Recent advances in the management of cystic fibrosis

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More effective management programmes and treatments mean that life expectancy for people with cystic fibrosis is improving. This article examines the expanding role of primary care in the management of cystic fibrosis and discusses the availability of new treatments that target the underlying cause of the disease.

A baby born with cystic fibrosis in 2000 has a median life expectancy of over 50 years, as effective treatments and refined disease management protocols continue to improve patient prospects. This is a remarkable achievement as it comes from a distressingly low base of families having to cope with their children dying way before their 10th birthday in the 1960s, when understanding of the inherited genetic condition was weak.

There is no cure for cystic fibrosis but successful therapy regimens are available, which combine medication, physiotherapy, exercise and nutrition. A multidisciplinary approach, combined with new inhaled therapies, mucolytics and antibiotics, has vastly improved both longevity and quality of life.

However, that success is altering the treatment dynamics, with patients with cystic fibrosis living into adulthood and presenting to GPs with a range of related and nonrelated medical conditions. Cystic fibrosis patients are susceptible to digestive problems, pancreas malfunction leading to increased risk of diabetes, bowel issues, osteoporosis, arthritis, sinusitis and stress incontinence.

Exciting advances are being made with genetic research but there is still concern about wrinkles in service provision and that new medicines are struggling to win approval from NICE and the Scottish Medicines Consortium (SMC) because of their cost.

A recent negative ruling from NICE on the gene mutation-specific lumacaftor/ivacaftor (Orkambi) – a twice daily combination drug treatment that improved lung function in clinical trials – sparked consternation among patients and the Cystic Fibrosis Trust. The charity is now campaigning to encourage the regulatory authorities and pharmaceutical company Vertex Pharmaceuticals to reduce the annual list price of the drug from £104,000 per person per year for what NICE describes as only a “modest” benefit.
What is cystic fibrosis?

There are more than 10,800 people with cystic fibrosis in the UK. Cystic fibrosis is caused by a fault in the gene that codes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. CFTR is a cell membrane protein and chloride channel that regulates the movement of chloride ions across epithelial cell membranes. Faults in the CFTR gene can reduce the ion channel’s functioning, disrupting epithelial fluid transport and causing abnormal levels of thickened mucus to gather in the lungs, digestive system and other organs. Build-up of mucus in the airways leads to breathing problems and cycles of respiratory infections, which can cause permanent damage such as the formation of scar tissue (fibrosis) and cysts.

More than 2.5 million people in the UK carry the faulty gene and each week five babies are born with cystic fibrosis and two people die from the condition. Cystic fibrosis is inherited in an autosomal recessive manner, meaning that males and females are equally affected and two copies of the faulty CFTR gene are necessary to have the disease, one from the mother and one from the father. If both parents carry the faulty gene, there is a 25 per cent chance their child will have cystic fibrosis, a 50 per cent chance a child will be a gene carrier but not have cystic fibrosis and a 25 per cent chance they will not have the faulty gene (see Figure 1).

Over 1900 different CFTR gene mutations have now been discovered but the most common is F508del, which accounts for about 70 per cent of cystic fibrosis genes worldwide.

Cystic fibrosis is normally picked up by the heel-prick blood tests at 72 hours and then again at six to eight weeks, provided as part of the newborn and infant physical examination (NIPE) screening programme, established in the UK in 2007. Babies with cystic fibrosis frequently struggle to gain weight and have frequent chest infections but early attention with high-energy diets, medicines and physiotherapy can reduce the impact.

Symptoms in early childhood include a persistent cough, recurring chest infections and a failure to thrive. The key is to diagnose and treat early to minimise the damage caused by infections.

Patients in the UK, who face daily physiotherapy and nebulising regimens, attend 23 adult and 27 paediatric cystic fibrosis centres around the country or hospitals with specialist services where a multidisciplinary approach provides the core of their care.

The role of primary care

Cystic fibrosis patients are now living longer and picking up co-morbidities, and so treating a range of related health conditions is increasingly falling on the GP caseload. A landmark qualitative study, based on interviews with 31 cystic fibrosis patients and published in the British Journal of General Practice, concluded that little attention had been paid to how patients with chronic conditions, such as cystic fibrosis, are handled in primary care.

“As more patients survive to adulthood and experience age-related conditions associated with cystic fibrosis, particularly cystic fibrosis-related diabetes, they are likely to rely more and more on primary care. Their increasing age also means that they will not only take over responsibility for their treatment and care from their parents but, having been encouraged throughout their lives to be active participants in their own care, they are also likely to consult within primary care as patients with specialised expertise,” stated the study authors. “With the increasing longevity of patients with cystic fibrosis, it is now important to integrate primary and secondary care services to ensure seamless care delivery,” they added.

Co-author of the study, Professor Karen Lowton, then of King’s College London, but now professor of sociology (ageing and health) at the University of Sussex, also presented evidence to a House of Commons Select Committee in 2013 on the management of patients with serious conditions who are now surviving into adulthood, known as “new ageing populations”. She highlighted that for the first time in history, the number of adults with cystic fibrosis exceeds the number of children with the condition. But her evidence questioned if primary care was equipped to deal with the range of complex physical and psycho-
logical conditions associated with cystic fibrosis.

