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Repurposed Therapeutic Agents Targeting the Ebola Virus: A Systematic Review

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ABSTRACT

Background: The Ebola virus has been responsible for numerous outbreaks since the 1970s, with the most recent outbreak taking place between 2014 and 2016 and causing an international public health emergency. Ebola virus disease (EVD) has a high mortality rate and no approved targeted treatment exists to date. A number of established drugs are being considered as potential therapeutic agents for the treatment of EVD.

Objective: We aimed to identify potential drug repositioning candidates and to assess the scientific evidence available on their efficacy.

Methods: We conducted a systematic literature search in MEDLINE, Embase, and other relevant trial registry platforms for studies published between January 1976 and January 2017. We included drug screening, preclinical studies, and clinical studies on repurposed drugs for the treatment of EVD. The risk of bias for animal studies and nonrandomized clinical studies was assessed. The quality of reporting for case series and case reports was evaluated. Finally, we selected drugs approved by established regulatory authorities, which have positive in vitro study outcomes and at least one additional animal or clinical trial.

Results: We identified 3301 publications, of which 37 studies fulfilled our inclusion criteria. Studies were highly heterogeneous in terms of study type, methodology, and intervention. The risk of bias was high for 13 out of 14 animal studies. We selected 11 drugs with potential anti-EVD therapeutic effects and summarized their evidence.

Conclusions: Several established drugs may have therapeutic effects on EVD, but the quality and quantity of current scientific evidence is lacking. This review highlights the need for well-designed and conducted preclinical and clinical research to establish the efficacy of potential repurposed drugs against EVD.

Introduction

Since its discovery in 1976, the Ebola virus has been the pathogen responsible for an increasing number of epidemics.[1] The most widespread epidemic took place in western Africa between December 2013 and June 2016, and resulted in a total of 28,652 reported cases and 11,325 reported deaths as of April 2016.[2] The World Health Organization declared the recent epidemic a public health emergency of international concern and called for intensified efforts to develop therapeutic agents targeting the Ebola virus.[3] Although the large-scale epidemic may have ended, the emergence of sporadic new cases continues to pose a risk for future outbreaks.[4]

Ebola virus disease (EVD) is often considered a disease of poverty because it takes place in the form of sudden outbreaks amongst poor populations and under limited resources.[5] As with many other diseases of poverty, research and drug development for EVD have been neglected for many years because it is commercially unattractive for drug developers to invest significant

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resources. For example, a study from 2002 revealed that in the period between 1975 and 1999, only 13 out of 1393 new, approved drugs were specifically indicated for tropical diseases, accounting for $< 1\%$ of all new approved drugs.[6]

Nonetheless, the recent EVD outbreak led to accelerated de novo drug development efforts for EVD.[7] These efforts were promoted by an expedited approval process by regulators such as the US Food and Drug Administration (FDA) and the European Medicines Agency.[8,9] Yet, after more than 2 years since the start of the epidemic, results of many experimental drugs are considered either questionable or negative, with only 1 potential vaccine being considered a true breakthrough.[10] To date, none of the experimental drugs has been fully approved for the treatment or prevention of EVD.

Due to the urgent need for an effective and accessible EVD treatment, there were additional efforts to study approved and established drugs as potential anti-EVD therapeutic agents, a concept known as drug repurposing or drug repositioning.[11] This concept may have significant advantages in the case of EVD, which overcomes the limitations of experimental drug development. First, repurposed drugs usually have well-known safety and pharmacokinetic profiles, which leads to shorter development cycles and lower costs.[12] In addition, these drugs may often tap into an already established manufacturing and distribution network, which shortens production and delivery times in cases of rapidly spreading epidemics. Finally, depending on which repurposed drugs are being identified, they may already be marketed as generics, which is a clear advantage in countries with resource-poor health care systems.

A variety of literature reviews have been published on potential therapeutic targets for EVD, some of which also include an overview of possible candidates for drug repurposing.[13-18] However, no systematic review dedicated to repurposed therapeutic agents targeting EVD exists to date. Herein, we present a systematic review with the aim of identifying potential drug repurposing candidates and assessing the scientific evidence available on their efficacy.

Methods and Design

Protocol and registration

We undertook a systematic review based on an a priori protocol that was registered with PROSPERO (CRD42015024349) and published in a peer-reviewed journal.[19] This systematic review was reported according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement.[20]

Eligibility criteria

Study designs

Study designs included drug library screening studies yielding at least 1 approved therapeutic agent (including high throughput screening studies or virtual, in silico drug screens); preclinical trials (including in vitro trials and studies on animal models); clinical trials (including randomized controlled trials, controlled clinical trials, prospective and retrospective comparative cohort studies, and caseã control studies); and cross-sectional studies, case series, and case reports.

Intervention

Potential repurposed drugs selected for further assessment must fulfill the following criteria: drugs that are already approved by at least 1 regulatory authority US Food and Drug Administration (FDA), European Medicines Agency (EMA), Japan Pharmaceuticals and Medical Devices Agency (PMDA), and drugs with positive in vitro study outcomes and at least 1 additional animal or clinical trial.

Study population, timing, and setting

There were no restrictions on the type of participants in preclinical or clinical trials. In addition, there were no restrictions on the type of setting. We included studies published from 1976, the year of discovery of EVD.

Comparators

There were no restrictions on the type of comparator.

Outcomes

The primary outcomes included mortality, sequelae of the infection, and serious adverse events. Secondary outcomes include adverse events. Outcomes were collected as reported. We extracted outcomes in all data forms (eg, dichotomous and continuous) as reported in the included studies.

Languages

We included articles reported in the English, German, French, and Spanish languages.

Publication status

We included articles published in scientific journals as well as unpublished ones.

Information sources

Literature search strategies were developed using medical subject headings and text words related to EVD. We performed a systematic literature search in MEDLINE, Embase, and Cochrane Central Register of Controlled Trials.

The search was carried out on January 2, 2017, for studies published between January 1, 1976, and the date the searches were run.

To identify ongoing and unpublished studies, we searched the World Health Organization International Clinical Trials Registry Platform, ClinicalTrials.gov, and European Union Clinical Trials Register. In addition, we searched the reference lists of selected studies as well as the Websites of regulatory authorities (FDA and European Medicines Agency).

Search strategy

We developed a search strategy with the help of an information specialist (**Supplementary file 1**). The database records yielded by all search strategies were exported into EndNote Version X7.5, Clarivate Analytics, USA and duplicates were manually removed. The results of our database searches and records identified from other sources were documented and depicted in a PRISMA flow diagram.

Study selection

Before formal screening, a preliminary study screen was used by 2 authors (HS and OE) to carry out a pilot screening of 50 randomly chosen studies from the search results spreadsheet. Following the pilot screening, both authors independently screened the titles and abstracts yielded by the search against the inclusion criteria. In addition, they screened the reference lists of all selected articles. Studies selected at title and abstract levels were further screened for eligibility by assessing the full text of the article. We retrieved additional information from study authors