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THE EVOLVING MANAGEMENT OF CYSTIC FIBROSIS

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SUMMARY

Introduction: *Cystic fibrosis is a genetic pathological condition, affecting chromosome 7, which encodes the CFTR protein. This pathology is characterised by abundant mucus production, which in turn leads to blockage of the airways and blockage of the digestive tract.*

Objective: *The aim of this literature review is to gather the largest available amount of information related to cystic fibrosis and analyse it in detail, indicating the results and expectations that have been had with the use of some drugs over time in patients with cystic fibrosis. It is also intended to mention updates of procedures and their effectiveness.*

Methodology: *a systematic and complete search was carried out using the Cochrane Library database, with the term Cystic Fibrosis. The documents found were in Spanish and English. Some articles were excluded due to lack of updated information.*

Results: *Inhalation Dornase alfa alfa is a useful drug for airway improvement and mucus viscosity reduction, as are bronchodilators. Pancreatic enzymes and ursodeoxycholic acid are beneficial in the gastrointestinal area, reducing intestinal symptomatology. In patients with diabetes, Insulin is preferred. Only glutathione has a beneficial effect in patients with cystic fibrosis. Rehabilitation and management of postural abnormalities is vital to improve patients' lives. In patients with nutritional deficiencies, nasogastric tube placement or gastrostomy is preferred to improve their nutrition.*

Conclusions: *Cystic fibrosis is a disease that has an inevitable progression. The treatments studied here show that they only help quality of life and pulmonary and gastrointestinal functions temporarily. Further studies are needed to determine therapies that can significantly improve patients, both physically and psychologically; and who knows, some therapy or therapies that may lead to a cure for this disease.*

KEYWORDS: *Cystic fibrosis, exacerbation, rehabilitation, bronchodilators, antibiotics.*

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INTRODUCTION

Cystic fibrosis (CF) is one of the most common autosomal recessive genetic life-shortening diseases, with around 100 000 people affected worldwide. CF affects multiple systems, primarily the lung; the leading cause of death in people with the condition is respiratory failure. Other body systems are also affected, particularly the digestive and reproductive systems. This disease is due to mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene, located on the long arm of chromosome 7, which encodes a transmembrane protein involved in the regulation of transepithelial transport of chloride ions (Cl-). The most frequent mutation is the deletion of amino acid 508 (phenylalanine), termed F508del. Absence or dysfunction of the CFTR protein results in a defect in Cl- transport and increased salt and water reabsorption, particularly in the bronchial epithelium, leading to a reduction in bronchial surface fluid. This generalised exocrinopathy leads to the production of "viscous mucus" which clogs various sites in the body, in particular the respiratory system, the digestive tract and its adnexa (1-3). The condition is subsequently directed towards the epithelial cells located in the mucous glands of the intestine, sweat glands, gall bladder, pancreas, liver and airways, where chloride transport is impaired along with elevated sodium and water reabsorption, inducing the formation of very thick mucus (4,5).

METHODOLOGY

A total of 44 scientific articles from the Cochrane Library, Pubmed and Star Pearl databases were analysed and the review focused on the most important therapies and the benefits they can provide to patients with cystic fibrosis. Fifteen papers related to cystic fibrosis were eliminated because none of these articles provided adequate information for this review.

RESULTS AND DISCUSSION

Inhalation Dornase-alpha is a drug currently used as a pulmonary mucolytic in cystic fibrosis. It reduces the viscosity of mucus in the lungs, promoting better clearance of secretions as this drug decreases sputum and its viscosity. Even children with cystic fibrosis with preserved lung function can be given Dornase alfa via inhalation prior to airway clearance techniques for greater benefit (6,7). When pulmonary involvement is present, fibrosis can lead to significant lung damage.

The potential beneficial effect of inhaled corticosteroids on reducing inflammation in patients with cystic fibrosis has been evaluated. Reducing lung inflammation is one of the goals of cystic fibrosis treatment. Inhaled corticosteroids are often used to treat children and adults with cystic fibrosis because of their potential to reduce lung damage arising from inflammation, as well as their effect on symptomatic wheezing. Unfortunately, no significant benefit in reducing inflammation has been conclusively demonstrated; and, in addition, use in children may slow their growth at high doses (8).

Short- and long-acting bronchodilators are prescribed for most people with cystic fibrosis to dilate the airways and improve symptoms. The effect of long-acting inhaled bronchodilators (beta-2 agonists such as salmeterol and muscarinic antagonists such as tiotropium) was evaluated in a study involving a total of 1,082 people aged between five months and 70 years, over a period of 28 days to 12 weeks. Beta-2 agonists were shown to produce some improvement in lung function measured as forced expiratory volume in one second (FEV1) compared to placebo. In contrast, studies comparing tiotropium with placebo found little difference in FEV1 between treatment and placebo (9).

