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Review Article

Cystic Fibrosis: Pathophysiology, Pharmacotherapy, CFTR Modulators and Emerging Therapeutic Strategies—A Contemporary Review

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ABSTRACT

Cystic fibrosis (CF) is an autosomal recessive multisystem disorder caused by pathogenic variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Defective CFTR-mediated chloride and bicarbonate transport produces dehydrated epithelial secretions, impaired mucociliary clearance, chronic airway infection and inflammation, pancreatic insufficiency and other systemic complications. Conventional therapy focuses on airway clearance, mucolysis, antimicrobial treatment, nutritional support and complication management. CFTR modulators have changed the therapeutic paradigm by targeting the underlying molecular defect. Ivacaftor acts principally as a potentiator, whereas lumacaftor, tezacaftor and elexacaftor act as correctors. Combination regimens, especially elexacaftor/tezacaftor/ivacaftor, produce clinically important improvements in lung function, sweat chloride, exacerbation frequency and quality of life in eligible patients. Pharmacokinetic interactions, hepatic monitoring, adherence, genotype-specific eligibility, cost and unequal access remain important limitations. Newer small-molecule combinations and mutation-agnostic approaches, including mRNA replacement, gene transfer and gene editing, aim to extend disease-modifying therapy to people who do not benefit adequately from existing modulators. This review summarizes CF pathophysiology, diagnosis, conventional pharmacotherapy, CFTR modulators, safety considerations and emerging therapies, with emphasis on concepts relevant to pharmaceutical sciences.

INTRODUCTION

Cystic fibrosis is a chronic inherited disease in which abnormalities of epithelial ion transport affect the

respiratory, gastrointestinal, pancreatic, hepatobiliary, reproductive and sweat-gland systems. The disease results from pathogenic variants in CFTR, which

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encodes an epithelial anion channel. Reduced CFTR quantity or function disturbs chloride and bicarbonate movement and alters hydration and pH at epithelial surfaces. In the lung, the resulting mucus stasis promotes persistent infection, neutrophil-dominated inflammation, airway remodeling and bronchiectasis.

The therapeutic history of CF illustrates the transition from symptomatic treatment to precision pharmacotherapy. Airway-clearance techniques, recombinant DNase, hypertonic saline, antibiotics, pancreatic enzyme replacement and nutritional support remain essential. However, CFTR modulators can improve the processing or activity of mutant CFTR protein and therefore act closer to the primary molecular defect. Recent medicinal-chemistry reviews classify approved and investigational compounds according to effects on CFTR folding, trafficking, gating, stability and expression [1,2].

This review focuses on the pharmacological basis of current CF management, with particular emphasis on CFTR modulators, drug interactions, adverse effects and emerging molecular therapies.

2. Molecular Basis and Pathophysiology

CFTR is an ATP-binding cassette family protein expressed at the apical surface of epithelial cells. It functions primarily as a chloride and bicarbonate channel and also influences other ion-transport pathways. Disease-causing variants can reduce CFTR synthesis, impair protein folding and trafficking, disturb channel gating or conductance, or decrease cell-surface stability. The common Phe508del variant causes major folding and processing abnormalities and also affects channel stability and function.

In the airway, defective anion secretion and abnormal epithelial fluid homeostasis reduce airway-surface hydration. Thick secretions are difficult to clear, allowing microorganisms to persist. Recurrent and chronic infection stimulates intense neutrophilic inflammation; proteases, oxidants and inflammatory mediators then contribute to airway injury. Repeated cycles of obstruction, infection and inflammation eventually produce bronchiectasis and progressive loss of pulmonary function.

Similar obstruction of exocrine ducts explains many extrapulmonary manifestations. Pancreatic duct obstruction can cause exocrine pancreatic insufficiency, maldigestion and fat-soluble vitamin deficiency. Intestinal obstruction syndromes, hepatobiliary disease, CF-related diabetes and male infertility are clinically important consequences.

3. Functional Classification of CFTR Variants

Traditional functional classification groups CFTR defects into classes. Class I variants markedly reduce protein synthesis; class II variants impair processing and trafficking; class III variants impair channel gating; class IV variants reduce conductance; class V variants reduce the quantity of otherwise functional protein; and class VI defects reduce stability at the cell surface. Individual variants may have more than one functional defect, so the classification is useful conceptually but does not fully predict clinical response.

This classification has direct pharmacological relevance. Potentiators improve channel opening of CFTR already present at the membrane, whereas correctors improve folding, processing and trafficking. The response to a modulator therefore depends on whether sufficient drug-responsive CFTR protein can be produced and delivered to the epithelial surface [1,2].

4. Clinical Manifestations and Diagnosis

Respiratory disease is the major cause of morbidity. Common features include chronic cough, sputum production, recurrent pulmonary exacerbations, wheeze, chronic rhinosinusitis and progressive bronchiectasis. Important airway pathogens include *Staphylococcus aureus* and *Pseudomonas aeruginosa*, although the microbiology changes with age, previous treatment and disease severity.

