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The Efficacy and Safety of Cystic Fibrosis Gene Therapy Clinical Trials: A Systematic Review and Meta-Analysis

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Abstract

Background

Gene therapy has been proposed as a treatment approach for cystic fibrosis by replacing the single defective gene, cystic fibrosis transmembrane regulator (CFTR), through topical lung delivery. Relatively few studies have addressed gene therapy for cystic fibrosis.

Objectives

Via referral to the published literature, this study aimed to identify any success of the gene therapy approach for cystic fibrosis regarding experimental and routine clinical outcomes in different drug development stages, and to determine any adverse effects noted.

Methodology

A search of the PubMed database (NCBI) for 1989–2020 was made using predefined selection criteria for clinical trials on patients with cystic fibrosis receiving viral and non-viral lung delivery systems of the CFTR gene. Several features in the reviewed studies were examined, including clinical phase (1–3), sample size, delivery target cells/vector, and reported adverse effects. A quantitative estimate of treatment intervention success was evaluated using a meta-analysis approach.

Results

A total of 20 studies with 549 patients were included in the review. The studies involved the delivery of the defective gene to the lung, nasal mucosa, and sinuses, and were mainly phase 1–2, randomized controlled trials; there were no phase three studies. The vector for gene transfer was liposome or viral. % predicted FEV1 was statistically significant between intervention and control patients in two trials. Gene transfer was detected to a higher degree in intervention patients than control; this outcome measure was assessed using bronchoscopy assessment of vector-specific DNA and mRNA expression in lung and nasal mucosa. These effects, however, were temporary. The safety of the gene therapy approach was confirmed.

Conclusion

Reportedly, the gene therapy approach is safe but has limited and temporary efficacy. Newer approaches should thus be engineered to deliver the necessary genetic material with the desired, full-scale efficacy.

Keywords: Gene therapy, Cystic fibrosis, Pharmacology, Pharmacogenetics, Clinical trial, Vector

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Introduction

Cystic fibrosis is a genetic disease caused by a mutation in the cystic fibrosis transmembrane regulator (CFTR) gene, which subsequently affects different organs in the body. The leading cause of death in approximately 90% of cystic fibrosis patients is lung damage [1]. Cystic fibrosis mutation is in the gene encoding CFTR which regulates the chloride and sodium channels in the epithelium of the cell surface [2]. This pathology increases the thickness of the mucus from mucus- and sweat-producing cells, which obstructs respiratory pathways and is associated with an increased risk of severe infection, mainly pseudomonas infection [3]. Tissue destruction can occur due to neutrophil infiltration, whereas digestive symptoms are often manifested by malabsorption due to the abnormal flow of enzymes and bile salts in the pancreas and gall bladder [4]. The incidence of cystic fibrosis is between 1/3000 and 1/6000 live births in the population of European descent [5]. Current efforts to manage cystic fibrosis are focused on replacing the mutated sequence of the CFTR gene, as a more root cause-directed approach for treatment involving the development of novel gene therapy interventions. If successful, gene therapy can replace the defective gene. Some features of the pathophysiology of cystic fibrosis have been seen as promising features for gene therapy, including single genetic mutation and respiratory symptoms [2–3]. Such features permitted delivery of the genes topically through the respiratory tract using viruses and liposomal drug delivery systems as carriers. The first delivery platforms with potential were AAV-based vectors. A stable but low level CFTR expression was demonstrated in cultured cells [6]. In general, AAV delivery was considered safe; however, their use is limited due to the small carrying capacity of ~4.6 kb. As an alternative to viral vectors, the focus became directed toward non-viral (i.e., plasmid) vectors, with no size constraints for CFTR delivery [7]. A number of clinical trials from 1995–2013 reported stable efficacy associated with an increase in FEV1 with repeat administration, and this clearly reflected phenotypic correction [8]. Additional efforts to improve transgene delivery have led to the development of retroviral- or lentiviral-based vectors, with regulatory elements to obtain lung-specific transgene expression. Elicitation of innate and adaptive responses to LV vectors remains a significant limitation to clinical applications [9].

