NHS England

Clinical Commissioning Policy Proposition:

Pasireotide: An injectable medical therapy for the treatment of Cushing's disease

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Clinical Commissioning Policy Proposition: Pasireotide: An injectable medical therapy for the treatment of Cushing's disease

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Plain Language Summary

The policy describes NHS England's commissioning approach to pasireotide in the treatment of patients with Cushing's disease (CD).

Cushing's disease is caused by a tumour of the pituitary gland that secretes high levels of adrenocorticotropic hormone (ACTH). ACTH causes the adrenal gland to release high levels of the hormone cortisol. It is a rare condition with an incidence of 1-2 per million population per year. Cushing's disease shortens life expectancy because it is associated with a number of medical complications. Without adequate treatment, the mortality rate is about four times higher than that of the normal population, with the main causes of death being heart disease and stroke.

Surgery to remove the pituitary tumour is the primary treatment, however in a significant proportion of people (20-40%) this does not result in cure. In this group, other treatments will be required, which may include: repeated pituitary surgery, pituitary radiotherapy and / or adrenal surgery. Medical therapy is often used as part of the treatment pathway to control the condition, however it is not curative and cannot be used for extended periods because of potential side effects. There are different medical treatments - those that block the making of cortisol, those that stop the adrenal gland from releasing cortisol, those that block the action of cortisol and those that reduce the release of ACTH (pasireotide).

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of pasireotide in the treatment of patients with Cushing's disease. Whilst the evidence is limited, it is recognised that the low number of patients who might be suitable for pasireotide means that high quality level 1 evidence is unlikely to become available to support the commissioning position.

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission pasireotide in the treatment of Cushing's disease.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether pasireotide in the treatment of Cushing's disease will be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

2. The proposed intervention and clinical indication

Cushing's disease is caused by a tumour of the pituitary gland that secretes high levels of adrenocorticotrophic hormone (ACTH) that in turn drives the adrenal gland to secrete high levels of the hormone cortisol. It is a rare condition with an incidence of 1-2 per million population per year, with a 50% 5-year mortality in the untreated condition.

With modern diagnosis and management, the prognosis is greatly improved although the condition is still associated with considerable morbidity including: cardiovascular disease, infection, hypertension, osteoporosis, depression, and psychosis. Despite treatment, mortality is still significantly higher than control populations, with cardiovascular disease the greatest risk. This is due, in part, to delays in diagnosis and also the availability of effective therapy.

Medical treatment for Cushing's disease is commonly used as second line treatment following pituitary surgery when further curative treatment is planned. The most effective agents currently used are metyrapone and ketoconazole and whilst these medications are effective for the majority of individuals, their usefulness is limited by toxicity in a significant proportion of people. Pasireotide has been proposed as a beneficial, alternative medical therapy used within its licence for those patients who are intolerant to, or whose symptoms are not appropriately managed by, the conventional therapies.

3. Definitions

Cushing's disease is a sub-type of Cushing's syndrome caused by pituitary adenoma releasing high levels of adrenocorticotropic hormone (ACTH).

Pasireotide is a novel cyclohexapeptide, injectable somatostatin analogue. Like the natural peptide hormones somatostatin-14 and somatostatin-28 (also known as somototropin release inhibiting factor (SRIF)) and other somastostatin analogues. Pasireotide exerts its pharmacological activity via binding to somatostatin receptors.

4. Aim and objectives

This policy proposition aims to describe NHS England's commissioning approach for pasireotide in the treatment of Cushing's disease.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for individuals with Cushing's disease.

5. Epidemiology and needs assessment

Cushing's disease is a rare condition with an incidence of 1-2 per million population per year. For a significant proportion of patients (20-40%) primary pituitary surgery is not curative and further treatment is required. Medical therapy is used in order to manage the condition whilst waiting for curative treatment to become possible or effective. Consensus of professional opinion is that an estimated 25 patients per year in England require medical therapy at any stage in the pathway and that 5-10 may require treatment with pasireotide when metyrapone and ketoconazole have not been tolerated or are not clinically effective (see section 8).

Cushing's disease is a heterogeneous disorder requiring a multi-disciplinary and individualised approach to patient management. Generally, the treatment of choice for Cushing's disease is curative surgery with selective pituitary resection. Second-line treatments include more radical surgery, pituitary radiation therapy, medical therapy, and bilateral adrenalectomy.

