Drugs for pulmonary arterial hypertension - comments on final scopeFrom: [redacted] [redacted]
Sent: 19 April 2007 15:45
To: Reetan Patel
Subject: Drugs for pulmonary arterial hypertension - comments on final scope

Attachments: Drugs... pulmonary arterial hypertension - submission.doc; RCP NICE submission April 2007 Drugs for the treatment of pulmonary arterial hypertension.pdf; UK PH centres census data.pdf; Pulmonary Hypertension Recommendations 2001.pdf; Epidemiology paper for RCP NICE submission.pdf; ESC PAH guidelines 2004.pdf

Dear Reetan

Please find attached a covering letter and the submission from the College for this HTA.

<<Drugs... pulmonary arterial hypertension - submission.doc>> <<RCP NICE submission April 2007 Drugs for the treatment of pulmonary arterial hypertension.pdf>> <<UK PH centres census data.pdf>> <<Pulmonary Hypertension Recommendations 2001.pdf>> <<Epidemiology paper for RCP NICE submission.pdf>> <<ESC PAH guidelines 2004.pdf>>

On the advice of [redacted] - the clinical expert who co-ordianted this response please note that attachment "UK PH centres census data" is CONFIDENTIAL and must not seen under any circumstances by any organisation other than NICE.

I would be grateful if you could please confirm receipt.
Best wishes
[redacted]

[redacted]
Professional Affairs Department
Royal College of Physicians
11 St Andrews Place
Regent's Park
London
NW1 4LE

Tel: [redacted]
Fax: [redacted]
E-mail: [redacted]

Royal College of Physicians
Setting higher medical standards

11 St. Andrews Place
Regent's Park, London NW1 4LE

Telephone +44(0) 20 7935 1174
Textphone +44(0) 20 7486 5687
Facsimile +44(0) 20 7487 5218

www.rcplondon.ac.uk

[redacted]

Telephone extension [redacted]
Direct facsimile [redacted]

Reetan Patel
Technology Appraisals Project Manager
National Institute for Health and Clinical Excellence (NICE)
MidCity Place
71 High Holborn
London
WC1V 6NA

18th April 2007

Dear Mr Patel

Re: Drugs for the treatment of pulmonary arterial hypertension

The Royal College of Physicians and the British Cardiovascular Society are grateful for the opportunity to contribute to this appraisal. In so doing, we have sought advice from a number of experts and the submission has been co-ordinated by Dr Simon Gibbs. However, as you will see from the attached, the statement is based on national audit and recommendations from respiratory medicine, paediatrics and surgery, as well as cardiology.

We trust these comments will be of use.

Yours sincerely

[redacted]

Drugs for the treatment of pulmonary arterial hypertension

Submission on behalf of the Royal College of Physicians

Compiled by Simon Gibbs, Hammersmith Hospital, London

18th April 2007

Attachments

1. UK pulmonary hypertension census data

2. British Cardiac Society recommendations 2001

3. ESC guidelines 2004

4. Epidemiology paper

Terminology

The terms disease-targeted therapy and treatment / therapy for PAH refer to the prostacyclins, endothelin receptor antagonists and phosphodiesterase inhibitors, many of which are being assessed in the NICE appraisal.

Current Clinical Practice

Designated Centres

In the UK patients with pulmonary arterial hypertension (PAH) are managed by centres designated by the National Specialist Commissioning Advisory Group (NSCAG) of the Department of Health. The centres in England were designated in September 2001 by a process of peer review and NSCAG inspection under the direction of Dr Geoffrey Carroll, Medical Adviser to NSCAG. Table 1 lists the designated centres in England. Since there are no centres in Wales or Northern Ireland, care has traditionally been sought from English centres. Scotland has a centre in Glasgow designated by the NSD.

TABLE 1. NSCAG DESIGNATED PULMONARY HYPERTENSION CENTRES.

Location	Hospital
Newcastle-upon-Tyne	Freeman
Sheffield	Royal Hallamshire
Papworth Everard	Papworth
London	Hammersmith
London	Royal Free
London	Royal Brompton
London	Great Ormond Street (UK Service for Children)

The formation of the National Pulmonary Hypertension Service was timely. With the exception of warfarin, until the 1990s PAH was considered untreatable. In 1996 the first randomised trial was published and established intravenous epoprostenol as the treatment of choice. With the development of two further classes of drugs, the treatment of PAH is now changing rapidly. During 2007 -8 a considerable number of new randomised trials will be published which are very likely to change clinical practice.

Role of designated centres

The need for an accurate diagnosis of the cause and severity of pulmonary hypertension was recognised since this affected the choice of treatment. While epoprostenol improved patients with PAH, it was shown to increase mortality in patients with pulmonary hypertension caused by pulmonary veno-occlusive disease or left ventricular failure. The investigation of pulmonary hypertension fell into the fields of both cardiology and respiratory medicine. This resulted in dysfunctional investigation of patients who would get sent from one specialist to another to undergo different tests. This could be overcome by specialist pulmonary hypertension centres.

