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Drug treatment of cystic fibrosis

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SUMMARY

Cystic fibrosis is the most common life-limiting autosomal recessive condition in Australia. A defect in the cystic fibrosis transmembrane conductance regulator protein affects chloride transport across epithelial cells.

Patients with cystic fibrosis produce thick sticky mucus. This causes problems in multiple organs, particularly the lungs.

Cystic fibrosis modulator therapies can partially correct the underlying pathophysiology and improve chloride transport, thereby improving morbidity. Life expectancy is improving, so many patients are now developing chronic diseases associated with ageing.

All health professionals should be aware that the cystic fibrosis modulator therapies are metabolised via cytochrome P450 pathways in the liver. There are therefore significant drug–drug interactions with medicines metabolised by the same pathways.

Introduction

Cystic fibrosis is the most common life-limiting autosomal recessive condition in Australia, with a disease incidence of approximately one in 2500 births.[1] Approximately one in 25 people are carriers of a cystic fibrosis gene mutation. While cystic fibrosis was previously fatal in infancy and childhood, its management has significantly improved such that the median life expectancy is now 53 years. In 2020 there were more adults than children living with cystic fibrosis in Australia.[1]

Pathophysiology

Cystic fibrosis is caused by mutations that result in a defect in the cystic fibrosis transmembrane conductance regulator protein. This protein regulates chloride transport across epithelial cells in the lungs, pancreas, intestines, sweat glands and male reproductive tract. Cystic fibrosis is therefore a multiorgan disease. It is classically characterised by chronic airway inflammation and infection, exocrine pancreatic insufficiency with nutrient malabsorption, hepatobiliary dysfunction and male infertility. Death is usually due to respiratory failure, secondary to chronic airway inflammation and infection.[2,3]

Mutations

More than 2000 mutations of the cystic fibrosis transmembrane conductance regulator gene have been identified. However, in Australia at least 90% of patients with cystic fibrosis have the F508del (also known as ΔF508) mutation, with 47% being homozygotes.[2] The next most common mutation (G551D) comprises only 4.2% of individual allele variants.[1]

Major advances in understanding the cystic fibrosis transmembrane conductance regulator have subsequently allowed for classification of mutations into six different categories (Table 1).[2,4,5] For example, the F508del mutation affects the way the regulator protein is folded.

Medical management

Cystic fibrosis is best managed by specialist multidisciplinary teams involving physicians, nurses, dieticians, physiotherapists, pharmacists, social workers and psychologists.[2] The management priorities include maintaining lung health, managing gastrointestinal complications, optimising nutrition by replacing exocrine pancreatic enzymes, and controlling cystic fibrosis-related diabetes.[6]

Treatment has traditionally focused on symptom control and prevention of complications.[2,3] However, drugs to modulate the cystic fibrosis transmembrane conductance regulator are now available to target the underlying dysfunction seen in cystic fibrosis.

Cystic fibrosis modulator therapies

Therapies that modulate the cystic fibrosis transmembrane conductance regulator aim to correct or improve the transport, function and expression of the regulator protein. They may therefore be referred to as correctors or potentiators. Different genotypes are suitable for different modulator therapies, creating a degree of personalised medicine. This can improve outcomes for many patients. However, these new drugs are not curative. Their effects are temporary and, when they are stopped, the dysfunction of the cystic fibrosis transmembrane conductance regulator returns.

Table 1 **Classes of cystic fibrosis mutations**[5]

Class	Effect of mutation	Defect types	Mutation examples	Required approaches
Class I	No functional cystic fibrosis transmembrane conductance regulator protein produced	No protein	G542X R553X W1282X	Rescue protein synthesis
Class II	Cystic fibrosis transmembrane conductance regulator protein misfolded, retained in the endoplasmic reticulum and subsequently degraded	No traffic	G85E Δ1507 ΔF508 N1303K	Correct protein folding
Class III	Impaired cystic fibrosis transmembrane conductance regulator channel regulation/opening	No function	V520F S549R G551D	Restore channel conductance
Class IV	Reduced conduction across channel	Less function	R117H R334W S1235R	Restore channel conductance
Class V	Reduced synthesis of cystic fibrosis transmembrane conductance regulator	Less protein	A455E 1680-886A>G 2657+5G>A	Maturation/correct mis-splicing
Class VI	Decreased cystic fibrosis transmembrane conductance regulator stability	Less stable	rΔF508 Q1412X	Promote protein stability

The new drugs are expensive. The Pharmaceutical Benefits Scheme (PBS) price for a one-month course of modulator therapy is currently around $17,000–21,000.

Ivacaftor

Ivacaftor was the first cystic fibrosis transmembrane conductance regulator modulator approved by the Therapeutic Goods Administration (TGA) in Australia. It is a potentiator which improves chloride transport. Ivacaftor is approved for treatment of a select group of Class III mutations in patients over 12 months old.