Because of the significant morbidity of Cushing's disease, early diagnosis and prompt therapy is important.

6. Evidence base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of pasireotide in the treatment of patients with Cushing's disease. Whilst the evidence is limited, it is recognized that the low number of patients who might be suitable for pasireotide means that high quality level 1 evidence is unlikely to become available to support the commissioning position.

The evidence for clinical effectiveness of pasireotide in Cushing’s disease (CD) comes from a single drug-company sponsored, relatively large, randomised study (Colao et al, 2012). This Phase III trial of pasireotide in CD was a multicentre study that included 162 patients with persistent or recurrent disease or who were ineligible for surgery. 128 patients had a history of pituitary surgery for the treatment of their Cushing’s disease, 78 were on medication and 7 had a past history of pituitary irradiation. Patients were randomized to receive pasireotide 600 µg(n = 82) or 900 µg (n = 80) subcutaneously twice daily for 12 months. There were high and similar levels of drop outs in both treatment arms. The rate of drop out remained broadly steady throughout the trial period (29 by month 3, another 26 by month 6 and 29 more by month 12). In total 26 were for adverse events, 37 for lack of

efficacy and another 21 either withdrew consent or breached the protocol.

Only the higher initial dose regime arm met the primary outcome measure (normalised urinary free cortisol) – which was a cohort of 53 at month 6. The authors correctly conclude that it would have been unethical to have a non-treatment control group, but also state there was no comparator arm as there is "no approved medical therapy". There are several concerns within the methodology including the lack of a comparator treatment arm and the shifting nature of patients between randomised and open-label participants.

An additional limitation of the Phase III study is the imbalance in baseline UFC levels between the two treatment groups (higher in the 600 µg group), which may have had an effect on outcomes. The mean daily dose of pasireotide in both treatment groups also increased over the 12 months study period (1353 µg/day in 600 µg group vs 1813 µg /day at month 12) suggesting the actual effective dose is likely to be much higher than the 600 µg and 900 µg dosage used in the study. The lack of blinding also increases the possibility of bias in the study - after month 3 only patients who met the primary endpoint continued in a double blind fashion through to month 6 and the rest entered into an open label phase. All patients were entered into an open label phase after 6 months of study. It is likely that this unbinding could have introduced some bias, more so in relation to patient reported outcome measures. As the primary outcome measure was based on urine estimation of UFC, it is recognised that unbinding is unlikely to have influenced the primary outcome measure.

There are two further publications based on data from this trial providing an analysis of the impact of pasireotide on secondary outcome measures (Pivonello et al, 2014) and quality of life (Webb et al, 2014). Decreases in urinary free cortisol from baseline to months 6 and 12 were statistically significant in both treatment groups ($P < 0.001$). Normalisation of urinary free cortisol was more likely to be achieved in patients with lower baseline levels than in patients with higher baseline levels. Most patients (approximately 90%) whose hypercortisolism was uncontrolled (UFC>ULN but with ≤ 50% reduction from baseline) at months 1 and 2 continued to have uncontrolled hypercortisolism at months 6 and 12 indicating patients unlikely to have a response to pasireotide can be identified within the first few months of treatment. Significant improvements in other secondary outcomes measures were seen including systolic blood pressure ($P = 0.03$), diastolic blood pressure ($P = 0.03$), low-density lipoprotein (LDL) cholesterol ($P < 0.001$) and weight ($P < 0.001$).

The impact of pasireotide on quality of life was studied using Cushing QoL. Cushing QoL increased as mUFC levels declined but a statistically significant correlation of -0.40 ($p<0.01$) was observed from baseline to 12 months and not at 6 months. This relation was maintained even after adjusting for number of variables through regression analysis. There was moderately large (0.53) effect sizes for Cushing QoL improvements from baseline to 6 months and 12 months. A strong correlation ($r=-0.70$) was observed between Cushing QoL and Becks Depression Index-II indicating lower QoL was associated with greater depression severity.

Long term effects of pasireotide (up to 4 years) have been reported in two studies (MacKenzie et al, 2014 and Simeoli et al, 2015). Both involved the study of a small number of phase 3 trial patients entering into an extension phase of treatment. Simeoli et al demonstrated that after 24 months of treatment of 8 patients with microadenoma with

pasireotide, a significant (>25 %) reduction in tumour volume was found in 62.5 % and in 100 % of patients after 6 and 12 months, respectively. The study by MacKenzie et al, 2014 involved 4 patients in an extension phase, of these two patients had sustained biochemical and clinical response after 9 months of treatment. All 4 patients developed glucose intolerance and complications included second degree atrioventricular block type 1 without QT prolongation in one patient with pre-existing sinus bradycardia, and symptomatic cholelithiasis requiring cholecystectomy.