The present review provides a recent overview of clinical gene therapy trials in cystic fibrosis over the last two decades (1990–2020). Several features of the reviewed studies were examined, including clinical phase (1, 2, 3), sample size, delivery target cells/vector, and reported adverse effects. A quantitative estimate of treatment intervention success was also evaluated using a meta-analysis approach.

Methods

Data collection

Data sources and search strategy

A literature search was conducted on the PubMed database (NCBI) covering 1990–2020 (inclusive), using the search term ((cystic fibrosis*) AND gene therapy*). The search term was selected after empirical testing of several search terms. Additional articles were obtained from other sources to complement the search process, including related reviews and other research articles.

The studies were adjudged to be qualifying if they met the following selection criteria:

1) Prospective clinical trials, phases 1–3;
2) The intervention (compared with

placebo or not) the defective gene of cystic fibrosis (CFTR) delivered topically to the respiratory system;

3) Inclusion of delivery sites to the lung. Delivery sites serving as models for cystic fibrosis, such as nasal and sinus, were also included in the review;

4) Inclusion of outcome measures relevant to efficacy or safety outcomes. Surrogate measures can also be deemed appropriate for outcome measure purposes, such as sinusitis relapse rate, to measure cystic fibrosis outcomes;

5) The studies were published in English.

Extraction of clinical studies data

Two authors independently assessed the search results to determine the qualifying articles against the predefined selection criteria for clinical trials on cystic fibrosis patients receiving viral and non-viral lung delivery systems of the CFTR gene. Studies reporting all clinical trial phases were qualified for inclusion. Data were extracted to specifically designed data extraction forms, including data on the study, intervention, the control utilized, masking procedure, and study sample. The other outcomes recorded in the forms were: pulmonary function test, including % predicted FEV1, FVC, CT gas trapping, and sinusitis recurrence; bronchoscopy, including vector-specific DNA and vector-specific mRNA in the lung and the nasal mucosa and bronchial chloride response; and, adverse effects in the following group categories: discontinued due to adverse effects, serious adverse events, and other toxicity issues.

Data analysis

Descriptive statistics were used to report the data. The point of the analysis was to conduct a review and meta-analysis to determine the efficacy of the gene therapy approach using data from several clinical trials. Meta-analysis was carried out, and pooled odds ratio and associated 95% confidence interval were calculated using Review Manager 5 software. An I-2 test was used to assess heterogeneity across the designs of the included trials. Statistical significance, when referred to in the manuscript, was set to ≤ 0.05.

Results

The search resulted in the identification of 20 studies that included a total of 549 patients. Full details of the assessment of qualifying articles are illustrated in Figure 1.

The target delivery site in the reviewed studies involved delivery of the defective gene to the lung, nasal mucosa, and sinuses. For the lung studies, four were phase 1 or phase 2a studies [10–13], and six were randomized controlled trials [12, 14–18]. The intervention vector was liposome in two studies [10, 14]), while the vector was viruses in eight studies [11–13, 15–18]. A double blind design was utilized in four studies [14–16]. For the nasal mucosa studies, two were phase 1 or phase 2a studies [10–11], and eight were randomized controlled trials [15, 19–25]. The intervention vector was liposome in seven studies [10, 15, 19–21, 23, 25] and viruses in three studies [11, 22, 24]. A double blind design was used in seven studies [15, 19–22, 24–25]. For the sinus studies, three were randomized controlled trials in which the vector was viruses [26–28]. One used a double blind design [28]. All the studies were in either phase 1 or 2; interestingly, a good proportion of them used randomized controlled designs. Full details of the data related to these studies are summarized in Table 1.

As noted above, there was a wide variation in the type of intervention. However, the more focused outcome measures included, among others, respiratory function tests, vector-specific DNA and mRNA, and changes in bronchial

chloride responses. The latter outcome measures served as a base for confirming the efficacy of an intervention and, as most of the studies were phase 1 or 2, these outcome measures were used as proof of concept evidence for the approach.