Exocrine pancreatic insufficiency can cause steatorrhea, poor weight gain and deficiencies of vitamins A, D, E and K. CF-related diabetes, hepatobiliary disease, distal intestinal obstruction syndrome, reduced bone health and reproductive abnormalities require long-term multidisciplinary care.

Diagnosis integrates a compatible clinical setting or newborn-screening result with objective evidence of CFTR dysfunction. Sweat chloride measurement



remains central, while CFTR genetic testing identifies pathogenic variants and can determine eligibility for variant-specific treatment. Additional CFTR functional tests may help resolve uncertain cases. Spirometry, respiratory cultures, imaging and nutritional assessment are used to monitor disease rather than establish the molecular diagnosis.

5. Conventional Pharmacotherapy

5.1 Airway hydration and mucus-directed therapy

Dornase alfa is recombinant human deoxyribonuclease I. It cleaves extracellular DNA released from degenerating inflammatory cells, reducing the viscoelasticity of purulent airway secretions and facilitating clearance. Inhaled hypertonic saline increases airway-surface hydration and improves mucus clearance. These therapies are generally integrated with individualized airway-clearance physiotherapy rather than used as substitutes for it.

5.2 Antimicrobial therapy

Antibiotic treatment is guided by clinical status, previous microbiology, respiratory cultures and local susceptibility patterns. Acute pulmonary exacerbations may require oral or intravenous antibiotics. Chronic or recurrent *Pseudomonas* infection can be managed with inhaled agents such as tobramycin, aztreonam lysine or colistimethate in appropriate settings. Long-term antimicrobial exposure creates challenges involving resistance, toxicity, treatment burden and adherence; antimicrobial stewardship is therefore important.

5.3 Anti-inflammatory and bronchodilator therapy

Azithromycin has immunomodulatory as well as antimicrobial effects and may reduce exacerbation burden in selected patients. Routine prolonged systemic corticosteroid therapy is generally avoided because toxicity can outweigh benefit, although corticosteroids remain appropriate for specific coexisting indications. Bronchodilators may be useful in patients with reversible airflow limitation or concomitant bronchial hyper-responsiveness.

5.4 Pancreatic and nutritional therapy

Pancreatic enzyme replacement therapy is administered with meals and snacks in patients with pancreatic insufficiency. Dosing is individualized according to dietary fat intake, symptoms, growth and nutritional status. Supplementation of fat-soluble vitamins and salt may be required. Nutritional management is a core component of CF care because nutritional status and pulmonary health are closely linked.

6. CFTR Modulators

CFTR modulators are small molecules that increase the quantity or function of mutant CFTR. Their introduction is the major pharmacological advance in CF because they target the primary protein defect. Potentiators increase channel-opening probability, while correctors improve protein folding, processing and delivery to the cell surface. Combining correctors with complementary mechanisms can increase the amount of rescued CFTR available for potentiation [1,2].

Agent/regimen	Pharmacological class	Principal action	Key point
Ivacaftor	Potentiator	Enhances opening of CFTR channels at the cell surface	Established proof of concept for mutation-targeted therapy
Lumacaftor + ivacaftor	Corrector + potentiator	Improves processing plus channel gating	Used for eligible Phe508del genotypes
Tezacaftor + ivacaftor	Corrector + potentiator	Improves trafficking plus potentiates surface CFTR	Demonstrated efficacy in Phe508del homozygotes [3]
Elexacaftor + tezacaftor + ivacaftor	Two correctors + potentiator	Complementary rescue of Phe508del processing with potentiation	Marked clinical benefit in eligible patients with ≥ 1 Phe508del allele [4,5]

6.1 Ivacaftor

Ivacaftor is a CFTR potentiator that increases channel-opening probability in responsive CFTR variants.

Its clinical development demonstrated that correcting a specific molecular defect could improve clinically meaningful outcomes. The drug is orally administered and is incorporated into several combination regimens.



Because eligibility is variant dependent, genotype interpretation is fundamental to prescribing.

6.2 Corrector combinations

Lumacaftor and tezacaftor are correctors developed to improve folding and trafficking of abnormal CFTR, particularly Phe508del protein. Tezacaftor/ivacaftor produced significant improvement in percent-predicted FEV1 and reduced pulmonary exacerbations compared with placebo in a phase 3 trial involving patients homozygous for Phe508del [3]. Corrector-potentiator combinations established the rationale for using multiple agents to address distinct defects in the same mutant protein.

6.3 Elexacaftor/tezacaftor/ivacaftor

Elexacaftor/tezacaftor/ivacaftor (ETI) combines two correctors with the potentiator ivacaftor. In the landmark phase 3 trial in patients aged 12 years or older with one Phe508del allele and a minimal-function allele, ETI increased percent-predicted FEV1 by approximately 14 percentage points versus placebo through 24 weeks, reduced pulmonary exacerbations by 63%, improved respiratory quality-of-life scores and substantially reduced sweat chloride [4]. A later active-controlled trial also demonstrated benefit in Phe508del-gating and Phe508del-residual-function genotypes [5].

