The clinical effectiveness and cost-effectiveness of pegvisomant for the treatment of acromegaly: a systematic review

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CRD summary
This generally well-conducted review concluded that pegvisomant was highly effective for improving IGF-1 levels in patients with acromegaly, but the evidence for its impact on signs and symptoms, quality of life, compliance and safety was lacking. The reliability of the conclusions is compromised by the paucity of good quality evidence.

Authors' objectives
To evaluate the clinical and cost-effectiveness of pegvisomant for the treatment of acromegaly in patients whose insulin-like growth factor 1 (IGF-1) levels fail to normalise after other treatments.

Searching
MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, DARE, CINAHL, ZETOC, National Research Register, ClinicalTrials.gov, the Endocrine Society’s 88th annual meeting abstracts and bibliographies of included studies and relevant reviews were searched without language restrictions. The search strategy was reported. Search dates spanned 1950 to 2007. Experts were contacted to identify further published and unpublished studies. Abstracts were excluded.

Study selection
Any study that evaluated pegvisomant for the treatment of acromegaly compared to any other treatment or no treatment, or which provided before and after data, and reported relevant clinical outcomes was eligible for inclusion if it included 10 or more patients. The dose of pegvisomant varied from 10 mg to 60 mg daily, titrated upwards over time (with or without a loading dose of up to 140 mg) unless combined with a long-acting somatostatin when the dose was 25 mg per week. The duration of treatment/follow-up ranged from 12 weeks to two years. Most studies had patients that were treated previously with surgery, radiotherapy and/or a somatostatin or dopamine agonist. The authors stated neither how studies were selected for the review nor how many reviewers performed the study selection.

Assessment of study quality
Randomised controlled trials (RCTs) were evaluated in terms of randomisation, allocation concealment, blinding, losses to follow-up and methods of analysis. Non-RCT studies were assessed in terms of eligibility criteria, patient spectrum, description of clinical details, method of diagnosis, reporting of individual patient data, blinding, follow-up duration and withdrawals. Validity was assessed by one reviewer and checked by a second.

Data extraction
Where reported, changes from baseline in serum growth hormone and IGF-1, signs and symptoms, tumour volume, inflammatory, bone and cardiovascular disease markers, median serum leptin, echocardiography findings, finger size and safety outcomes were extracted. Data were extracted by one reviewer and checked by a second; disagreements were resolved by consensus.

Methods of synthesis
Studies were combined in a narrative synthesis. Study details were presented in tables. Differences between studies were discussed in the text.

Results of the review
Eighteen studies met the inclusion criteria (n was at least 818 and the range was 10 to 177): one RCT (n=112) from which the placebo group was used for two subsequent placebo-controlled before/after studies (n=75); 13 uncontrolled before/after studies (n=558); one retrospective case series (n=142); and one retrospective uncontrolled before/after study (n=118). The RCT did not report the method of randomisation or allocation concealment. It was described as double blind, but provided no detail. And it did not use an intention to treat analysis. Only four of the non-randomised studies reported methods of sample selection, three reported the method of diagnosis, two reported blinding of outcome.
assessors and seven stated reasons for withdrawals.

The RCT reported statistically significant improvements (p≤0.05) in scores for soft tissue swelling and excessive perspiration and reduction in finger ring size for the two high-dose groups (15 mg and 20 mg daily). There were increases in adverse events at the highest dose and improvement in fatigue, reduction in serum IGF-1 values and increases in growth hormone levels for all treatment groups compared to placebo. No difference in tumour size was observed. Results from the non-randomised studies generally reflected those of the RCT.

Cost information
Pegvisomant was unlikely to be cost-effective compared to standard treatment in relation to applied value-for-money criteria.

Authors' conclusions
Pegvisomant was highly effective for improving IGF-1 levels in patients with acromegaly. Evidence for its long-term impact on signs and symptoms, quality of life, compliance and safety was lacking.

CRD commentary
The authors addressed a clear research question. An extensive search was undertaken, including attempts to reduce both language and publication bias. Validity assessment and data extraction were conducted in duplicate, however, it was unclear whether similar methods to reduce bias were employed during study selection. Validity assessment was assessed using appropriate criteria and data presented in relation to level of evidence. The authors highlighted that baseline characteristics were poorly reported and it was unclear whether the population studies reflected that seen in clinical practice. The decision to present the results in a narrative synthesis seemed appropriate. This was a generally well-conducted review, however, the reliability of the conclusions is compromised due to the paucity of good quality evidence.

Implications of the review for practice and research
Practice: The authors did not state implications for practice.

Research: The authors stated that longer-term studies monitoring IGF-1, growth hormone levels and safety, primarily as national or large regional registries that have high levels of follow-up were required. Areas where studies were needed included quality of life, compliance, economic analysis of the use of pegvisomant as an alternative to radiotherapy and repeated economic analyses as more data become available.

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Bibliographic details

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Other publications of related interest

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.