Research Article

An Observational Descriptive Pharmacological Research and A Meta-analysis on the Clinical Pharmacotherapeutics of Rectal Organoids in Cystic Fibrosis

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ABSTRACT

Rectal organoid cultures, derived from the rectal epithelia, are three-dimensional (3D) primary stem cell cultures that self-organize into tissue-recapitulating "mini-guts" in vitro that enable the long-term expansion and biobanking of primary patient tissue using defined growth conditions. The objective of this study was observational descriptive pharmacological research and a meta-analysis on the clinical pharmacotherapeutics of rectal organoids in cystic fibrosis. The study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration in June, 2016. An observational descriptive clinical pharmacotherapeutic research study was also conducted. This pharmacological research and meta-analysis, contributed 6354 refined and relevant medical records, among total 8754 records obtained from the study databases search. It also described the clinical pharmacology of rectal organoids in cystic fibrosis, which further explained this meta-analysis and observational descriptive pharmacotherapeutic research. To conclude, this descriptive pharmacological research and meta-analysis provided the refined qualitatively synthesised medical records, study literature and databases, as well as a descriptive analysis on the clinical pharmacotherapeutics of rectal organoids in cystic fibrosis.

Keywords: Rectal Organoids, Cystic Fibrosis, Clinical Pharmacotherapeutics, Observational Descriptive Pharmacotherapeutic Research, Meta-analysis.

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INTRODUCTION

Organoids are three-dimensional cell structures, grown *in vitro* from the stem cells, mainly isolated from the biopsies or from the pluripotent stem cells, that are extensively similar to the endogenous organs, in both their structural development and functional performance.

Rectal organoid cultures, derived from the rectal epithelia, are three-dimensional (3D) primary stem cell cultures that self-organize into tissue-recapitulating "mini-guts" *in vitro* that enable the long-term expansion and biobanking of primary patient tissue using defined growth conditions.[1-6]

This pharmacological research and meta-analysis was conducted for systematically investigating the clinical pharmacotherapeutics of rectal organoids in cystic fibrosis, with thorough explanations and analysis of the medical study literature and evidences compiled from the various studies conducted, which explained the clinical pharmacotherapeutics of rectal organoids.

Objective

The objective of this study was observational descriptive pharmacological research and a meta-analysis on the clinical pharmacotherapeutics of rectal organoids in cystic fibrosis.

MATERIALS AND METHODS

Ethical principles

The study was conducted in accordance with the ethical principles of Declaration of Helsinki and Good Clinical Practices, and in compliance with the global regulatory requirements.

Study Type

This study was a multi-variate, observational, descriptive, analytical, qualitative pharmacological research study and a multi-variate meta-analysis on the clinical pharmacotherapeutics of rectal organoids.

Study Materials

The study materials consisted of pharmacological clinical research database of global heterogenous research analyses and similar study literature on the clinical pharmacotherapeutics of rectal organoids in cystic fibrosis.

Study Period

The study period for this research project and the compilation of the study literature was 7 months, from November, 2021 to May, 2022.

Place of Study

This research study and the compilation of the study literature was conducted in the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Rational Pharmacotherapeutics, Pharmacoepidemiology, Pharmacogenomics, Evidence-Based Medicine, Clinical Pathology, Molecular Diagnostics, Respiratory Medicine, Clinical Medicine and Clinical Research, at Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Hazra Nursing Home, Hazra Polyclinic And Diagnostic Centre, Mamata Medical College, Mamata Hospitals, Fortis Hospitals, and Global Institute Of Stem Cell Therapy and Research (GIOSTAR), Institute of Regenerative Medicine (IRM), Institutes, Hospitals and Laboratories.

Study Procedure

The study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration in June, 2016. At first, the steps of identification included the records which were identified through database searching and the additional records which were identified through other sources. This led to the steps of screening, which included the screened records after the duplicates were removed. From these screened records, few records were excluded, as per the exclusion criteria. Then, in the eligibility step, the full text articles were assessed for eligibility, from which few full text articles were excluded, according to the exclusion criteria, with adequate reasons. This led to the final inclusion step, where the studies were included in the qualitative synthesis of a systematic review, according to the inclusion criteria, and ultimately the studies were included in the quantitative synthesis, of a meta-analysis.

The study selection criteria were the following:

(a) The inclusion criteria were : The published articles on the clinical pharmacotherapeutics of rectal organoids in cystic fibrosis; the original research studies, systematic reviews, meta-analyses, case reports, case series, narrative reviews, study series, parallel studies and similar kind of studies or reviews, of any or all types, which were either qualitative, or quantitative, or both qualitative as well as quantitative; the publication time-frame within a span of the past 5 years; and any or all types of observational, descriptive and analytical research studies.

(b) The exclusion criteria were : Irrelevant studies; and studies older than 5 years.

Each study was assessed for allocation concealment, blinding, reporting of losses to follow-up or missing outcome assessments, evidence of important baseline differences between the groups, analysis on an intention-to-treat basis and use of a sample size calculation.