A statistically significant improvement in lung function tests was noted in some of the interventions compared with the control. These trials looked at % predicted FEV1 [14]; p=0.039; [16]; p=0.04). Other trials were not significant [12, 16]. Full details of these outcomes and other performed respiratory function tests are shown in Table 2.

A bronchoscopy, a type of invasive procedure, was used to determine the outcome measure. This procedure detected vector-specific DNA and mRNA in the lung and nasal mucosa, so that the intervention and control patients could be compared. Across different clinical trials, more subjects were positive for vector-specific DNA compared with vector-specific mRNA. Among the intervention patients, detection of vector-specific DNA and mRNA was higher compared with the control patients. Some improvements were noted concerning bronchial chloride secretion, which represents an improvement in the root cause of the pathology of cystic fibrosis. A statistically significant (p=0.032) example of such an improvement can be found in [14]. Full details are shown in Table 3. Figure 2 illustrates the meta-analysis results of the vector-specific DNA expression in the intervention and control groups. It showed that the analysis favors the intervention group, with a pooled odds ratio of 0.01 (95% confidence interval =0.00–0.08), meaning that the odds of non-detection of vector-specific DNA in the treatment group are 0.01 those of the control group and, as such, the treatment seems to be beneficial. Also, no heterogeneity was noted as I^2=0%.

An overview of the adverse effects/risk associated with vector DNA administration revealed that the adverse effects were tolerable and mild, and that no serious adverse effects were associated with the vector administration. Serious adverse effects were only related to the trial procedures [10, 14] and were unrelated to vector administration [11, 18, 24]. All procedures were well tolerated and mild symptoms were experienced in several studies [12–13, 15–16, 19, 28]. In other studies, little or no inflammatory response [26] or no adverse effects were reported [20, 23–24]. Overall, the frequency of adverse events was similar across treatment and placebo groups [17].

Discussion

This review has considered the evidence for a gene therapy approach for cystic fibrosis administered topically to the lung, utilizing viral and liposomal correct cystic fibrosis gene. The search included systematic cystic fibrosis gene therapy phase 1–3 clinical trials which summed 549 patients in 20 studies. The present study reviewed any promising benefit of gene therapy. A meta-analysis was carried out to estimate intervention treatment success. The detection of the cystic fibrosis gene (vector-specific) was complete in the experimental group, and the pooled odd ratio of the non-detection of vector-specific DNA in the treatment groups is 0.01 of those of the control group. Thus, patients in the experimental groups benefited from the gene transfer, and the pooled effect of different studies demonstrated the effect. However, the temporary effect of the transfer limits such promising results, despite multiple doses being administered. Notably, adverse effects were minimal.

Cystic fibrosis is a severe disease and, as such, it is essential to reduce the suffering it

causes. Patients suffer from pulmonary symptoms concurrently with long-term bacterial infections and inflammation [29]. Some of the features of the pathophysiology of cystic fibrosis had been seen as promising features for gene therapy, including single genetic mutation (autosomal recessive mutation in the CFTR gene that codes the anion channel that is cAMP-regulated), and respiratory symptoms. Such features allowed for delivery using viruses and liposomal drug delivery systems to carry the correct genes through the respiratory tract, hoping that this would lead to correct gene expression. Despite the proof of concept for gene therapy replacement of the defective CFTR gene (ΔF508 mutation) being quickly identified after the CFTR mutation was found [30], this gene therapy and other innovative approaches for cystic fibrosis gene therapy still require further research.

Current treatments for cystic fibrosis focus on the treatment of sequela from the genetic mutation responsible for the disease, a more root cause-directed approach for the treatment involving novel gene therapy. If successful, gene therapy can replace the defective gene. The momentum to achieve this goal started with identifying and characterizing the genetic mutation, cloning the correct gene, and restoring channel potential [31–32]. *In vitro* and *in vivo* studies were carried out, alongside several viral and non-viral trials. The present study focused on these viral (adenovirus and adeno-associated virus) and non-viral approaches (plasmid with cationic liposomes).