The purpose of developing specialist centres was to provide best clinical care of patients with a rare condition. The formation of such centres was supported by patients. Centres were set up where there was existing expertise. The national service in England was set up around patient needs to provide investigation and treatment with the minimum of delay and well coordinated care. The appointment of specialist nurses was required of centres, and together with medical staff, and in some cases pharmacists, social workers and chaplains, they provide patient care through a multiprofessional team. All centres offer outpatient and/or day case facilities, inpatient care, on-call, the full range of medical therapies and research and development. Centres undertake audit and are inspected annually by NSCAG and commissioners.

When new patients are seen by designated centres, the first priority is to achieve the correct diagnosis. Most patients require extensive investigations including heart and lung imaging, blood tests, lung function and cardiac catheterisation. At the end of this process while some patients will proceed with disease-targeted therapy, others will be monitored or even discharged from the service with an alternative diagnosis.

An additional important role of centres is to provide advice to other health care professionals, share the care of patientswith their local health care professionals, and provide an educational programme for those in secondary care who may refer patients.

The service was set up with agreed Standards of Care, a NHS Service Specification and agreement that clinical care should follow the British Cardiac Society *Recommendations on the management of pulmonary hypertension in clinical practice* (Heart 2001), a document in which all lead clinicians participated in the preparation.

All centres organise clinical data collection for audit. Later in 2007 this will be centralised at the Central Cardiac Audit Database (CCAD) to provide national data which hitherto has not been available.

Disease-targeted therapies and designated centres

At the heart of the designation of centres was the requirement by NSCAG that all disease-targeted therapies for pulmonary arterial hypertension must be prescribed, for as long as the drugs were taken by a patient, only by designated centres. This remains a key requirement.

This is logical not just from a cost perspective because first, the complexity of administration of the prostacyclins requires specialist training and 24 h back-up; second, vigilant monitoring of liver function in patients taking endothelin receptor antagonists is essential; third, patients on disease-targeted therapy may deteriorate insidiously and without careful monitoring this will be missed or treated too late; and fourth, large cohorts of patients provide a base for urgently needed clinical research.

Such drug therapy is funded by each patient's Primary Care Trust (PCT) on an individual patient basis. While some PCTs have formed groups who wish to be notified when a patient is started on therapy, the majority consider each individual case separately (so called "postcode prescribing"). Some parts of England have developed PAH treatment policies but there is no uniform approach to treatment. For patients commencing a single treatment for the first time, the vast majority of PCTs agree to fund treatment. This is not always without considerable delay and risk to the life of patients who are referred late in the course of their illness (see below).

The complexities of deciding which treatment are compounded by the fact that patients with PAH constitute a very heterogenous population. While some patients will follow a highly malignant course and die within weeks or months after the onset of symptoms, others will survive for decades. The majority fall somewhere in between. A further difficulty for designated centres is that too many patients are referred too late in the course of their illness even although the diagnosis of PAH has been known for several years. At Hammersmith Hospital 85% of referrals are in NYHA functional class III or IV. Worse symptoms are associated with a worse prognosis. Late referral remains a challenge for a timely approach to treatment and educating our peers.

Clinical activity in designated centres

To provide an annual snapshot of treatment of patients with pulmonary hypertension in the UK, the designated centres participate in an annual census on the 31st March each year. Data has now been collected for 4 consecutive years and is shown in the accompanying document. Please note that this data is confidential and for the eyes of NICE only.

This details patients who were alive on census day. This means that it underestimates the annual workload as well as the number of patients who have received treatment during the previous year (since dead patients are not included). Details are provided for each designated centre in England including the Children's service (since many of these patients will become adults), and the Scottish service for comparison. Differences between centres do not reflect any major differences in opinion between professionals. Rather they most probably reflect differences in referrals including the cause and severity of pulmonary hypertension. For example, the Royal Free Hospital has a special interest in scleroderma-associated PAH, the Royal Brompton in grown-up congenital heart disease, Great Ormond Street in children and Papworth in chronic thromboembolic disease. Another reason for a referral difference may be that lead clinicians in the London hospitals are cardiologists whereas

outside London they are respiratory physicians. Each specialty may attract different patient populations.

These census tables also provide evidence for the rapidly changing approach to treatment, not only with individual drugs, but also with combination therapy prescribed mainly when another monotherapy fails. Although trial data for combination therapy is limited, it is used because drugs work by different mechanisms in a disease which is otherwise fatal. The use of combination therapy is more frequent in some other European countries and the USA.

The progressive rise in patient numbers has been associated with a progressive increase in referrals of patients to designated centres. This may be both a consequence of improved recognition of pulmonary hypertension and better awareness. It does raise questions about prevalence of PAH. This is discussed in the attached paper which is in press.