An observational descriptive clinical pharmacological research study was also conducted.

RESULTS

(i) The results of this Meta-Analysis:

In accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration, June, 2016, in identification stage, the study literature search on the clinical pharmacotherapeutic aspects of rectal organoids in cystic fibrosis, contributed 3027 records in PubMed search, 2344 records in EMBASE search, 2665 records in Scopus search, and 720 records in additional databases search, identified through other sources. The total 8756 records, after removing 756 duplicates, were 8000. In the screening stage, the records screened were 8000. From these records, 1299 records were excluded, according to the exclusion criteria. In the eligibility stage, the full text articles assessed for eligibility were 6701. From these records, 347 full text articles were excluded, according to the exclusion criteria. In the final inclusion stage, the records ultimately included in the qualitative synthesis, according to the inclusion criteria, was 6354. These 6354 records were the refined contributions of this meta-analysis. Thus, this meta-analysis contributed 6354 refined and relevant medical records, among total 8756 records obtained from the study databases search, as depicted in Figure 1.

(ii) The selected investigative elucidations on the clinical pharmacotherapeutics of rectal organoids in cystic fibrosis:

From the compilation of pharmacotherapeutic databases and evidences and the observational descriptive clinical pharmacological research study, the clinical pharmacotherapeutics of rectal organoids in cystic fibrosis was described, in complete details, to explain the qualitative details of the conducted clinical pharmacological research and meta-analysis.

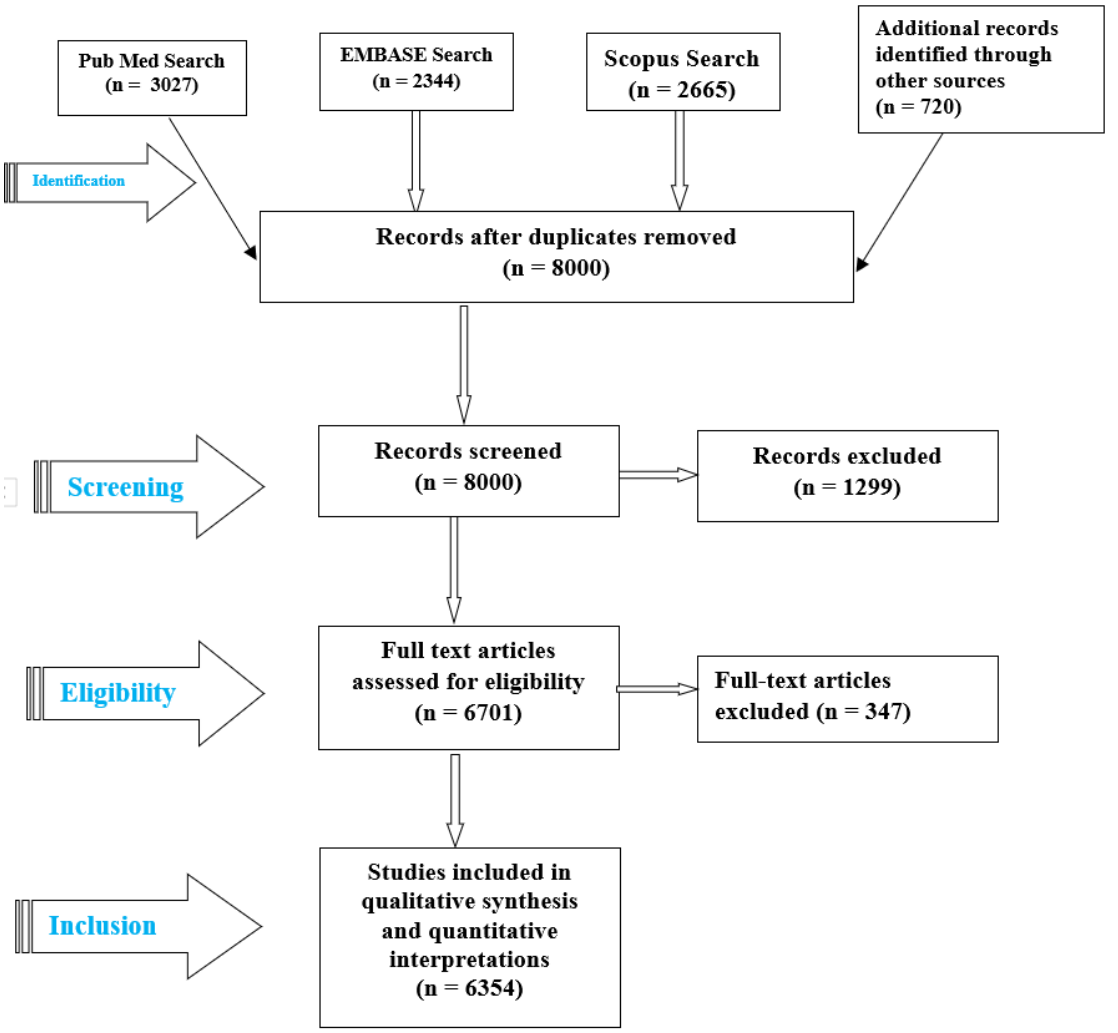

Figure 1: The Stages in PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009