Interestingly, Knowles carried out a study of 12 cystic fibrosis patients using an adenoviral vector; this demonstrated that gene therapy can correct, to a certain degree, the chloride defect in the lung mucosa, even though the effect was temporary and caused local inflammation [22]. The study represented early trials in which an adenoviral vector was used to deliver the CFTR gene to cystic fibrosis patients and, as mentioned earlier, was with improved chloride exertion.

Although the studies reported in the present review are based on the theoretical foundation of the concept of a genetic transfer in animal models [30], several of these same studies were human trials beginning at phase 1, which in turn primed phase 2 trials, which are also reported. The reviewed studies utilized gene therapy using different approaches associated with safe and modest gene transfer. Such approaches are dependent on the use of a vector of inert nature, such as an adeno-associated serotype virus [12] or liposomes. Unlike viral vectors, liposomes are not associated with a loss of efficacy upon repeated administration [27], or with the use of special techniques, such as aerosol administration, which are used to distribute viral vectors to the respiratory tract [19]. Despite proof of concept, such approaches provided safe, temporary gene transfer and mixed outcomes. Such findings may encourage scientists to engineer newer approaches for delivering correct genes with feasible, convenient, safe, well tolerated, permanent gene expression and positive outcomes in clinical trials and routine clinical practice. Unique, innovative approaches that address genetic mutation include: plasmid delivery via nanoparticles, clustered regularly interspaced short palindromic repeats (CRISPR/Cas9), stem cell, and CFTR modulator therapies [33].

To approve gene therapy products, it is necessary to demonstrate the safety of the product, particularly the absence of severe adverse effects. In the present review, most of the conducted studies were trials with comparative groups. Thus, a control group should mimic the intervention group without the

correct gene component, i.e., it should have similar administration techniques, including the vector. Safety results were comparable in terms of adverse effects in the intervention and control groups. Safety is essential in the delivery of innovative interventions, and indeed it is not uncommon to have RCTs suspended or finalized due to safety concerns [34]. While the interventions in the present review were demonstrated to be safe, there are grounds for introducing new interventions and standards of care due to decreased use of the intervention.

The studies included in the review described patient selection. Moreover, although the studies were described as randomized, when relevant, they did not report how the randomization method was carried out and concealed. Some of the studies were blind but did not provide information on whether the blinding was adequate. Drop out was also described. Outcome measures were described and were appropriate [35]. These points and others reflect the methodological quality of the clinical trials and confirm that a certain degree of rigor decreased the bias and inaccurate assessment of the treatment effect [36]. Despite the presence of some shortcomings, the utilized methodological quality was appropriate for the type of intervention.

Conclusion

The present study had two main aims: to identify any success gained by the gene therapy approach to cystic fibrosis in experimental and routine clinical outcomes in different clinical trial stages; and, to determine any adverse effects noted via referral to the published literature in the research area.

Phases 1–2 were reviewed and randomized controlled studies, using different viral and liposome vectors to deliver the CFTR gene topically to the lung, nasal mucosa, and sinuses (the latter is considered a surrogate or disease model for cystic fibrosis). Gene transfer to the lung mucosa was achieved, as shown in the bronchoscopy assessments of vector-specific DNA and mRNA to the lung and nasal mucosa, and such transfer was higher in the intervention than in control patients. However, the genetic transfer was temporary and not demonstrated in some patients. A temporary improvement in bronchial chloride secretion was also demonstrated.

The present review supports the perception that the gene therapy approach for cystic fibrosis is safe, although at the same time it has limited, temporary efficacy. We recommend that newer approaches are engineered to deliver the necessary genetic material with the desired, full-scale efficacy.