People with cystic fibrosis often have altered gut bacteria and inflammation. Probiotics are known to be live bacteria that will provide a health benefit to the individual. Probiotics are commonly used by people with cystic fibrosis and can improve intestinal inflammation and overall health. In a study of 464 patients with cystic fibrosis who were given probiotics, it was observed that they had an improvement in their health status; ultimately, a reduction in cough, sputum and dyspnoea (lung exacerbations) was found. At the intestinal level, probiotics reduce faecal calprotectin, a marker of intestinal inflammation, in children and adults (10).

The use of pancreatic enzymes in cystic fibrosis patients is important because the pancreas of these patients cannot produce them; the effect of non-production is malnutrition, abdominal pain, frequent and foul-smelling stools with steatorrhoea (11); moreover, an important condition caused by cystic fibrosis is diabetes due to lack of insulin production. Therefore, gastrointestinal symptoms improve with the administration of pancreatic enzymes. The use of pancreatic enzymes in the form of extended-release microspheres is recommended, as they produce less steatorrhoea in the stool and reduce the frequency of abdominal pain (12). There is even limited evidence that acid-reducing agents improve intestinal absorption and improve gastrointestinal symptomatology (13). However, the increased mucus in the intestine caused by the disease, coupled with the lack of pancreatic enzyme action in the intestine, allows this mucus to mix with the faeces, producing a mass, which leads to partial or total occlusion of the intestine, a pathology known as Distal Intestinal Obstruction Syndrome. The patient may also present with vomiting, abdominal distention, and abdominal pain. Unfortunately, in these cases, pancreatic enzymes are ineffective (14).

Cisapride has been used in patients with this syndrome and has been shown to decrease gastrointestinal symptoms (15). Although oral hypoglycaemic therapy is preferred in cystic fibrosis patients with diabetes, according to the American guidelines of the Cystic Fibrosis Foundation, insulin is preferred (16).

The administration of vitamin K, due to the deficiency in the absorption of fat-soluble vitamins, is a subject for discussion, since patients who consume it have a lower probability of hip fracture, thanks to the decrease in osteocalcin decarboxylase (a substance that indicates the risk of hip fracture) (17).

Another important factor in these patients is bile and its tendency to produce liver disease, due to an increase in the consistency of the bile, as it becomes obstructed and can lead to cirrhosis. Therefore, ursodeoxycholic acid at a dose of 20 mg/kg per day has been used to prevent progression of liver disease

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(18). Although the evidence is rather limited, omega-3 consumption has reduced the risk of pulmonary exacerbations and antibiotic use. In addition, a decrease in the amount of sputum is observed, along with an improvement in lung function (19).

Airway infection leads to progressive lung damage in cystic fibrosis and oxidative stress has been implicated in the aetiology. Therefore, supplementation with antioxidant micronutrients (vitamin E, vitamin C, ß-carotene and selenium) or glutathione may potentially help to maintain an oxidant-antioxidant balance. In relation to the consumption of dietary supplements, there is no difference between the consumption or not of dietary supplements and lung function (20,21). There appears to be conflicting evidence regarding the clinical efficacy of antioxidant supplementation in cystic fibrosis. According to the available evidence, glutathione administered orally or by inhalation appears to improve lung function in some cases and decrease oxidative stress; however, due to the very intensive antibiotic and other treatments that cystic fibrosis patients receive, the beneficial effect of antioxidants is very difficult to assess in chronically infected patients without a very large, long-term population sample (22).

Physiotherapy in patients with cystic fibrosis is a key element in improving respiratory function. One technique used in physiotherapy is postural drainage. When postural drainage is performed at 30 degrees and head up, patients have a lower risk of reflux and fewer respiratory complications (23).

Mycobacterium abscessus and Mycobacterium avium are a type of mycobacterial species most frequently found in patients with cystic fibrosis. Therefore, clinical practice guidelines for their treatment should always be followed (24). Other bacteria present in these patients are: Stenotrophomonas maltophilia and Pseudomona aeruginosa; these bacteria should be treated based on clinical judgment (especially if found incidentally, as these bacteria are present in these patients and are resistant to antibiotics (25- 28). However, studies have reported that administration of inhalation antibiotics in Pseudomonas aeruginosa infection improves lung function and reduces the likelihood of exacerbations, especially with the use of Aztreonam over Tobramycin. However, both drugs can be used equally well (29).

Even if inhaled and oral antibiotics are administered, significant improvement is obtained. In relation to inhaled Tobramycin in children, when receiving a regular course of inhaled Tobramycin, fewer patients develop Pseudomonas aeruginosa from their sputum (30). However, there is no such benefit between the use of Aztreonam and the presence of Burkholderia cepacia infection (31). In the case of pulmonary exacerbations, administration of aminoglycosides in 1 dose per day has been found to be effective in the treatment of pulmonary exacerbations, as well as having a lower risk of nephrotoxicity (32).