DISCUSSION

In this study, in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration, June, 2016, in identification stage, the study literature search on the clinical pharmacotherapeutic aspects of rectal organoids in cystic fibrosis, contributed 3027 records in PubMed search, 2344 records in EMBASE search, 2665 records in Scopus search, and 720 records in additional databases search, identified through other sources. The total 8756 records, after removing 756 duplicates, were 8000. In the screening stage, the records screened were 8000. From these records, 1299 records were excluded, according to the exclusion criteria. In the eligibility stage, the full text articles assessed for eligibility were 6701. From these records, 347 full text articles were excluded, according to the exclusion criteria. In the final inclusion stage, the records ultimately included in the qualitative synthesis, according to the inclusion criteria, was 6354. These 6354 records were the refined contributions of this meta-analysis. Thus, this meta-analysis contributed 6354 refined and relevant medical records, among total 8756 records obtained from the study databases search.

The following selected qualitative investigative elucidations on the clinical pharmacotherapeutics of rectal organoids in cystic fibrosis:

From the compilation of the pharmacotherapeutic databases and evidences, an observational descriptive pharmacological research study on rectal organoids in cystic fibrosis provided the following descriptive details.

Biobank research on patient-derived organoids has given rise to successful personalized treatment of various complicated diseases, like, cystic fibrosis. Cystic fibrosis (CF), caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that encodes an epithelial anion channel, associates with a wide spectrum of phenotypes, including CF or milder single-organ CFTR-related diseases. CFTR mutations, classified into six classes according to their effect on CFTR protein expression and function, includes (i) no synthesis, (ii) impaired trafficking, (iii) defective channel gating, (iv)

altered conductance, (v) reduced amounts of functional CFTR, and (vi) impaired cell surface stability of the protein.

The process of identifying subjects with cystic fibrosis (CF) who may benefit from cystic fibrosis transmembrane conductance regulator (CFTR)–modulating drugs is time-consuming, costly, and especially challenging for individuals with rare uncharacterized CFTR mutations. In a study, the CFTR function and responses to two drugs—the prototypical CFTR potentiator VX-770 (ivacaftor/ KALYDECO) and the CFTR corrector VX-809 (lumacaftor)—was analysed, in organoid cultures derived from the rectal epithelia of subjects with CF, who expressed a broad range of CFTR mutations. In this study, it was observed that CFTR residual function and responses to drug therapy depended on both the CFTR mutation and the genetic background of the subjects. *In vitro* drug responses in rectal organoids positively correlated with published outcome data from clinical trials with VX-809 and VX-770, thus, helping to predict from preclinical data the potential for CF patients carrying rare CFTR mutations to respond to drug therapy. The proof of principle was demonstrated by selecting two subjects expressing an uncharacterized rare CFTR genotype (G1249R/F508del) who showed clinical responses to treatment with ivacaftor and one subject (F508del/R347P) who showed a limited response to drug therapy both *in vitro* and *in vivo*. These data suggest that *in vitro* measurements of CFTR function in patient-derived rectal organoids may be useful for identifying subjects who would benefit from CFTR-correcting treatment, independent of their CFTR mutation. In this study, a relationship was established between the CFTR genotype, residual CFTR function, and response to therapy using rectal organoids from CF patients. Also, a proof of principle was provided that individual *in vitro* functional measurements in rectal organoids may be used to preclinically select those subjects with CF who will respond to CFTR-modulating drugs. The study findings indicated that organoid-based CFTR function measurements can play an important role in the study of rare CFTR mutations and may help to identify subjects with CF who may benefit from CFTR modulator therapy independent of their CFTR mutation.

Because of their characteristics, organoids have enormous potential for drug development and precision medicine, which aims to increase cost effectiveness and risk-benefit ratios of therapies by more precisely targeting therapies to individual patients. The ultimate application of organoid technology is to use them for organ regeneration and replacement therapies, reducing whole organ transplant requirements and improving the life quality of patients. The recent development of edited pluripotent stem cells with targeted disruption of HLA genes by CRISPR/Cas9 technology should also facilitate the generation of immune-compatible healthy organoids for widespread therapeutic purposes.[1-6]

This pharmacological research and meta-analysis provided the refined qualitatively synthesised medical records, study literature and databases, with well-comprehensible elaborations, on the clinical pharmacotherapeutics of rectal organoids in cystic fibrosis.

CONCLUSION

Therefore, this meta-analysis contributed 6354 refined and relevant medical records, among total 8756 records obtained from the study databases search. It also analytically described the clinical pharmacotherapeutics of rectal organoids in cystic fibrosis, which comprehensively elaborated this pharmacological research and meta-analysis.

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