Health Technology Appraisal

GUIDANCE ON HUMAN GROWTH HORMONE (SOMATROPIN) IN ADULTS WITH GROWTH HORMONE DEFICIENCY

Post Appeal Considerations

Following the appeal hearing, the appraisal committee has been asked to reconsider its advice to the Institute on the use of HGH in adults, specifically in three areas:

1. Identification of a group of HGH deficient adult people who would derive most benefit from hormone replacement therapy, and to develop selection criteria for this group if possible.

2. The guidance relating to the continuity of treatment into adulthood for children who have been receiving HGH therapy

3. To ensure that any particular needs of survivors of childhood cancer with 'iatrogenic' pituitary failure are adequately considered.

This paper aims to outline issues related to these aspects of the guidance, as considered by the Committee in reaching their conclusion.

Additionally we have identified the main areas in need of consideration prior to the next meeting of the appraisals committee.

1. Identification of adult patient groups who would most benefit from HGH treatment

The evidence base

Both the Southampton and the ScHARR assessment reports reviewed the randomised control trial (RCT) evidence on quality of life as assessed principally by the QoL AGHDA questionnaire[1]. It was apparent that the RCTs were generally of poor quality and several shortcomings were identified, including the use of out-dated treatment regimens (most trials used a weight-based regimen as opposed to the dose-titration method currently in use) and concerns regarding the appropriateness of the patient selection criteria (patients often had good quality of life before beginning treatment). Thus although it seemed possible (although not proven) that HGH therapy conferred some benefits to adults with

[1] QoL_AGHDA is a 25-point scale, disease- specific quality of life questionnaire, in which the higher score corresponds to worse QoL. .

HGH deficiency in terms of improvements in their quality of life, identification of the sub group in whom this benefit was most apparent was more difficult.

The ScHARR assessment report also reviewed the observational data (including the KIMS database), which indicated a clearer advantage of HGH therapy in terms of quality of life. The evidence supplied by professional and patient/carer groups further supported the results from the observational data. However, it has been difficult to quantify the treatment effect attributable to HGH in these observational studies, in the absence of a control group. The magnitude of this reported effect also varied widely, with estimates (of improvement) from different studies ranging between 2.8 and 7.2 points on the QoL AGHDA scale[2], the mean change being 3.7 points.

Two RCTs, available in abstract form only, investigated the efficacy of HGH on improving quality of life using the QoL-AGHDA questionnaire. One of them reported a small improvement on this scale in favour of the placebo group compared to the HGH treated group, although this was not statistically significant. The other RCT (McKenna et al) estimated that the overall treatment effect for HGH against this scale was of the order of an improvement of 2.7 points, which can be translated into a change in utility of 0.047 QALYs. This estimate was used in the 'McKenna 1 scenario' of the ScHARR economic model. The other scenario in the ScHARR economic model (ScHARR optimistic scenario) used the utility estimate from the observational data (from KIMS database), which was between 0.02 – 0.12 QALY.

The ScHARR economic analysis suggested that the overall incremental cost effectiveness ratio (ICER) for HGH treatment across all patients is over £45,000 per QALY for the ScHARR optimistic scenario, and over £90,000 per QALY for the scenario in which the estimated utility gain was taken from the RCT (McKenna trial) which reports a treatment-related improvement in QoL-AGHDA scores. The ICER (for the optimistic scenario) was estimated to be £37,000 per QALY for those who had QoL-AGHDA score of more than 16, and over £47,000 per QALY for those who had the QoL-AGHDA score of between 11 and 15. See Figure 1.

[2] QoL_AGHDA is a 25-point scale, disease- specific quality of life questionnaire, in which the higher score corresponds to worse QoL. .

Figure 1: ICER for HGH by age and AGHDA group

QoL AGHDA group					Overall by AGHDA
	18-30	31-55	56-64	65+	
0-5	*	*	*	*	
6-10	£124,941	£114,789	£94,866	£38,185	£94,123
11-15	£55,358	£50,884	£42,420	£27,885	£47,471
16+	£40,746	£37,483	£30,971	£25,286	£36,738
Overall	£45,136				

Overall results calculated by using current age/AGHDA proportions of treated patients in UK(KIMS) –see figure 2

The assessment report also considered the long-term effects of HGH deficiency such as cardiovascular morbidity and mortality and the possibility of reduction in bone fractures secondary to improvements in bone mineral density. Although it was accepted that there could be long-term benefits associated with HGH use for both of these clinical endpoints, the assessment team's analysis convincingly showed that any potential long-term benefits would not have a significant impact on the cost-effectiveness estimates. Thus these potential long-term benefits for HGH treatment accounted for less than 3% of the cumulative costs and less than 1% of the total QALYs gained. Therefore, the long-term benefits will not be further scrutinised as it is considered highly unlikely (even in the most optimistic of circumstances) that this 1-3% effect will be crucial in determining the overall cost-effectiveness of HGH treatment.