Advantages and disadvantages of the disease-targeted therapies

All patients undergoing treatment with these drugs require long-term monitoring. In general they are reviewed 3 monthly with history, clinical examination, assessment of quality of life, six minute walk test and blood tests. These are supplemented as required by echocardiography, cardiac magnetic resonance imaging and cardiac catheterisation. The purpose of these investigations is to detect deterioration which would have implications for treatment. In most patients PAH will break through the treatment at some stage.

Indications for starting therapies in PAH are described in the ESC guidelines (2004). Indications for stopping are not described. This is partly because once started it is recommended by guidelines that therapy is continued because of the risk of rebound pulmonary hypertension and death on discontinuation which seems to be a particular problem with prostacyclins but does occur with drugs in other classes; and partly because no appreciable change on therapy may suggest that the therapy is preventing further deterioration. In practice only a minority of patients have no response to the therapies, and in such patients after a 3 month trial it may be reasonable to discontinue therapy and try another class of drugs.

Patients included in clinical trials may not always represent typical patients managed in real life clinical practice. This is certainly true in PAH. Clinical practice tends to attract older patients with more comorbidities compared to trials. Although most patients are in NYHA functional class III, at least at Hammersmith Hospital, their six minute walk test before treatment is less good than trials (approximately 260 m at Hammersmith versus 340 m in trials). This suggests that since NYHA functional class III is fairly broad, patients are being referred later in the course of their disease.

The rate of onset of treatment effect is important in sick patients. While epoprostenol has a rapid onset (within minutes to hours) vasodilatory and probably positive inotropic effect, bosentan may take up to 6-8 weeks to have a noticeable effect to the patient. Individual responses are of course variable.

The major problem with clinical trials has been small numbers of patients. This is reflected in the short duration (12 – 16 weeks) in many trials which is much shorter than many patients would hope to benefit from the drugs and to survive. Only one study (epoprostenol trial) has demonstrated

survival benefit. It is now unethical to undertake randomised placebo-controlled trials in PAH patient groups who have been shown to benefit from therapy in short-term trials, making registry survival data the only source.

Multicentre randomised clinical trials have failed to define the optimal first line therapy in NYHA functional III.

The most useful outcomes from multicentre trials are survival, six minute walk test and quality of life. Trials are unable to measure the non-specific improvements which most patients report by 3 months of therapy.

Guidelines

The British Cardiac Society's *Recommendations on the management of pulmonary hypertension in clinical practice* published in 2001 was the first attempt to produce a clinical consensus document. It identified highly restrictive cardiac catheter based criteria for treatment with disease-targeted therapies based on retrospective UK data. These criteria for treatment are now outdated since the publication of many randomised trials which have used entry based on NYHA functional class, often with certain limits on six minute walk distance.

The UK clinicians are in the process of finalising an update on their 2001 document and this *Consensus statement on the management of pulmonary hypertension in clinical practice* will be published in autumn 2007. This will contain new treatment algorithms.

Since 2001 a major contribution has been made by the European Society of Cardiology (ESC) and the American College of Chest Physicians. In the UK, the ESC guidelines published in December 2004 are current.

The ESC and ACCP will probably publish updated guidelines in 2008. In addition the World Symposium on Pulmonary Hypertension will meet for the 4th time in February 2008 and produce recommendations as it has done previously in 2003 and 1997.

Alternative therapies to technologies being assessed

There are currently no important alternative therapies to those being assessed by NICE. While heart and lung transplantation is curative for PAH, it is beset with its own problems and limited survival. In practice few patients are transplanted because of lack of donor organs.

The only option for patients who are not treated is palliative care. It is noticeable how current disease-targeted therapies have helped to keep many patients out of hospital and at home. It would be expected that untreated patients would occupy hospital beds more frequently. For example, sick patients referred for the first time can often only be discharged from hospital once the disease-targeted therapy starts to become effective. Without treatment such patients would remain in hospital since they are too sick to discharge and often require high flow oxygen at levels which cannot be delivered at home or in a hospice.

There are now many therapies being investigated which would work in PAH through novel mechanisms. Of note, there is particular interest in anti-proliferative agents (eg statins, imatinib and

others) to reverse the intraluminal smooth muscle cell proliferation in the pulmonary circulation. There is also a trial of stem cell therapy. It is therefore expected that the choice of therapies and how they are best used will change rapidly over the next decade.

Treprostinil (subcutaneous and intravenous) and iloprost (intravenous) are not part of the current evaluation but are currently used in the UK. In addition, sildenafil is used in the form of Viagra (not being evaluated) as well as Revatio (which is being evaluated).

Implementation Issues

The guidance would affect delivery of care by designated centres making demand on resources to achieve this limited. The general nature of guidance could be put in place in three months.