Table 1 **General characteristics of identified trials**

Study	Design	Sample size	Intervention
Alton et al., 2015 (a)	- Phase I/IIa - No control - Open label	35 patients	- Single dose - Nebulized +/- nasal dose - Vector: liposome
Alton et al., 2015 (b)	- RCT phase 2b - Placebo controlled - Double blind	136 patients	- Multiple dose - Nebulized - Vector: liposome
Moss et al., 2007	- RCT Phase 2B Trial - Placebo controlled - Double blind	Intervention: 51 patients Control: 51 patients	- Multiple dosing - Vector: AVV - Aerosolized to the lung

Study	Design	Sample size	Intervention
Moss et al., 2004	- RCT phase II trial - Placebo controlled - Double blind	Intervention: 20 patients Control: 17 patients	- Multiple dosing - Vector: adeno-associated - Aerosolized to the lung
Flotte et al., 2003	- Phase 1 - No control - open label	25 patients	- Single dose - Nasal and lung - Vector: adeno virus
Joseph et al., 2001	- Phase 1 larger - No control - Open label	20 patients (lobar instillation) 16 patients (aerosol administration)	- Single dosing - Vector: adenovirus - Aerosol and lobar administration
Perricone et al., 2001	- Phase 1 - No control - Open label	Bronchoscopy administration: 6 patients Aerosolization: 2 patients	- Single dose - Bronchoscopic instillation or aerolization - Vector: adeno virus
Hyde et al., 2000	- RCT - Placebo controlled - Double blind	Intervention: 9 patients Placebo: 2 patients	- Multiple dose - Nasal - Vector: liposome
wagner et al., 1999 (a)	- Phase 1 randomized - Placebo controlled - Open label	10 patients (bilateral maxillary antrostomies)	- Single dose - Vector: adeno associated virus
wagner et al., 1999 (b)	- Phase 1 randomized - Placebo controlled - Open label	10 patients (bilateral maxillary antrostomies)	- Single dose - Vector: adeno associated virus
Alton et al., 1999	- RCT - Placebo controlled - Double blind	Intervention: 8 Placebo: 8	- Single dose - Vector: lipid complex - Nose and Lung (nebulization)
porteous et al., 1997	- Randomized - Placebo controlled - Double blind	Intervention: 8 Placebo: 8	- Single dose - Vector: liposome - Nasal epithelium
Gill et al., 1997	- Phase 1 - Placebo controlled - Double blind	Intervention: 8 patients Placebo: 4 patients	- Single dose - Vector: liposome - Nasal epithelium
Knowles et al., 1995	- Randomized - Placebo controlled - Double blind	12 patients	- Single dose - Nasal epithelium - Vector: adenoviral
Harvey et al, 1999	- Phase 1 - Placebo controlled	Intervention: 7 patients Control: 7 patients	- Multiple dosing - Vector: adenovirus - Endobronchial spray
Joseph et al., 2001	- Phase 1 larger - No control - Open label	20 patients (lobar instillation) 16 patients (aerosol administration)	- Single dosing - Vector: adenovirus - Aerosol and lobar administration
Noone et al., 2000	- Phase 1 - Placebo controlled - Open label	11 patients (control and intervention in between patients)	- single dose - Vector: liposome - Nasal Epithelium

Study	Design	Sample size	Intervention
Zabner et al., 1996	- Phase 1 - Placebo controlled - Double-blind	6 patients (control and intervention in between patients)	- Multiple dose - Vector: adenovirus - Nasal epithelium
Zabner et al., 1997	- Phase 1 - No placebo - Double-blind	6 non-CF subjects 12 CF subjects (DNA lipid and DNA alone in between subjects)	- Single dose - Lipid Complexes; DNA alone - Nasal Epithelia
Zuckerman et al., 1999	- Phase I - No control - Open label	11 patients	- Single dose - Vector: adenovirus - Lung bronchoscopy
Wagner et al., 2002	- Phase II RCT - Placebo controlled - Double-blind	23 patients existing maxillary antrostomies (control and intervention in between patients)	- Vector: AAV - Maxillary Sinus Delivery

