SYSTEMATIC REVIEW, META-ANALYSIS OF PER OS ADMINISTERED DRUGS IN CYSTIC FIBROSIS

A. Koutsovasili[1], K. Gkogkas[1], C. Kani[2], K.Souliotis[3], S. L. Markantonis[1]

[1]Department of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, Athens, Greece, [2]University Research Institute of Maternal and Child Health &Precision Medicine, and UNESCO Chair on Adolescent Health Care, Athens, Greece, [3] University of Peloponnese, Department of Social and Educational Policy, Corinth, Greece

INTRODUCTION

❖Cystic fibrosis (CF) is a progressive, inherited disease caused by mutations in the CF transmembrane conductance regulator (CFTR) gene which results in disruption of the normal production or functioning of the CFTR protein found in the various cells of the body. This in turn causes mucus to build up and damage body organs, particularly the lungs and pancreas (1).

❖New pharmaceutical therapies called CFTR modulators have been developed that target distinct parts of the CFTR protein to help it function properly. Four CFTR modulators are currently on the market: Ivacaftor(VX-770) (**IVA**), Lumacaftor(VX-809)/Ivacaftor (**LUM/IVA**), Elexacaftor(VX-445)/Tezacaftor(VX-661)/ Ivacaftor (**ELX/TEZ/IVA**), and Tezacaftor/ Ivacaftor (**TEZ/IVA**). The modulator drugs are classified as either potentiators or correctors, depending on their effects on the CFTR protein. Potentiators (Ivacaftor) increase the channel opening activity of the mutant protein and correctors (Lumacaftor, Tezacaftor, Elexacaftor) improve CFTR maturation and delivery of the mutant protein to the surface of the cell (2).

OBJECTIVES

The purpose of this study was to systematically evaluate clinical studies on the four CFTR-modulators approved for the management of cystic fibrosis, to determine the clinical and economic benefits of their use.

METHODS

❖All available information on **IVA, LUM/IVA, ELX/TEZ/IVA** and **TEZ/IVA**, was collected from EMA reports, as well as published phase III, placebo-controlled trials on patients with cystic fibrosis.

❖A systematic review and meta-analysis including GRADE qualification was performed to evaluate the clinical benefit of the treatments.

❖The primary outcomes evaluated were the number of pulmonary exacerbations (Pex) and the absolute change from baseline at Week 24 in the % predicted forced expiratory volume in one second (ppFEV1) as a measure of lung function changes.

❖The secondary outcomes evaluated were an absolute change in the: Cystic Fibrosis Questionnaire-Revised (CFQ-R) a disease-specific health-related quality of life (HRQOL) measure, Body mass index (BMI) from baseline at Week 24 as a measure of the difference in growth and sweat chloride concentration as a measure of lung function changes.

❖The expenditure associated with cystic fibrosis modulator therapies was estimated.

RESULTS

❖Study patients showed a positive response to treatment for all outcomes. (Pex: Rate Ratio 0.66, ppFEV1: Mean difference 3.07 - 6.38, CFQ-R: Mean difference 2.62 - 8.11, BMI: Mean difference 0.16).

❖The risk of bias (Fig. 1) for each included study ranged from low to high depending on the criterion and the quality of the data (GRADE) was judged to be moderate or low. For these reasons, the results of the meta-analysis cannot be stated with absolute certainty (Fig. 2).

❖The target population in Greece, based on data from the largest children's hospital in the country, is 754 patients with cystic fibrosis. Of these, 248 (33%) are homozygous for the F508del mutation, 339 (45%) are heterozygous for the F508del mutation, and 180 (24%) have another mutation in the cystic fibrosis' gene.

❖The estimated cost of therapy for these patients was lowest for **IVA** followed by the **LUM/IVA** combination. (Fig. 3)

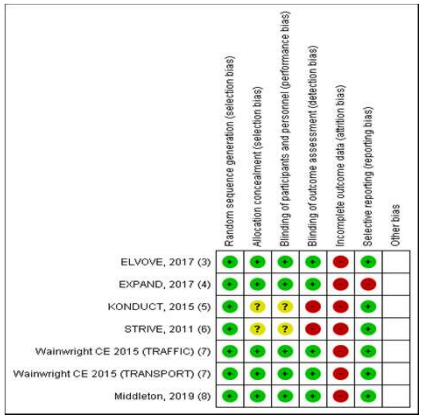

Fig. 1. The risk of bias for each included study.

Outcome	Drug vs Placebo	Number of patients**	Number of studies	Direct Evidence	
				Result	GRADE
ppFEV1	IVA	230	2	6.38 * [-1.94, 14.70]	+2 Low
	LUM/IVA	1072	2	3.07 [2.17, 3.97]	+3 Moderate
	TEZ/IVA	820	2	5.37 * [2.63, 8.11]	+2 Low
SwCl	IVA	219	2	-35.95 * [-59.40, 12.50]	+2 Low
	TEZ/IVA	784	2	-9.97 [-11.21, -8.72]	+3 Moderate
CFQ-R	IVA	218	2	8.11 [5.25, 11.08]	+2 Low
	LUM/IVA	1076	2	2.62 [0.64, 4.59]	+3 Moderate
	TEZ/IVA	800	2	8.04 * [2.16, 13.92]	+2 Low
Number of Pex	LUM/IVA	1108	2	0.66 [0.56, 0.77]	+3 Moderate
Percentage of participants with at least one Pex	LUM/IVA	1108	2	0.59 [0.47, 0.73]	+3 Moderate
BMI	LUM/IVA	357	2	0.16 * [0.02, 0.29]	+2 Low
ppFEV1	ELX/TEZ/IVA	403	1	14.3 [12.7, 15.8]	-
SwCl		403		-41.8 [-44.4, -39.3]	-
Number of Pex		403		0.37 [0.25, 0.55]	-
CFQ-R		403		20.2 [17.5, 23.0]	-
BMI		403		1.04 [0.85, 1.23]	-

*Outcomes' results based on the random-effects model.
** The sum of the participants of the two groups (drug group and control group) analyzed for each outcome.

Fig. 2. GRADE.

❖Each patient requires 13 packages of medication per year, regardless of formulation. For the **TEZ/IVA** and **ELX/TEZ/IVA** combinations, an additional 13 packages of the **IVA** formulation are also required.

Formulation	(€)/ package	(€) per year
IVA	5.630,72	73.199,36
LUM/IVA	8.546,52	111.104,76
TEZ/IVA	9.563,83	124.329,79
ELX/TEZ/IVA	8.803,56	114.446,28

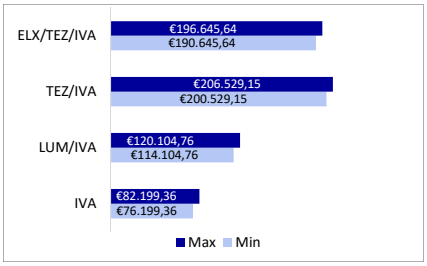

Fig. 3. Min and max insurance company charge for each formulation according to the below equation.

Charge of an insurance company = Drug's cost * + Z ** × Hospitalization cost ***

*Greece's and Demmark's (Tez/Iva) Ministry of Health Price List
** z= Number of hospitalizations per year (2-6 on average)
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CONCLUSIONS

❖The clinical efficacy of the CFTR-modulators seems to be greater than that of the placebo for all outcomes. However more studies are needed to draw safe conclusions.

❖The expenditure associated for treatment with CFTR-modulators was high, but lowest for Ivacaftor (VX-770).

❖There is a gap in the registration of patients with cystic fibrosis in Greece, which needs to be eliminated, in order to have more data on patients with cystic fibrosis.

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