A condition that indicates progression of cystic fibrosis is the presence of postural abnormalities. Therefore, in these patients, the decision is made to initiate muscle stretching and strengthening therapies, which is important as it can improve quality of life and reduce pain in patients with these abnormalities (33). Physical training can even improve lung capacity and quality of life (34). Muscle training by generating a 60-80% maximal effort in patients leads to improved lung function (35). A less common technique, such as singing, can help improve peak expiratory pressure and quality of life (36).

All cystic fibrosis patients inhaling hypertonic saline before or during airway clearance is more effective than inhalation after airway clearance. In addition, a long-term benefit has been shown when inhaled twice daily (37). Hypertonic saline-based nebulisations improve lung function and reduce the likelihood of pulmonary exacerbations. Furthermore, the use of hypertonic saline as an effective adjunct to physiotherapy is a very beneficial technique in patients with acute pulmonary exacerbations (38). Inhaled mannitol has also been used; this drug improves lung function by clearing mucus from the airways (39).

The F508del variant lacks significant cystic fibrosis transmembrane conductance function, so corrective therapy may benefit many people with CF. A relatively new technique has been the development of drugs that target the cystic fibrosis gene; specifically the F508del protein. The aim of these protein-modifying drugs is to allow salt exchange to resume and, therefore, correction of the chronic problems of cystic fibrosis. When evaluating the effects of cystic fibrosis transmembrane conductance regulator (CFTR) correctors (with or without enhancers) on clinically important beneficial and detrimental effects in CF individuals of any age with CFTR class II mutations (most commonly F508del), it was observed that corrector monotherapy had no clinically important effects. Dual therapies (lumacaftor-ivacaftor, tezacaftor-ivacaftor) resulted in similar improvements in quality of life and respiratory function with lower rates of pulmonary exacerbation. This effect was most beneficial with the tezacaftor-ivacaftor combination. Lumacaftor-ivacaftor was associated with an increase in early transient shortness of breath and long-term increases in blood pressure, not observed with tezacaftor-ivacaftor. In children, lumacaftor-ivacaftor had a significant impact on respiratory function with no apparent immediate safety concerns. For triple therapy with elexacaftor- tezacaftor-ivacaftor, the evidence indicates high quality of clinical efficacy with probably little or no difference in adverse effects in CF patients with one or two F508del variants aged 12 years or older (40).

People with CF often have malnutrition and stunted growth. Adequate nutritional supplementation does not optimally improve growth and therefore an anabolic agent, recombinant human growth hormone (rhGH), has been proposed as a possible intervention to improve weight, height, bone density, as well as to improve lung function, quality of life and clinical status in children and young adults with CF. Studies with this therapy indicated that when compared to no treatment, rhGH therapy is effective in improving intermediate outcomes in height, weight and lean body mass. Some measures of lung function showed moderate improvement (41).

Progressive lung damage causes most deaths in cystic fibrosis. Nonsteroidal anti-inflammatory drugs (NSAIDs) (such as ibuprofen) may prevent progressive lung deterioration and morbidity in cystic fibrosis. In evaluating the effectiveness of

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oral NSAID therapy in cystic fibrosis, it was shown that ibuprofen, at high doses, can delay the progression of lung disease in CF, especially in children, suggesting that strategies to modulate lung inflammation may be beneficial for people with cystic fibrosis (42).

For people with severe CF and advanced lung damage, lung transplantation is an available and viable option. However, graft rejection is an important potential consequence after lung transplantation. Immunosuppressive therapy is necessary to prevent episodes of graft rejection and thus reduce subsequent morbidity and mortality in this population. There are several classes of immunosuppressive drugs that act on different components of the immune system. In a study comparing tacrolimus with cyclosporine in all lung transplant recipients (not restricted to those with cystic fibrosis) no significant differences in mortality and risk of acute rejection were observed. However, tacrolimus use was associated with a lower risk of bronchitis obliterans syndrome and hypertension and an increased risk of diabetes mellitus (43).

Finally, when patients present with significant malnutrition due to lack of calorie absorption, nasogastric tube feeding or gastrostomy feeding is routinely used in many cystic fibrosis centres when oral diet and supplementation fail to achieve adequate nutritional status. However, although there are benefits such as nutritional and respiratory improvement, these are costly and may have a negative effect on patients' self-esteem and body image (44).

CONCLUSIONS

Cystic fibrosis is a pathology that affects both the gastrointestinal and respiratory systems. Its effects can be temporarily alleviated; however, its progression is inevitable. Several therapeutic alternatives are currently available to slow its progression, and in some cases, even cure it. However,

more clinical studies are needed to determine definitive therapies for the cure of this pathology or, failing that, to find the most appropriate therapies with the least adverse effects to improve the pulmonary and gastrointestinal capacity and, above all, the quality of life of patients.

FINAL STATEMENT

This review is based on an article by Santiago Vintimilla called “La evolución del manejo de la Fibrosis Quística. Revisión Bibliográfica”, whose author authorized the translation and rewriting from the Spanish language version to the english language version.

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