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Methods Article

The Efficacy and Safety of Interferons for the Treatment of Patients with COVID-19: Protocol for Systematic Review and Meta-Analysis of Controlled Trials

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Abstract

Context: COVID-19 has been declared a global pandemic by the World Health Organization (WHO), infecting millions worldwide. The use of interferon (INF) subtypes previously examined in the treatment of SARS and MERS is also being initiated in some clinical trials. Although different clinical trials were evaluated IFNs in the treatment of COVID-19, their efficacy and safety remain unknown.

Objectives: This study aimed to systematically assess IFNs efficacy and safety in treating patients with COVID-19.

Methods: The protocol has been registered in the PROSPERO International Prospective Register (CRD42020200643) on 24 July 2020. This protocol has been arranged according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 checklist.

Conclusions: Owing to lack of approved medication for COVID-19 treatment as well as various mutations of this virus, evaluation of the efficacy and safety of medications by various studies may help in finding treatments with high effectiveness. Interferons are one of the medications that have been administered in COVID-19. Moreover, the best time of administration and dose of this medication was unknown. Although meta-analysis is a potent source for assessing the accuracy of subjects, heterogeneity of articles is a potent limitation of this work.

Keywords: COVID-19; Interferons; Systematic Review; Meta-Analysis

1. Context

Coronavirus disease 2019 (COVID-19), the disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-COV2), was first detected in late December 2019 in Wuhan, China (1, 2). Afterward, COVID-19 was declared a global pandemic by the World Health Organization (WHO), infecting millions worldwide. The disease manifests several symptoms, including dyspnea, fever, cough, myalgia, diarrhea, and other symptoms, which can cause more severe diseases like acute respiratory distress syndrome (ARDS), organ failure, and death. A body of deviance suggests an inflammatory response characterized by a cytokine storm syndrome may be the cause of this deterioration (3).

In the absence of an approved antiviral treatment, several medications are currently being evaluated for their therapeutic effectiveness in the treatment of COVID-19 (4-11).

The use of interferon (INF) subtypes previously examined in the treatment of SARS and MERS is also being initiated in some clinical trials (12-15). Interferons have direct antiviral and immunomodulatory effects. Antiviral effects may include inhibition of viral replication, protein synthesis, virus maturation, or virus release from infected cells. Interferon subtypes are broad-spectrum antivirals with direct inhibitory effects on viral replication and decrease the vascular leakage that improved ARDS complications (16-20).

Although different clinical trials evaluated IFNs in the treatment of COVID-19, their efficacy and safety remain unknown.

2. Objectives

This study aimed to systematically assess the efficacy and safety of IFNs in treating patients with COVID-19.

3. Methods

3.1. Protocol and Registration

The protocol has been registered in the PROSPERO International Prospective Register (CRD42020200643) on 24 July 2020. This protocol has been arranged according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist.

3.2. Eligibility Criteria

All of the Randomized Controlled Trials in English that have assessed the efficacy and safety of various types of IFNs compared with standard care, placebo, or without any comparison for the treatment of patients with confirmed COVID-19 were included. No language and time limitations were considered. The primary outcome measure consisted of all-cause mortality, and the secondary outcomes included time to clinical response, length of hospital and ICU stay, duration of mechanical ventilation, the incidence of adverse drug effects, COVID-19 specific mortality, and respiratory specific mortality. Publications with inaccessible full text and defective data were not included.

3.3. Study Selection

A comprehensive search was conducted on MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov using related keywords, including medical sub-heading (MeSH) terms and EMTREE terms. Furthermore, the pre-print servers, including medRxiv, bioRxiv, as well as gray literature, were searched. Additionally, the reference lists of eligible primary studies, systematic reviews, and meta-analyses were manually searched. Keywords included disease-related terms (severe acute respiratory syndrome, coronavirus infection, coronavirus disease, COVID-19) and treatment-related terms (interferon, INF, interferon-beta, interferon-alpha). The obtained papers from the primary search were assessed by two reviewers independently. In the case of any conflict, the full-text was analyzed by a third reviewer.

3.4. Data Extraction and Data Items

Data were extracted and recorded into the prepared checklist, including author details and publication year, study design and recruitment strategy, sample size, diagnosis method for COVID-19, demographics data of patients, including age, gender, smoking status, comorbidities, laboratory findings, Imaging findings, characteristics of the intervention including type, start date, dose, route, and duration of interferons, treatment-related adverse events, requirement and duration of mechanical ventilation, use and dosage of oxygen, requirement and duration of non-invasive ventilation, duration of intensive care unit (ICU) stay, duration of hospital stay, survival outcome measures, and follow-up duration.

3.5. Risk of Bias in Individual Studies

The risk of bias was assessed using the Cochrane risk of bias tool for randomized controlled studies, which included allocation sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, for-profit bias, and overall risk of bias. The risk of bias was carried out by two reviewers independently.

3.6. Data Synthesis

The random-effect model meta-analyses were used for data synthesis. Pooled relative risk (RR) or odds ratio (OR) and 95% confidence interval (95% CI) were estimated for categorical outcomes, and pooled mean differences and 95% CI were estimated for continuous outcomes. The data collection was completed by two reviewers independently.

4. Discussion

Owing to lack of approved medication for COVID-19 treatment as well as various mutations of this virus, evaluation of the efficacy and safety of medications by various studies may help in finding treatments with high effectiveness. Interferons are one of the medications that have been administered in COVID-19. Moreover, the best time of administration and dose of this medication was unknown. Although meta-analysis is a potent source for assessing the accuracy of subjects, heterogeneity of articles is a potent limitation of this work.

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