Clinical trials showed ivacaftor significantly reduces concentrations of sweat chloride and increases forced expiratory volume in one second (FEV_1) by 10.6%, compared to placebo. It also increases faecal elastase – a marker of exocrine pancreatic function.[7] An open-label extension study found ivacaftor to have persisting benefits in weight gain and lung function with an ongoing reduction in pulmonary exacerbations.[8] Cystic fibrosis registry studies show improved patient survival and reduced transplantation rates with ivacaftor.[9]

Drug interactions

Ivacaftor is a substrate of cytochrome P450 (CYP) 3A4 and CYP3A5 isoenzymes. Drugs that inhibit or induce CYP3A activity will therefore interact with its pharmacokinetics (see Table 2). With strong (e.g. ketoconazole, itraconazole, posaconazole, or clarithromycin) or moderate (e.g. fluconazole or erythromycin) CYP3A inhibitors, ivacaftor will require a less frequent dosing regimen. CYP3A inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital and St John's wort) may reduce the exposure and effectiveness of ivacaftor.

Ivacaftor has weak CYP3A inhibitory effects. Care should therefore be taken with concomitant use of benzodiazepines, as ivacaftor may increase the risk of their adverse effects.

Table 2 **Commonly prescribed drugs with significant CFTR-modulator interactions involving cytochrome P450 3A4**

CYP3A4 inducers	CYP3A4 inhibitors
Barbiturates (phenobarbital)	Azole antifungals
Carbamazepine	Amiodarone
Phenytoin	Erythromycin
Rifampicin	Clarithromycin
St John's wort	Protease inhibitors (ritonavir)

CFTR cystic fibrosis transmembrane conductance regulator
CYP cytochrome P450

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Adverse effects

The adverse effects of ivacaftor include headache (24%), abdominal pain (16%), rash (13%), dizziness (9.2%) and more frequent upper respiratory tract infections. Liver dysfunction with a rise in transaminases can also occur.

Ivacaftor/lumacaftor

Ivacaftor/lumacaftor is a combination therapy, comprising both ivacaftor, a potentiator, and lumacaftor, a corrector. Correctors are designed to improve the folding, processing and trafficking of the defective regulator protein in Class II mutations.

Initial trials in F508del homozygous patients reported only a 2.6–4% improvement in FEV_1 and a small increase in weight. However, the combination reduces the rate of pulmonary exacerbations and events leading to hospitalisation or the use of intravenous antibiotics by 30–39%.[10] Extension studies have shown ongoing mild improvement in lung function and body mass index.[11] Ivacaftor/lumacaftor is PBS-listed for F508del homozygous patients over two years old.

Drug interactions

Lumacaftor is a strong inducer of CYP3A. Ivacaftor/lumacaftor may therefore decrease the systemic exposure of products that are substrates of CYP3A. The dose of ivacaftor in the combination takes account of ivacaftor's metabolism by CYP3A. Importantly, ivacaftor/lumacaftor may decrease the effectiveness of oral, injectable, transdermal and implantable hormonal contraceptives. These contraceptives should not be relied on as a sole contraceptive method. Other common drug classes that may be affected by ivacaftor/lumacaftor include antidepressants (citalopram, escitalopram, sertraline), proton pump inhibitors (esomeprazole, omeprazole, lansoprazole) and anticoagulants (warfarin and dabigatran).

Adverse effects

Common adverse effects of the combination include dyspnoea (14%), diarrhoea (11%), nausea (10%) and headache. Potentially serious adverse reactions include hepatobiliary events – transaminase elevations, cholestatic hepatitis and hepatic encephalopathy.

Tezacaftor/ivacaftor, ivacaftor

Tezacaftor/ivacaftor is taken as a fixed-dose combination tablet in the morning with a further dose of ivacaftor in the evening. Tezacaftor, like lumacaftor, improves cellular processing of the cystic fibrosis transmembrane conductance regulator protein so is suitable for Class II mutations.

Phase III placebo-controlled trials in patients homozygous for F508del showed FEV_1 improved by 4% and pulmonary exacerbations reduced by 35%.[12] Tezacaftor/ivacaftor also increased FEV_1 by 6.8% in comparison to ivacaftor monotherapy (4.7%) in patients who were heterozygous for F508del and had a residual function mutation.[13] It has PBS approval for patients over six years old who are homozygous for F508del or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator gene that is 'responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence'.

Drug interactions

Although tezacaftor/ivacaftor is also a CYP3A inducer, it is weak in contrast to ivacaftor/lumacaftor. Consequently, tezacaftor/ivacaftor has relatively fewer significant drug–drug interactions and does not appear to affect hormonal contraceptives.

