

Original Research Article

An observational analytical clinical research study and asystematic review on the clinical pharmacology ofrectal organoids in cystic fibrosis

Moumita Hazra*

Associate Professor, Head of Department In Charge, Department of Pharmacology, Mamata Medical College and Hospitals, Telangana, India

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Abstract

Introduction: 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. This clinical research and systematic review was conducted for systematically investigating the clinical pharmacological aspects of the rectal organoids in cystic fibrosis, with thorough explanations and analyses of the medical study literature and evidences compiled from the various studies conducted, which explained the clinical pharmacology of rectal organoids. **Objectives:** The objective of this study was an observational analytical clinical research and a systematic review on the clinical pharmacology of rectal organoids in cystic fibrosis. **Methods:** 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. An observational analytical clinical pharmacological research study was also conducted. **Results:** This clinical research and systematic review, contributed 5898 refined and relevant medical records, among total 8371 records obtained from the study databases search. It also described the clinical pharmacology of rectal organoids in cystic fibrosis, which elaborated this systematic review and observational analytical clinical research study. **Conclusions:** To conclude, this clinical research and systematic review provided the refined qualitatively synthesised medical records, study literature and databases, as well as a descriptive analysis on the clinical pharmacology of rectal organoids in cystic fibrosis.

Keywords: Rectal Organoids, Cystic Fibrosis, Clinical Pharmacology, Observational Analytical Clinical Research, Systematic Review.

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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. The organoids are formed of cells which differentiate, undergo spatially restricted lineage commitment, and acquire the specific tissue patterning to develop into several endoderm, mesoderm, and ectoderm-derived tissues. These organoids mostly tend to resemble the *in vivo* original organs, with the preservation of their genetic, phenotypic and behavioural traits. These are not only complex structures, but also possess unique capabilities of modeling human organ development and disease, showing wide similarities with the human organ system.

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 clinical research and systematic review was conducted for systematically investigating the clinical pharmacology 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 pharmacology of rectal organoids.

Objective

The objective of this study was an observational analytical clinical research and a systematic review on the clinical pharmacology 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 an multi-variate, observational, descriptive, analytical, qualitative clinical research study and a multi-variate, systematic review on the clinical pharmacology of rectal organoids.

Study Materials

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

Study Period

The study period for this research project and the compilation of the study literature was 1 year.

Place of Study

This research study and the compilation of the study literature was conducted in the Departments of Pharmacology, Clinical

*Correspondence

Dr. Moumita Hazra

Associate Professor, Head of Department In Charge, Department of Pharmacology, Mamata Medical College and Hospitals, Telangana, India

E-mail: drmoumitahazra.198017thjune@gmail.com

Pharmacology, Molecular Pharmacology, Rational Pharmacotherapeutics, Pharmacoepidemiology, Pharmacovigilance, 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, Rama Medical College Hospital and Research Centre, Rama University, Mamata Medical College and 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.

The study selection criteria were the following:

- a) **The inclusion criteria were:** The published articles on the clinical pharmacology 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 analytical clinical pharmacological research study was also conducted.

Results

i) The results of this Systematic Review

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 pharmacological aspects of rectal organoids in cystic fibrosis, contributed 3007 records in PubMed search, 2124 records in EMBASE search, 2567 records in Scopus search, and 673 records in additional databases search, identified through other sources. The total 8371 records, after removing 745 duplicates, were 7626. In the screening stage, the records screened were 7626. From these records, 1289 records were excluded, according to the exclusion criteria. In the eligibility stage, the full text articles assessed for eligibility were 6337. From these records, 439 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 5898. These 5898 records were the refined contributions of this systematic review. Thus, this systematic review contributed 5898 refined and relevant medical records, among total 8371 records obtained from the study databases search, as depicted in Figure 1.

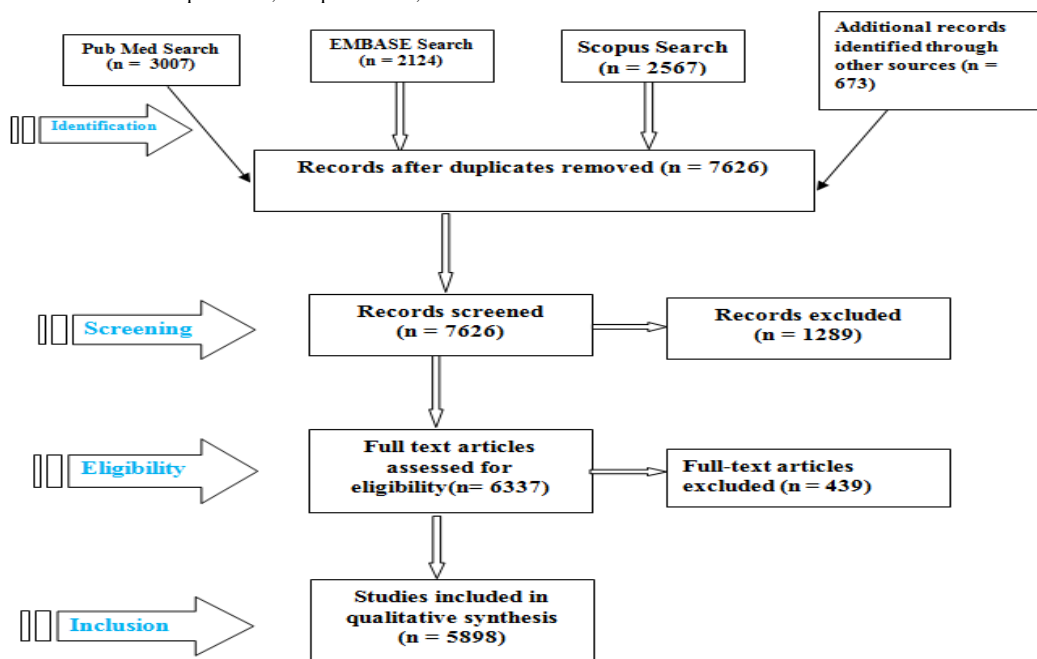


Figure 1: The Stages in PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009

ii) Theselected investigative elucidations on the clinical pharmacology of rectal organoidsin cystic fibrosis

From the compilation of pharmacotherapeutic databases and evidences and the observational analytical clinical pharmacological

research study,the clinical pharmacology of rectal organoids in cystic fibrosis was described,in complete details, to elaborate on the qualitative details of the conducted clinical research and systematic review.

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 pharmacological aspects of rectal organoids in cystic fibrosis, contributed 3007 records in PubMed search, 2124 records in EMBASE search, 2567 records in Scopus search, and 673 records in additional databases search, identified through other sources. The total 8371 records, after removing 745 duplicates, were 7626. In the screening stage, the records screened were 7626. From these records, 1289 records were excluded, according to the exclusion criteria. In the eligibility stage, the full text articles assessed for eligibility were 6337. From these records, 439 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 5898. These 5898 records were the refined contributions of this systematic review. Thus, this systematic review contributed 5898 refined and relevant medical records, among total 8371 records obtained from the study databases search.

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

From the compilation of the pharmacotherapeutic databases and evidences, an observational analytical clinical 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 clinical research and systematic review provided the refined qualitatively synthesised medical records, study literature and databases, with well-comprehensible elaborations, on the clinical pharmacology of rectal organoids in cystic fibrosis.

Conclusion

Therefore, this systematic review, contributed 5898 refined and relevant medical records, among total 8371 records obtained from the study databases search. It also analytically described the clinical pharmacology of rectal organoids in cystic fibrosis, which comprehensively elaborated this clinical research and systematic review.

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