“Many GPs have limited exposure to cystic fibrosis patients and run the risk of attributing any new symptom to the underlying condition,” Professor Lowton cautions. The challenge, therefore, is to bring GPs more into the care continuum.

“As long as we keep the divide between secondary and primary care, patients are never going to get wrap-around care because GPs are unlikely to see more than a handful of patients with cystic fibrosis during their careers,” explains Professor Lowton. “Some patients had knowledgeable GPs who were learning as they grew up within a partnership but another group of patients said they automatically contacted the specialist centre, so GPs didn’t get the experience they needed. Realistically, it is a problem at the moment how informed a GP can be.”

Dr Nadia Shafi, consultant physician at the Cambridge Centre for Lung Infection and clinical lead for cystic fibrosis at Papworth Hospital NHS Trust, believes therapy changes have increased the treatment burden for patients and the requirement for primary care to address the need. “As patients get older and live longer this need increases, and good communication between primary and secondary care is essential to ensure that this is seamless. There are also the challenges of adherence to therapy that go along with this,” she says.

“It would be ideal for GPs with cystic fibrosis patients on their books to have an understanding of the principles of cystic fibrosis care and to ensure that the lines of communication between themselves and the secondary care providers are well established. We rely on GPs often for rescue treatments for cystic fibrosis patients in the community and therefore the importance of prompt recognition, treatment and escalation to secondary care when necessary is paramount.

“Although some of the specialist drugs we use are now supplied by homecare companies, such as inhaled mucolytics and antibiotics, it is clearly essential that GPs are aware of all of the medications patients are on. Patients are still reliant on GP provision of most of their medications including pancreatic enzyme supplementation, vitamins and inhalers and oral antibiotic treatments, which often add up to a lot. It is also very important that there is an awareness of the newer mutation-specific oral treatments, such as ivacaftor (Kalydeco), as the complexity of drug interactions with some of these newer treatments is increasing,” Dr Shafi adds.

A GP’s ability to learn more can be compromised by patients being loyal to their cystic fibrosis centres so that the disease is not widely discussed in GP surgeries. Some patients will regularly travel 150 miles or even move house to maintain contact with their cystic fibrosis team.

This point is underscored by Nuala Harnett, chair of the Association of Chartered Physiotherapists in Cystic Fibrosis, who says effective teams have been established at cystic fibrosis centres, with medicine, physiotherapy and nutrition providing trusted treatment routes. Funding is also focused on specialist centres.

Cystic fibrosis patients are impacted by a sweep of issues stemming directly from their conditions and Mrs Harnett highlights that the physiotherapy input stretches way beyond the exercise regimens that help with mucus clearing and nebulising. Around 80 per cent of female patients suffer from stress incontinence due to persistent coughing causing weakening of the pelvic floor. Musculoskeletal and posture problems are also common from the years of the body bending and arching through coughing episodes, she notes.

“The key is the multidisciplinary approach of medical, physiotherapy and nutrition. Nothing works in isolation,” explains Mrs Harnett, who is also a clinical specialist physiotherapist, based at the Great North Children’s Hospital, in Newcastle. “We keep in close contact with GPs but they don’t generally deal directly with cystic fibrosis patients so it is hard to build up specialist knowledge.

“The progress has been incredible over the past 10 years and there are very exciting times ahead. There is a huge amount of work going on to find new treatments that work with other genetic mutations. Our role is to keep these
patients as well as we can so they can benefit from these drugs when they do come on the market.”

**Current treatments**

Up until recently, the drug treatments available for cystic fibrosis only controlled symptoms or prevented and reduced complications. Such treatments include antibiotics for chest infections and bronchodilators and steroids for airway inflammation, as well as the mucolytics dornase alfa and mannitol, which are specifically licensed for cystic fibrosis. However, in the past few years, medicines that target the underlying cause of the disease by improving the functioning of CFTR ion channels have become available (see Table 1).

The first of these, ivacaftor, was launched in the UK in 2012. It was adopted for use within NHS England the following year for patients aged six years and over with a G551D mutation in the CFTR gene and later extended to the rarer gating mutations within its licensed indications. About four per cent of UK cystic fibrosis patients have the G551D mutation and a further 0.5 per cent have one of the rarer gating mutations.

At the end of 2015, the combined therapy lumacaftor/ivacaftor, licensed for patients aged 12 years and older who are homozygous (have two copies) for the F508del mutation in the CFTR gene was launched. This combination has the potential to treat more patients as over half of people in the UK with cystic fibrosis have this genotype. However, this treatment was refused by both NICE and the SMC in the spring of this year and, despite pleas from the Cystic Fibrosis Trust and a 20,000 signature petition, the guidance remains in place.2,7

The NICE committee concluded that although the acute improvements in lung function were modest, the reductions in pulmonary exacerbations seen with lumacaftor/ivacaftor were clinically significant and important for managing cystic fibrosis. However, they calculated that overall the treatment did not represent a cost-effective use of NHS resources.