Issues to be considered: -

1) There is no obvious correlation between the biochemical indicators of the severity of HGH deficiency and the clinical presentation or the quality of life status of the person with HGH deficiency.

2) The QoL-AGHDA questionnaire is commonly used in clinical trials, but it is understood that its use is less wide-spread in daily clinical practice. There are also some concerns regarding the robustness of this instrument in both identifying people with very poor QoL and in monitoring the efficacy of HGH treatment in day-to-day clinical practice.

3) The evidence from the KIMS database, indicates that in current clinical practice HGH treatment is being prescribed to people with a wide range of perceived impairment of QoL as assessed by the reported QoL-AGHDA

scores. Thus 57% of the patients receiving HGH treatment have QoL-AGHDA scores below 16 (i.e. only mild to moderate impairment of QoL), which on the evidence available is not the most cost-effective way to use HGH therapy. See Figure 2.

There remains, therefore, concerns that the current patient selection criteria fails in identifying those patients in whom the benefit of HGH treatment is both clinically and cost effective.

Figure 2: Age/AGHDA breakdown in UK (KIMS)

	Age			
QoL- AGHDA Score at baseline	18 - 30	31 - 55	56 – 64	65+
0-5	2%	7%	2%	2%
6-10	2%	10%	3%	2%
11-15	4%	15%	4%	2%
16+	9%	25%	8%	1%

4) The current evidence on the relative efficacy of HGH in different sub-groups and the economic analysis relates to subgroups based on age and the QoL-AGHDA score only. Any suggestion of other potential subgroups needs to be supported by evidence (of sufficient quality) that the utility gains would be large enough for this group to ensure cost-effectiveness when these values (in terms of QALY gained) are assessed within the available economic models.

5) Identification of lack of response after an initial period of treatment is also an important consideration in order to ensure that treatment is stopped in those individuals. The 'stopping' criteria in terms of quality of life improvement, incorporating the QoL-AGHDA scoring system should be defined in patients for whom HGH treatment does not prove to be effective after a defined time period.

2. Continuity of treatment from childhood to adulthood

There remains uncertainty regarding the appropriate management of individuals who have been treated with HGH during childhood as they move into adulthood, mainly due to the lack of evidence on this area. This transitional phase is of importance to all children who have been treated with HGH under the guidance published by the Institute, including those with growth failure due to HGH deficiency as well as those with renal failure, Turner's syndrome and the Prader-Willi syndrome.

In the present guidance for children with growth hormone deficiency and growth failure it is suggested that: -

“After attainment of final height, GH therapy will normally be discontinued, but it should not be discontinued by default. The decision to stop treatment should either be made by a paediatrician with special expertise in the management of children with GH disorders in consultation with patient and carers, or therapy should be continued until re-evaluation by an adult endocrinologist has been undertaken. The transition to adult care for people with GH disorders will require a close collaboration between the responsible clinicians.”

It is suggested that the guidance should be further clarified on the use of HGH for this group of patients.

Issues to be considered: -

1) When should children with HGH deficiency consider stopping HGH treatment? For example:
   a) After reaching predicted adult height
   b) After attaining adult bone mineral density
   c) When the stability of other physiological parameters is achieved

2) Under what circumstances is continuation of HGH treatment into adulthood justified? For example:
   a) In all individuals who have received HGH during childhood
   b) Those in whom it is considered that discontinuing HGH would lead to significant deterioration in health however defined
   c) Those in whom QoL deteriorates significantly after stopping HGH treatment

3. Survivors of childhood cancer

It is suggested that the guidance considers the needs of survivors of childhood cancer (with iatrogenic pituitary failure) specifically.

Issues to be considered:

1) What is the evidence for the use of HGH treatment in these patients relative to its use in other individuals with HGH deficiency?

2) What is the available evidence on the clinical and cost effectiveness of HGH treatment of these patients?