane IMS).

Grading the strength of evidence

We graded the strength of evidence for the association between use of nitazoxanide and the outcomes of interest as high, moderate, low, or very-low using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) rating system [11,12]. In the GRADE system, RCTs begin as high-quality evidence but may be downrated according to the risk of bias assessment, inconsistency, indirectness, imprecision in the results, and publication bias [13]. Certainty is uprated for estimates with large (RR > 2.0 or RR < 0.5) or very-large (RR > 5.0 or RR < 0.2) magnitude of effect.

Although the funnel plot asymmetry was not evaluated, we reduced the potential for publication bias planning a comprehensive search including grey-literature without restrictions. In this criterion, we analyzed discrepancies in findings between studies and the influence of small trials (< 100 patients per arm) on estimated treatment effects. The influence of small trials on the pooled estimates was analyzed using a "leave-one-out" sensitivity approach [14].

RESULTS

Study selection

Search strategy yielded 514 potentially relevant records. After screening of titles and abstracts and evaluation of completed trials retrieved from ClinicalTrials.gov, seven full-text articles were assessed for eligibility and four [15-18] blinded, placebo-controlled RCTs were included in the meta-analysis. A flow diagram of the study selection process and specific reasons for exclusion are detailed in the Supplement (eFigure 1).

Study characteristics and risk of bias assessment

The studies were conducted in the USA, Puerto Rico, Brazil, and Argentina and included individuals with mild or moderate laboratory-confirmed SARS-CoV-2 infection. All trial protocols were registered on ClinicalTrials.gov, had a parallel design, and were classified as Phase 2 or Phase 3. Population characteristics, dosage of nitazoxanide, outcomes of interest, and the time of outcomes assessment are detailed in Table 1. Most trials evaluating nitazoxanide as treatment for patients with COVID-19 had a low risk for selection, performance, detection, attrition, and information bias. Two studies were classified as high-risk for reporting bias [16,17] and two studies as high-risk for operational bias [15,16] (eFigure 2; supplementary file).

Clinical outcomes

In this meta-analysis, we found no difference between nitazoxanide and placebo in the frequency of positive RTP-PCR results (RR = 0.83; 95% CI 0.58 to 1.17) (Figure 1A) and there was no decreased risk for composite measure of disease progression (severe COVID-19, ICU admission or invasive mechanical ventilation) (RR = 0.40; 95% CI 0.08 to 2.13) (Figure 1B) and deaths (RR = 0.55; 95% CI 0.18 to 1.68) (Figure 1C) among patients with COVID-19 receiving nitazoxanide. No difference was shown between groups regarding the frequency of individuals with any adverse events (RR = 0.83; 95% CI 0.64 to 1.08) (Figure 2).

Serum biomarkers of inflammation

There were no differences for patients treated with nitazoxanide and placebo in the levels of C-reactive protein (SMD -0.11; 95% CI -0.63 to 0.40; I^2 = 69%; p = 0.67), IL-6 (SMD -0.21; 95% CI -0.74 to 0.32; I^2 = 70%; p = 0.43), and IL-8 (SMD 0.15; 95% CI -0.21 to 0.50; I^2 = 44%; p = 0.42).

Strength of evidence

The quality of evidence was grade as moderate for death, low for the composite measure of disease progression and any adverse events, and very-low for RT-PCR status and serum inflammatory biomarkers (Table 2).

DISCUSSION

Nitazoxanide is a broad-spectrum antiparasitic and antiviral drug, originally approved for the treatment of parasite-mediated infectious diarrhea and enteritis, that has been tested for COVID-19 due to the anti-inflammatory effects [19] and *in vitro* anti-viral activity and promising clinical benefits against influenza and other viruses [20-22]. Moreover, there is *in vitro* evidence that nitazoxanide may induce a significant down-regulation of IL-6/JAK2/STAT3 [23] and may increase the eIF2α and PKR phosphorylation, critical mediators involved in IFN-induced antiviral response [24].

Individual studies [15] have suggested that nitazoxanide reduces SARS-CoV-2 viral load in Vero E6 cells by 75% at a minimal dose of 0.1 μM with no cytotoxic effects. High SARS-CoV-2 viral load was found to be associated with lymphopenia, increased markers of inflammation, and poor clinical outcomes in hospitalized patients with COVID-19 [25,26]. Therefore, the use of nitazoxanide might accelerate viral clearance, improve clinical symptoms, and decrease the risk of hospitalization and death for patients with SARS-CoV-2 infection.