Adverse effects

The most common adverse effects include headache (13.7%), nasopharyngitis (11.5%) and nausea (7.7%). There was no significant difference in transaminase elevations between tezacaftor/ivacaftor and placebo.

Elexacaftor/tezacaftor/ivacaftor, ivacaftor

Elexacaftor is a corrector. Elexacaftor/tezacaftor/ivacaftor is taken as a fixed-dose combination in the morning with another dose of ivacaftor in the evening. This regimen is suitable for Class II, III, IV and V mutations. It is therefore indicated for all patients with F508del mutations. It has PBS approval for patients over 12 years old.

Three phase III, double-blind, controlled studies reported the regimen had significant clinical benefit, particularly a rapid and sustained improvement in FEV_1 and a reduction in the rate of pulmonary exacerbations when compared to matched controls receiving placebo. One trial was in F508del homozygotes,[14] one was in F508del heterozygotes with a gating or residual function mutation,[15] and one was in F508del heterozygotes with minimal or no-function mutations.[16]

F508del homozygotes had 10% improvement in FEV_1 while taking elexacaftor/tezacaftor/ivacaftor compared with tezacaftor/ivacaftor. Sweat chloride and pulmonary exacerbations also significantly decreased.

Drug interactions

Elexacaftor is a CYP3A substrate and has similar drug interactions to the other modulators. It is not predicted to have clinically significant effects on hormonal contraception.

Adverse effects

Adverse effects of the combination regimen include headache (17.3%), diarrhoea (12.9%), rash (8.9%) and increased liver transaminase concentrations.

Cystic fibrosis and chronic disease

With improvement in life expectancy, patients with cystic fibrosis are increasingly likely to develop chronic health conditions associated with ageing – particularly malignancy and cardiovascular disease. A chronic pro-inflammatory state and intestinal dysbiosis (possibly secondary to prolonged antibiotic therapy) are thought to contribute to a higher incidence of colorectal cancer.[17] Guidelines for screening, including colonoscopy, have consequently been developed.[18]

Patients with cystic fibrosis have higher rates of cardiac sequelae, particularly pulmonary hypertension and right heart dysfunction, which correlates with declining FEV_1.[19] The cystic fibrosis transmembrane conductance regulator has been identified in cardiomyocytes,[20] suggesting there is dysfunction at a cellular level.

Systemic vascular disease is now a more frequent comorbidity of cystic fibrosis,[21] and atherosclerosis and coronary artery disease are likely to continue to increase in prevalence.[22] Microvascular changes are recognised as a complication of diabetes related to cystic fibrosis, especially with renal disease and retinopathy.[23]

How cystic fibrosis modulator therapy affects the development of chronic conditions is not clear. The modulators reduce systemic long-term inflammation, and this may reduce intestinal and cardiovascular dysfunction. However, cystic fibrosis transmembrane conductance regulator modulators also increase body mass index, serum lipids and blood pressure, all of which may predispose to cardiovascular sequelae.[24] Nonetheless, development of cystic fibrosis cardiovascular screening guidelines is clearly warranted.

Future directions

Further advances in cystic fibrosis management are likely to occur in the coming decade. Postmarket experience has shown that cystic fibrosis transmembrane conductance regulator modulators are safe and effective, and their role will likely expand. This will not only be with development of new, more efficacious therapies, but also with extra subgroups of the cystic fibrosis population becoming eligible – for example, at younger ages and for patients with other mutations.

Other small-molecule therapies and gene therapy are potential areas of treatment development in cystic fibrosis.[2] mRNA-based repair of mutations via antisense oligonucleotides may be an effective therapeutic tool, as seen with Duchenne's muscular dystrophy and spinal muscular atrophy. Direct delivery of the cystic fibrosis transmembrane conductance regulator gene to the airway epithelium via inhaled viral vectors also shows promise.[25]

In addition to cystic fibrosis transmembrane conductance regulator-based approaches, ongoing development of novel antimucolytic, anti-inflammatory and antimicrobial therapies will likely contribute to future therapy.

Conclusion

While cystic fibrosis remains a life-limiting disease, the outlook is increasingly positive. Treatment has shifted to improving the structure and function of the cystic fibrosis transmembrane conductance regulator, thereby altering the pathophysiology of the disease.

Cystic fibrosis transmembrane conductance regulator modulators are now a mainstay of management and therapeutic decisions can be based on genotype rather than just phenotype. These new drugs are expensive, and treatment may be limited or delayed by regulatory approval processes and funding negotiations.

With greater life expectancy, patients with concomitant cystic fibrosis and age-associated comorbidities are more likely to present in primary healthcare. It is therefore important for all healthcare professionals to understand cystic fibrosis transmembrane conductance regulator modulators, their potential adverse effects and drug–drug interactions.

Conflicts of interest: none declared

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