The importance of ETI extends beyond spirometry. Observational and review literature describes effects across nutritional, respiratory and extrapulmonary domains, while also highlighting the need for continued surveillance of long-term outcomes. The therapeutic landscape continues to evolve, with newer modulator combinations and medicinal-chemistry strategies intended to improve efficacy, dosing convenience and tolerability [1,6].

7. Pharmacokinetics, Interactions and Safety

CFTR modulators are orally administered small molecules with clinically important hepatic metabolism. CYP3A pathways are particularly relevant to ivacaftor, tezacaftor and elexacaftor. Strong or moderate CYP3A inhibitors can increase exposure, whereas strong inducers can substantially reduce exposure and therapeutic effectiveness. Medication review is therefore

essential when patients receive azole antifungals, macrolides, rifamycins, anticonvulsants or other interacting drugs.

Adverse effects vary by regimen but can include headache, gastrointestinal symptoms, rash and elevations in hepatic transaminases. Liver-function monitoring and attention to hepatic impairment are important. Pharmacokinetic variability in special populations, including children and patients with hepatic dysfunction, remains an active area of study. A recent systematic review specifically examined the pharmacokinetics of ivacaftor, tezacaftor, elexacaftor and lumacaftor in special CF populations [7].

Adherence is another pharmacological determinant of real-world effectiveness. CF treatment burden is high, and the addition of chronic oral modulators does not automatically eliminate airway, nutritional or antimicrobial therapies. A 2024 systematic review found that adherence to CFTR modulators is an important and measurable component of treatment effectiveness, reinforcing the pharmacist's role in counselling and medication-management support [8].

8. Emerging Therapeutic Strategies

Current modulators require the presence of CFTR protein that can respond to pharmacological rescue, leaving an important unmet need for people with variants that produce little or no rescuable protein. Consequently, drug discovery is expanding toward both improved small-molecule modulators and mutation-agnostic approaches [6].

Messenger RNA replacement aims to deliver functional CFTR mRNA to airway epithelial cells, allowing temporary production of normal protein without permanent genomic alteration. Gene-addition strategies seek durable expression of functional CFTR using viral or non-viral delivery systems. Gene-editing technologies, including CRISPR-based approaches, attempt to correct pathogenic DNA variants directly. Each strategy faces challenges involving delivery to airway cells, immune responses, duration of expression, off-target effects, repeat dosing and scalable manufacturing.

Other investigational strategies include amplifiers that increase CFTR protein production, stabilizers that prolong membrane residence, read-through approaches



for selected premature-termination variants, alternative ion-channel targets, improved anti-inflammatory therapies and novel infection-directed treatments. Recent reviews emphasize that rare and non-responsive variants, treatment access and efficient theratyping remain major priorities in CF drug development [6,9].

9. Role of the Pharmacist

CF is characterized by polypharmacy, complex dosing schedules and clinically significant drug interactions. Pharmacists can contribute by reconciling medicines, checking genotype-linked modulator eligibility, identifying CYP3A interactions, monitoring adverse reactions, supporting hepatic monitoring, optimizing antibiotic dosing and promoting antimicrobial stewardship. They also reinforce

correct administration of pancreatic enzymes, inhaled therapies and CFTR modulators, assess adherence barriers and counsel patients regarding food and dosing requirements.

For M.Pharm practice, CF is an important model of precision pharmacotherapy. The link between molecular defect, medicinal chemistry, pharmacokinetics, pharmacogenomics and clinical response demonstrates how pharmaceutical sciences can translate a genetic mechanism into individualized drug selection.

10. Challenges and Future Perspective

Major challenges include the persistence of established bronchiectasis and chronic infection despite improved CFTR function, treatment-emergent adverse effects, long-term safety surveillance, drug interactions and high lifetime treatment burden. Access to expensive modulators remains uneven across countries and health systems. In addition, patients with rare variants may be difficult to study in conventional randomized trials, increasing interest in validated laboratory theratyping and alternative evidence pathways.

The future of CF therapy is likely to combine increasingly effective small-molecule modulators with genotype-independent genetic or RNA-based interventions. Better delivery systems, longer-acting formulations, individualized pharmacokinetic monitoring and integration of real-world evidence may further improve outcomes. The central scientific objective is to provide

safe disease-modifying therapy to all people with CF, irrespective of genotype [6,9].

CONCLUSION

Cystic fibrosis pharmacotherapy has progressed from predominantly symptomatic management to molecularly targeted treatment. Airway hydration, mucolytic therapy, antimicrobial treatment, pancreatic enzyme replacement and nutritional support remain essential, but CFTR modulators now address the underlying protein defect in a large proportion of eligible patients. Ivacaftor established the value of CFTR potentiation, corrector-potentiator combinations expanded treatment, and elexacaftor/tezacaftor/ivacaftor produced major improvements in lung function and exacerbation outcomes in Phe508del-containing genotypes. The next phase of therapeutic development seeks more convenient and effective modulators and mutation-agnostic RNA and gene therapies. For pharmacists, careful management of interactions, adherence, safety monitoring and individualized therapy is increasingly important as CF treatment becomes more precise and pharmacologically complex.

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