There are no published studies evaluating cost effectiveness of pasireotide. Similarly there are no published studies comparing pasireotide with other drugs used in management of Cushing's disease or studies evaluating pasireotide in combination with other drugs used in CD.

The evidence of effectiveness on a number of other drugs used in CD comes from limited number of small retrospective case series with varying definition of primary end point and therefore difficult to compare effectiveness against each other.

7. Proposed criteria for commissioning

Pasireotide should be used, according to its licensed dose, for patients with Cushing's disease requiring medical therapy who have not achieved control, or who are unable to tolerate, metyrapone and ketoconazole.

As a number of treatment modalities are available, patients will have their condition managed by a full multi-disciplinary team with access to a dedicated pituitary surgeon, pituitary endocrinologist, laparoscopic adrenal surgeon and pituitary radiotherapist. The decision to use pasireotide must be endorsed by the patient's multi-disciplinary team (with experience in the management of Cushing's disease) with support from other relevant service areas.

Pasireotide may only be used where a definitive curative therapy is planned (further surgery, radiotherapy or bilateral adrenalectomy) and should only be used for a defined period (for example, while waiting for radiotherapy treatment to become effective or to stabilise prior to surgery). In all cases initial therapy will be for a defined period of 2 months. Pasireotide therapy may continue if tolerated by the patient and if measures of cortisol production show a 50% fall compared to levels measured before commencing treatment. Cortisol production must be monitored every 2 months with a trial of withdrawal as cortisol production returns to the normal range.

Exclusions: Patients who require medical therapy but have not trialed,and are not contraindicated to, metyrapone and ketoconazole. Patients who are contraindicated to pasieriotide as per the licence.

Starting Criteria: Pasireotide may be used as defined above.

Stopping Criteria: Pasireotide will be stopped if treatment is not tolerated by the patient. Pasireotide will be stopped if measures of cortisol production do not show an improvement at 2 months and a 50% fall from baseline at 4 months. Pasireotide will be withdrawn when

definitive therapy becomes effective. This may require a trial period off pasireotide therapy to demonstrate normal or low cortisol production (pasireotide may need to be reinstated if unsuccessful).