Table 2: Pulmonary function tests and bronchoscopy results

Trials that looked at respiratory outcome measures					
Study	**Pulmonary function test**				
Alton et al., 2015 (b) [per protocol]	Relative change in % predicted FEV1 (95% confidence interval): 3.7% (0.1-7.3); *p*=0.046				
Alton et al., 2015 (b) [intention to treat]	Relative change in % predicted FEV1 (95% confidence interval): 3.6% (0.2-7.0); *p* value=0.039				
Moss et al., 2004	FEV1; *p*= 0.04 (30 day) days 60, 90, and day 150 were not statistically significant				
Moss et al., 2007	Spirometric lung function over time (FEV1 % predicted, FEF25–75% and forced vital capacity (FVC) (not significant)				
Joseph et al., 2001	Pulmonary function tests (not significant)				
Alton et al., 2015 (b)	FVC: *p*=0·031 CT gas trapping: *p*=0·048				
Wagner et al., 1999 (b)	Sinusitis recurrence: 45% IL8, leukocytes (in sinus fluid): increased Bacterial culture and CT scan confirmed the sinusitis				
Wagner et al., 2002	Rate of relapse/recurrent sinusitis: 78% (all); 52.2% (placebo); 43.5 (tgAAVCF) (not significant) CT imaging revealed no significant differences between treated and untreated sinuses Histopathology: mild to moderate chronic inflammation (not significant)				
Bronchoscopy Results					
Study	**Bronchoscopy**		**Bronchial chloride responses**	**Nasal group**	
	Vector-specific DNA (detected)	**Vector-specific mRNA (detected)**		**Vector-specific DNA (detected)**	**Vector-specific mRNA (detected)**
Alton et al., 2015 (a)	10/10	2/10	A trend toward increase	17/21	3/21
Alton et al., 2015 (b)	12/14 (intervention) 0/7 (control)	0/14 (intervention) 0/7 (control)	Increase in intervention (p=0.032)	14/14 (intervention)	0/14 (intervention) 0/7 (control)
Flotte et al., 2003	2/3			12/25	
Perricone et al., 2001	4/5 (brochscopic administration) 16/18 (aerolization)	3/5 (brochscopic) 4/18 (aerolization)	N/A	N/A	N/A
Hyde et al., 2000	N/A	N/A	N/A	9/9	9/9
Wagner et al., 1999a	N/A	N/A	- Sinus Transepithelial potential (statistically	6/10	

			significant)		
Alton et al., 1999	8/8 (intervention) 0/8 (placebo)		- Pulmonary (p<0·05) - Nasal (not significant)	intervention > placebo	
porteous et al., 1997	N/A	N/A	CFTR function partial, sustained: two intervention patients	7/8	2/7
Gill et al., 1997	N/A	N/A	- improvement in nasal potential difference: 2 patients - potential difference (not significant)		
Knowles et al., 1995	N/A	N/A	- High dose cohort decreased basal PD	6/12 (intervention) 2/12 (control)	5/12 (intervention) Not reported (control)
Moss et al., 2004	6/6 (intervention) 0/2 (control)		N/A	N/A	N/A
Harvey et al, 1999		4/14	N/A	N/A	N/A
Joseph et al., 2001	- **labor** - week 1(1/3); day 2 (4/5) **aerosol**: 7 day (negative); 2 days (14/14)	- **labor** 1 week (negative); 2 days (3/8-high dose) - **aerosol**: - 7 day (negative); 2 days (4/14)	N/A	N/A	N/A
Noone et al., 2000	N/A	N/A	- CFTR-medicated Cl- conductance: no significant differences	- up to 10 days: vector specific DNA detected (all subjects) - day 1: all subjects - up to 2–3 days: most subjects	vector specific mRNA detected: day 3 (all subjects) and day 5 (5/7)