The Cystic Fibrosis Trust has suggested providing lumacaftor/ivacaftor to patients on a trial basis using its registry of patients (the UK Cystic Fibrosis Registry) to provide extra efficacy data, which they believe will strengthen the drug’s case for approval.

Dr Shafi, while welcoming NHS drugs provision for cystic fibrosis patients, says lumacaftor/ivacaftor offers a chance of tackling the underlying condition rather than slowing progression.

“It is with drugs like lumacaftor/ivacaftor, which are aimed at correcting the cellular defects that cause the damage in cystic fibrosis, that the real hope for the future lies, because by correcting the function of the CFTR protein we may be able to prevent the changes from occurring in the first place,” she explains. “The cost of [lumacaftor/ivacaftor] is very high. However, it is disappointing that we are not yet in a position to offer this drug to patients in whom the clinical trials have demonstrated beneficial outcomes, as clearly time is of the essence in a condition such as cystic fibrosis, which is progressive.”

**Future targets**

Dr Imran Rafi, a GP based in Surrey and the Royal College of General Practitioners chair of clinical innovation, has called for the drug to be made available for adults and children. Currently, the treatment is only licensed for adults aged 18 years and older who have an R117H mutation in the CFTR gene.

**Table 1.** Treatments licensed for cystic fibrosis in the UK (source: BNF and electronic Medicines Compendium (eMC))

<table>
<thead>
<tr>
<th>Drug</th>
<th>Method of delivery</th>
<th>Mode of action</th>
<th>Indications</th>
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<tbody>
<tr>
<td>Dornase alfa (Pulmozyme)</td>
<td>Inhalation (nebulised solution)</td>
<td>Cleaves extracellular DNA to reduce sputum viscosity</td>
<td>Management of cystic fibrosis patients with a forced vital capacity (FVC) of greater than 40% of predicted and over 5 years of age to improve pulmonary function</td>
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<tr>
<td>Ivacaftor (Kalydeco)</td>
<td>Oral tablet (6 years and over and weighing ≥25kg)</td>
<td>CFTR potentiator that enhances chloride transport by increasing CFTR channel gating at the cell surface</td>
<td>Treatment of patients with cystic fibrosis aged 2 years and older who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R</td>
</tr>
<tr>
<td></td>
<td>Oral granules (2 years and over, weighing &lt;25kg)</td>
<td></td>
<td>Treatment of patients with cystic fibrosis aged 18 years and older who have an R117H mutation in the CFTR gene</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Inhalation (dry powder)</td>
<td>Hyperosmotic that improves mucous clearance in the lungs</td>
<td>Treatment of cystic fibrosis in adults aged 18 years and above as an add-on therapy to best standard of care</td>
</tr>
<tr>
<td>Lumacaftor/ivacaftor (Orkambi)</td>
<td>Oral tablet</td>
<td>Lumacaftor: CFTR corrector that acts directly on F508del-CFTR to improve its cellular processing and trafficking, thereby increasing the quantity of functional CFTR at the cell surface</td>
<td>Treatment of cystic fibrosis in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene</td>
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**CFTR = cystic fibrosis transmembrane conductance regulator**

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**Dr. Shafi Shafi, Consultant in Respiratory Medicine, London**

Dr. Shafi Shafi is a consultant in respiratory medicine based in London. She is a member of the Cystic Fibrosis Trust’s clinical advisory group and a former member of the UK Cystic Fibrosis Registry.”
tion and research, believes intensive management and early screening for cystic fibrosis have worked well but that strengthening returns from genome sequencing research are providing a springboard for fresh progress.

“Our genetic knowledge has improved; we now know nearly 2000 gene variations in cystic fibrosis,” says Dr Rafi. “There is a lot of genomic and genetic work being done that can help new targets for medicines, which is exciting.” There is now a genuine prospect that gene editing could develop so that couples with cystic fibrosis could have children without fear of passing on the condition, he says.

Another novel treatment that is under investigation for the management of cystic fibrosis is ataluren (Translarna), which is currently licensed for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene. Ataluren works by allowing ribosomal readthrough of mRNA with premature stop codons, allowing a functional protein to be made. The drug has also shown efficacy in patients with cystic fibrosis and a nonsense CFTR gene mutation.

In addition, scientists at Queen’s University Belfast have discovered a new protease inhibitor that prevents activation of epithelial sodium channels in the airways of people with cystic fibrosis, and hence has the potential to aid airway hydration and increase mucus clearance. This strategy may offer hope for all cystic fibrosis patients, regardless of their genotype, as targeting epithelial sodium channels is independent of the underlying CFTR gene mutation. The breakthrough preclinical research is funded by the Cystic Fibrosis Trust.

Clinicians agree that medicine needs to keep up with the fast-paced research, which is pushing the boundaries of potential for cystic fibrosis patients.

References

Declaration of interests
See http://www.mjauk.org/author/bucklandd/

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