8. Proposed patient pathway

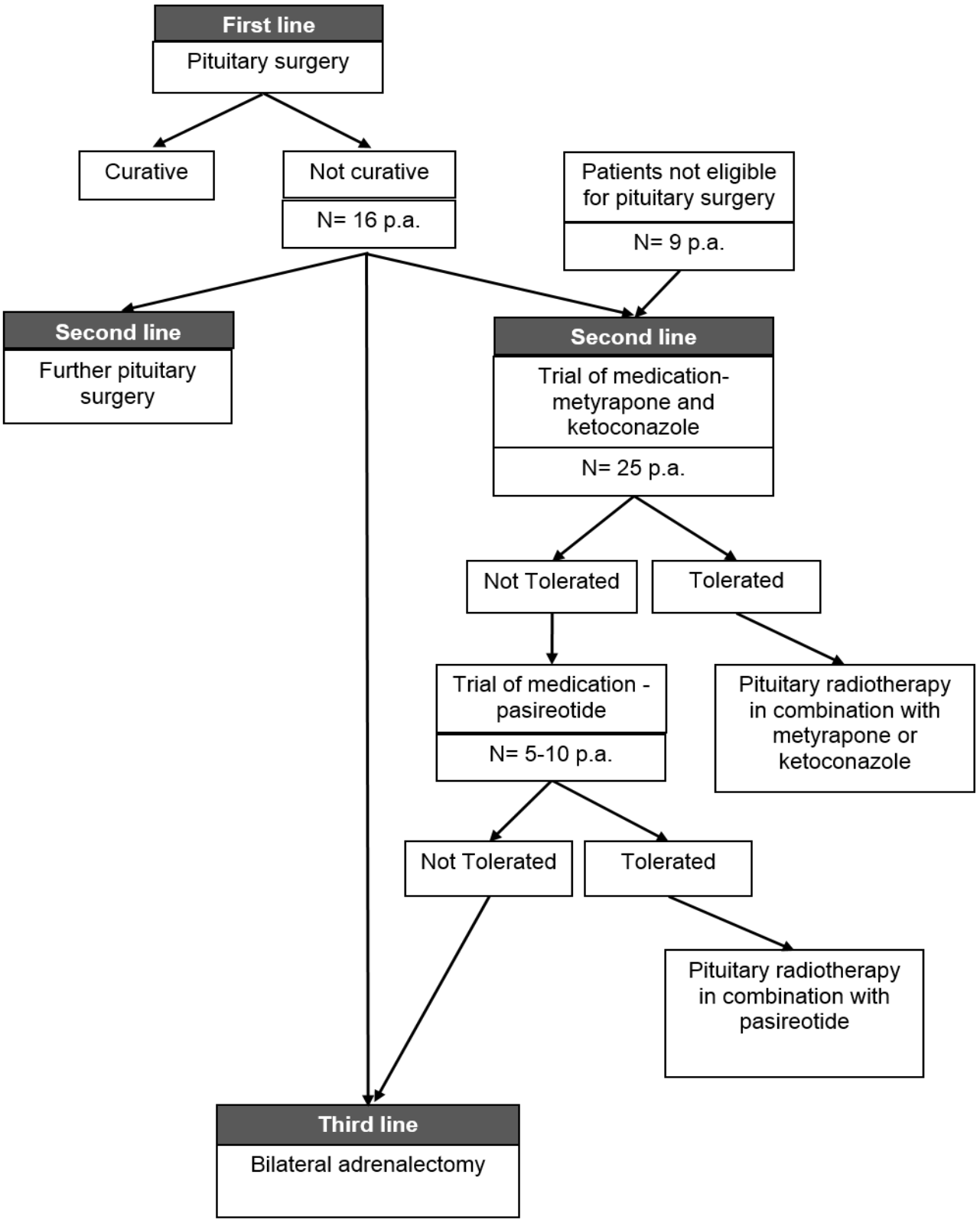
Patients with recurrent/persistent Cushing's will have their condition managed by a full multi-disciplinary team with access to a dedicated pituitary surgeon, pituitary endocrinologist, laparoscopic adrenal surgeon and pituitary radiotherapist. The structure of the service will be developed locally, however will usually involve joint care between local hospitals and specialised centres.

Primary treatment for Cushing's disease is pituitary surgery. For a significant proportion of patients (30-40%) this is not curative and radiotherapy to the tumour remnant can result in cure over the following months or years. Medical therapy is most commonly used at this stage in order to manage the condition whilst waiting for radiotherapy to become effective. In all cases where medical therapy is prescribed, pasireotide is proposed as a second line treatment where metyrapone and ketoconazole have not been tolerated or are not clinically effective. Pasireotide should only be used for a defined period for patients who are on a curative pathway - for example patients who are waiting for radiotherapy treatment to become effective or require additional condition management prior to surgery. The current licenced indication is for a two month initial period with regular monitoring of cortisol levels to ensure continued efficacy during and beyond this initial phase.

For some patients who are unable to tolerate medical therapy, adrenalectomy may be considered as a more radical approach to reduce treatment time.

In summary, the treatment pathway for an individual patient can be complex and medical therapy may be used at a number of stages to stabilise the condition however it will not in itself result in a long-term cure. Patients who do not receive or respond to curative therapy would likely require lifelong palliative support.

A flow diagram of the most common patient pathway is outlined below.



- In addition, some patients may require medical therapy prior to surgery to improve metabolic status.

9. Proposed governance arrangements

The service specification for Specialised Endocrinology describes the care pathways and key aspects being commissioned and should be referred to in conjunction with this policy. Accurate assessment of disease activity is essential to determine both the eligibility for pasireotide and assessing efficacy of treatment. This will require a multidisciplinary assessment of disease by clinicians experienced in assessing and treating Cushing's disease.

10. Proposed mechanism for funding

Pasireotide will be funded through local Specialised Commissioning teams.

11. Proposed audit requirements

Clinicians will be required to record both short term and long term outcomes of individuals with Cushing's disease who receive pasireotide, including consistent monitoring of the patients' cortisol levels.

12. Documents which have informed this policy

2013/4 Specialised Commissioning Service Specification for Specialised Endocrinology Services (Adult) [A03/S/A]

13. Date of review

This document will lapse upon publication by NHS England of a commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016)