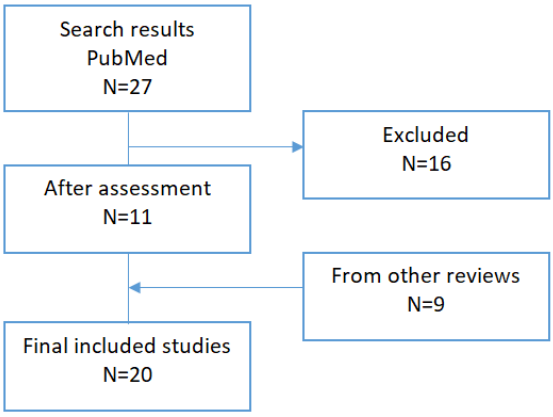

Figure 1. Flowchart of assessment of qualifying articles in the review

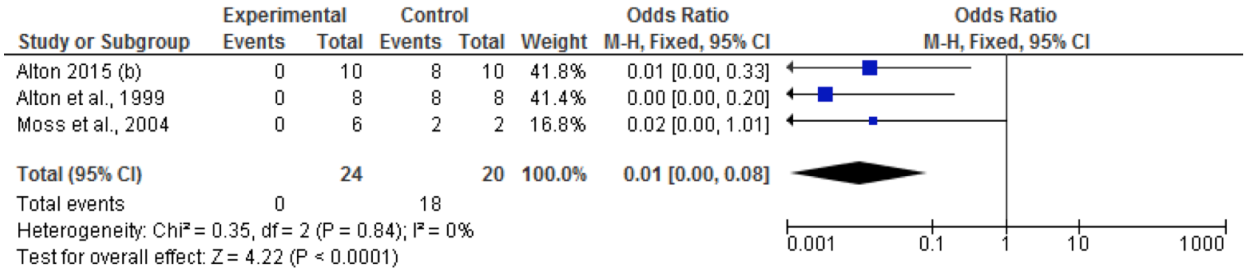

Figure 2. Meta-analysis results of the vector-specific DNA expression in the intervention and control groups

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العلاج الجيني لمرض التليف الكيسي: تحليل منهجي تجميعي

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الملخص

نبذة عن موضوع البحث: يُعد العلاج الجيني أحد أهم الاستراتيجيات المطروحة لعلاج مرض التليف الكيسي، بحيث يهدف هذا العلاج إلى إيصال الجين الفعال إيصالاً موضعيا للرئة. عدد محدود من الدراسات السريرية المنشورة تضمنت تجارب لإعطاء العلاج الجيني لمرضى التليف الكيسي.

هدف البحث: تهدف هذه الدراسة إلى تقييم مدى فاعلية العلاج الجيني لمرض التليف الكيسي، و الآثار الجانبية المسجلة في الدراسات السريرية المنشورة.

المنهجية: تمت مراجعة الدراسات السريرية المنشورة من عام 1989 إلى عام 2020، و التي استخدم فيها الناقل فيروسي وغير فيروسي لإيصال الجين الفعال، و تم جمع المعلومات المتعلقة بالمرحلة السريرية لكل دراسة، و الخلايا المستهدفة بالعلاج، بالإضافة إلى الآثار الجانبية المسجلة. تم تقييم نتائج العلاج المقدم في الدراسات تقييماً تجميعياً.

النتائج: بلغ عدد الدراسات المقيمة في هذا البحث عشرون دراسة. اختلفت الدراسات في نوع الخلايا المستهدفة بالعلاج الجيني و المرحلة السريرية. تم تسجيل إيصال فعال للعلاج الجيني عند المرضى، إلا أن فعالية العلاج الجيني كانت قصيرة الأمد، كما و تمت الاشارة إلى تأكيد سلامة العلاج الجيني في الدراسات المقيّمة

الخلاصة: العلاج الجيني الحالي يتصف بفعالية محدودة و قصيرة الأمد، إلا أنه آمن. من الضروري العمل على تطوير طرق جديدة لإيصال العلاج الجيني لمرضى التليف الكيسي.

الكلمات الدالة: العلاج الجيني ، التليف الكيسي ، علم الأدوية ، علم الأدوية الجيني ، دراسة سريرية تجريبية ، ناقل.