TREATMENT OF CHILDREN AND ADOLESCENTS WITH CYSTIC FIBROSIS WITH NEW CFTR MODULATORS, THE EXPERIENCE OF CF CENTRE FOR CHILDREN AND ADOLESCENTS AT THE UNIVERSITY CHILDREN'S HOSPITAL IN LJUBLJANA

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Cystic fibrosis (CF) is the most common autosomal recessive genetic disease that affects many organs, especially the respiratory and gastrointestinal tract. Since we start with appropriate preventive treatment for patients by performing regular daily inhalation therapy and respiratory physiotherapy even before the clinical signs of the disease are expressed, we prolong the time until the appearance of chronic changes in the lungs. With all the listed treatment methods and the possibilities of using the latest drugs, from replacement pancreatic enzymes to inhaled antibiotics and CFTR modulators, we delay the time until the necessary organ transplantation. Life expectancy for people with CF has increased dramatically over the past few decades. The reason for this is the progress in the treatment of the disease, and in particular the comprehensive multidisciplinary treatment of patients in CF centers. The new CFTR modulator drugs will undoubtedly contribute to the additional improvement of lung function and the extension of life expectancy.

Descriptors: CHILDREN, ADOLESCENTS, CFTR MODULATORS

Introduction

CF is the most common lethal genetic disorder in the Caucasian population, affecting >70.000 people worldwide (1). The frequency varies between populations, with the frequency being much lower in Asian and African countries than in European and North American populations. The highest incidence of the disease is in Ireland 1:1.800, and the lowest in Finland 1:20.000. In Slovenia, the incidence of CF is 1:4.500 live births (2). Lung disease is the major cause of morbidity and mortality, with frequent symptoms in the pancreas (exocrine and endocrine), gastrointestinal tract, sinuses, liver and biliary tree, sweat gland, and vas deferens. CF is caused by autosomal recessive mutations in the gene that encodes the cystic fibrosis transmembrane conductance regulator protein (CFTR), with >2,000 mutations reported (1). As it affects multiple organs, patients with CF are treated by multidisciplinary teams of experts in specialized CF centers. One of these is the CF center at the University Children's Hospital in Ljubljana,

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where all children and adolescents with CF in Slovenia are monitored. A database of patients that has been maintained since the center's establishment helps us analyze conditions and compare the quality of treatment of our patients with other European CF centers. In 2020, in our centre we treated 78 patients, of which 56% (44/78) were male patients. The mean age of the patients was 13.2 years (SD 6.4 years), with a range of 1.2 years to 25.5 years. The F508del mutation was the most frequently represented, as 88.5% were carriers of at least one, and 64.1% of patients had the mutation on both alleles. 19.2% (15/78) of all patients had chronic P. aeruginosa infection, of which 7.7% (4/52) were patients under 18 years of age (2).

CF has been at the forefront of clinical research for the past decade. The discovery of the gene in 1989 was followed by the search and development of new drugs that would definitively cure the disease. We have entered the era of precision medicine, when patients with certain mutations are treated with certain drugs. The drugs are effective only in patients with certain mutations, and so far have not resulted in a definitive cure for the disease and are not effective in all CF patients (2). CFTR modulators represent one of the most important discoveries in the treatment of cystic fibrosis. These are targeted drugs that affect the production, intracellular processing and/or function of defective CFTR protein (2). Understanding the cellular and molecular basis of the disease has paved the way for the development of therapeutic strategies targeting the underlying dysfunctions caused by CF mutations. CFTR modulator therapies are in clinics and they represent a landmark in patients' lives, demonstrating short- and long-term benefits in clinical outcomes (3).

We distinguish two main groups of modulators, correctors and enhancers: correctors (lumacaftor, tezacaftor and elexacaftor) affect the CFTR protein by they improve the synthesis and transport of the tubule to the surface of the cell membrane and potentiators (ivacaftor) improve the functioning of the CFTR channel, which has already arrived at the cellular top, by improving the opening and thus the better passage of chloride ions (4).

Experience in CF center for children and adolescents at University Children's Hospital in Ljubljana, Slovenia

In August 2020, in the program of orphan medicine, we started introducing a triple CFTR modulating drug and initially introduced the drug to nine patients with advanced diseases who were carriers of the F508del mutation. Following the official registration of the drug in November 2020, we continued to introduce the drug to other patients for whom the drug is indicated. By the end of 2020, we introduced the treatment to sixteen patients, which represents 20.5% of all our patients. By 2023 ivacaftor, lumacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor are available to patients from 6 years old. Medicines are effective for carriers of a specific CFTR mutation, so it is important that both CF-specific mutations are identified in all patients. Ivacaftor is effective as monotherapy in patients with certain IV mutations. class, and in combination with other modulators, it is suitable for patients with the F508del mutation on one or both alleles (4).

Research to date has shown that CFTR modulators are safe drugs. Common side effects are rashes and headaches, which are usually transient in nature and resolve spontaneously without additional measures. Serious side effects (e.g. high elevation of liver enzymes, severe pulmonary deterioration) that require treatment to be completely discontinued, at least temporarily, are rare (4).

Because of possible transient pulmonary deterioration, CFTR modulators are introduced in the hospital. Before the introduction of the drug, the patient's liver tests (AST, ALT, gamma GT), bilirubin and ultrasound of the abdomen are checked. He must also undergo an examination by an ophthalmologist. Liver tests are checked every three months in the first year after the introduction of the drug, then once a year if the results are appropriate. Based on the description of cataracts in animal models, an ophthalmologist examination once a year is recommended (4). Patients data shows that lung function, nutrition, physical performance and quality of life improve significantly in patients who receive modulatory treatment. These results are most pronounced in patients receiving a triple modulator treatment (4).

It is important that the patient and parents are well informed about the disease and the action of the drugs. CFTR modulators are not a substitute for all other drugs that successfully manage cystic fibrosis. Our experience shows that the drugs are effective, but at the same time we face new challenges, such as poorer cooperation with physiotherapy and inhalation therapy, because the patients have fewer respiratory symptoms, excessive weight gain and poorer detection of mild exacerbations of the disease.

Nevertheless, strategies to achieve optimal, lifelong adherence to treatments should be optimized. Several barriers have still been preventing equitable access worldwide to the current CFTR modulators, including the costs and regulatory national issues, and as such further discussions are needed to identify feasible and sustainable solutions for these therapies to achieve all eligible patients. Furthermore, many rare and ultra-rare CF-causing mutations are still without any efficient, corrective therapy (3).

Conclusion

We were among the first countries in Europe to introduce CFTR modulatory drugs, which promise a significant improvement in the clinical condition and quality of life of CF patients. Data shows that lung function, nutrition, physical performance and quality of life improve significantly in patients who receive modulatory treatment. These results are most pronounced in patients receiving a triple modulator treatment. We need to address new treatment challenges, such as poor compliance, excessive weight gain and find solutions to treat patients with more severe side effects, as well as find new treatment options for those patients who have rare mutations for which currently available drugs do not work.

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