Despite promising theoretical and experimental findings, this systematic review showed no evidence of clinical benefits on the use of nitazoxanide to treat patients with mild or moderate COVID-19. To date, there is still no optimal approach toward COVID-19 management. Symptomatic cases require supportive care with medical evaluation, risk factor stratification for unfavorable clinical outcomes, and clinical monitoring of symptoms. In outpatients, symptomatic treatment includes analgesics and antipyretics. In the hospital setting, patients may need supplemental oxygen and adequate management of pulmonary ventilation. The use of dexamethasone has been indicated for patients with COVID-19 who are receiving respiratory support [27]. Recently, open-label RCTs showed that prophylactic or therapeutic anticoagulation did not result in clinical improvement for hospitalized patients with COVID-19, except in the context of diagnosing a thromboembolic event [28,29].

Our study has some major limitations and include trials with a high-risk of reporting and operational bias. Despite most studies were double-blinded, changes in urine color caused by nitazoxanide could potentially induce a high-risk of performance or detection bias. In one trial [17], the patients received a vitamin B complex supplement to mask any potential chromaturia attributed to nitazoxanide. Finally, the results of this study cannot be generalized to severe or critical COVID-19.

In this systematic review and meta-analysis, we found no current evidence from blinded, placebo-controlled, RCT on the efficacy of nitazoxanide in treating patients with COVID-19. The quality of evidence for most outcomes analyzed in this study is limited. This living systematic review should be updated as soon as the results of ongoing RCT are published.

DECLARATION OF INTERESTS

The authors declare that there is no conflict of interest.

DATA SHARING STATEMENT

The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

AUTHORS' CONTRIBUTIONS

PRMF: conceptualisation, methodology, project administration, supervision, study selection, data extraction, data analysis, risk of bias assessment, and writing. EMNJ: study selection, data extraction, risk of bias assessment, and writing. LCF, JABA and RF: methodology, literature search, and writing. All authors discussed the results and contributed to the final manuscript.

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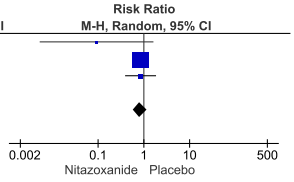
Figure legends

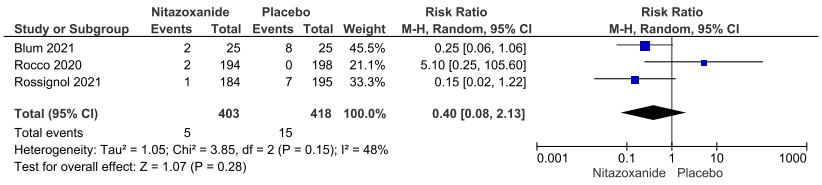
Figure 1. Forest plots showing the effects of nitazoxanide on the frequency of positive RTP-PCR results (A), disease progression (B), and deaths (C).

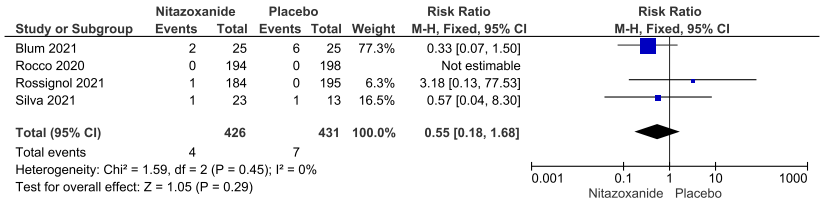
Figure 2. Forest plot showing the risk of adverse events for patients treated with nitazoxanide compared to placebo.

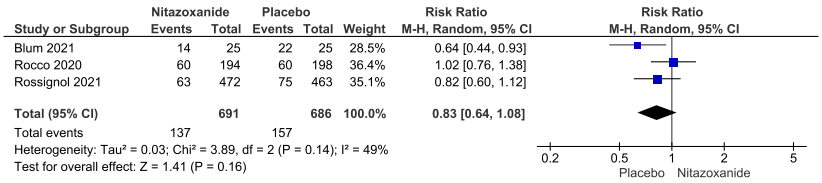
Study or Subgroup	Nitazoxanide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Blum 2021	0	23	4	19	1.5%	0.09 [0.01, 1.62]
Rocco 2020	136	194	162	198	82.0%	0.86 [0.77, 0.96]
Silva 2021	9	23	6	13	16.6%	0.85 [0.39, 1.84]
Total (95% CI)		**240**		**230**	**100.0%**	**0.83 [0.58, 1.17]**
Total events	145		172			

Heterogeneity: Tau² = 0.04; Chi² = 2.48, df = 2 (P = 0.29); I² = 19%
Test for overall effect: Z = 1.06 (P = 0.29)









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