Society for Endocrinology media release

For immediate release

Drugs fail to meet hormone targets in control of rare growth disorder

Over a quarter of UK patients treated for growth hormone-producing tumours do not achieve 'safe' growth hormone (GH) levels, according to a 30 year UK multi-centre study of clinical management of the rare disease acromegaly. The findings by the Society for Endocrinology UK Acromegaly Register, published in the November issue of *Clinical Endocrinology*, show that drugs to control acromegaly often fail to bring the disease completely under control in routine clinical practice.

Acromegaly is caused by a benign, GH-producing tumour in the pituitary gland, which normally releases GH in a controlled daily rhythm. GH promotes the release of IGF-1, and together an excess of these two hormones gradually manifests the symptoms of acromegaly which can include an increase in the size of the hands and feet, thickening of the skin and a change in facial characteristics. Only when the tumour occurs in childhood can this lead to an increase in height. Comorbidities include high blood pressure, diabetes and arthritis. High GH levels are associated with decreased life expectancy, and it has been suggested that IGF-1 also contributes to mortality risk, therefore 'control' of the disease aims to suppress GH and IGF-1 levels to a threshold that is accepted as safe (defined in this study as <2µg/L GH and normal IGF-1).

The UK Acromegaly Register was established to collect a meaningful volume of data on real life clinical management of acromegaly, which with a prevalence of about 60 per million is rarely encountered in clinical practice. It is the largest such national registry. 32 UK centres submit data to the registry, comprising over 2500 patients with acromegaly treated over 30 years. Data on GH and IGF-1 levels and treatment regimens were collected throughout the patients' history, which can involve multiple surgical/radiological procedures and courses of medication; 4206 courses of medical treatment were recorded in total.

The researchers, led by Dr Trevor Howlett of University Hospitals of Leicester, describe a general improvement in the management of acromegaly over three decades: mean GH levels dropped over time and the percentage of patients achieving control of GH, IGF-1, and both, increased.

"*We suggest that improvement in the management of acromegaly is due to improved surgical outcomes, which we demonstrated in a previous paper, and to the development of new drugs, as we found no evidence of drift in the data due to improved assay techniques*" said Dr Howlett.

IGF-1 appeared more difficult to control than GH and, despite a general improvement, across all treatment courses 'control' of both GH and IGF-1 levels was achieved in fewer than 40% of samples on average during that course, and control of GH levels alone was achieved in only 75% of samples on average**.** When these data were analysed by the type of treatment course, whether

the course was preceded by surgery or radiotherapy, whether the course was the latest and was used long-term (suggesting that it was continued and considered to be clinically effective, instead of being trialled and quickly abandoned), and stratified by the pre-treatment GH-levels, the researchers made a number of observations:

- Control with medical treatment is more likely when the baseline GH level pre-treatment is lower.

- Control of GH was significantly better in patients who had received surgery and/or radiotherapy before their medical treatment – probably because the basal GH was then lower although still not fully controlled.

- The newer drugs (somatostatin analogues) tended to give better control of both GH and IGF-1 than an older class (dopamine agonists), although control of GH alone was similar (75% for both).

- Control of both GH and IGF-1 on long-term somatostatin analogues was achieved in an average of 55% of samples, and in 36% on long-term cabergoline (a dopamine agonist).

- Of the somatostatin analogues, newer, longer-acting preparations achieved greater control of both GH and IGF-1, although this does not take into account lower pre-course levels.

- At most, 40% of patients on somatostatin analogues were not on the maximum therapeutic dose, despite the fact that control was achieved in only around 70% of samples in these courses.

This 'real life' study emphasises that full medical control of acromegaly may be far more plausible in the context of a closely-controlled clinical trial than it is in routine clinical practice. In terms of control of acromegaly by medical treatment, the highest percentage control was achieved when surgery or radiotherapy was employed. The newer somatostatin analogues were more successful than the older dopamine agonists at controlling GH and IGF-1, which could be improved even further by more appropriate dose escalation. The researchers now aim to establish whether control of both GH and IGF-1 is necessary to restore morbidity and mortality in these patients, or whether control of GH alone is an adequate target.

Dr Trevor Howlett, lead author and Consultant Endocrinologist at University Hospitals of Leicester said:

"*The UK Acromegaly Register aims to investigate how acromegaly, which is a very rare disease, is being managed in the hospital setting.*

"*Endocrinologists treating acromegaly aim to bring their patient's growth hormone and IGF-1 levels under control to an accepted target, which has been defined from closely-controlled trials of the drugs and from studies linking raised growth hormone with mortality. This study suggests that in real-life clinical practice, the targets are not being met for many patients*.

"It seems we are not generally optimising the dose of some drugs despite incomplete control. This could be improved. As high growth hormone is associated with reduced life expectancy we should perhaps also be more ready to consider additional surgery or radiotherapy if control is not achieved with drugs.

"*Whilst growth hormone targets are developed from accepted mortality data, there is less published support for IGF-1 targets. We next aim to investigate whether control of both growth hormone and IGF-1 is necessary to prevent morbidity and mortality in these patients."*

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Notes for Editors:
This research is published in the November 2013 issue of *Clinical Endocrinology,* DOI: 10.1111/cen.12207. The abstract is reproduced below.

Please mention the Society for Endocrinology meeting in any story

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The Society for Endocrinology is Britain's national organisation promoting endocrinology and hormone awareness. For general information, please visit our website: http://www.endocrinology.org

For more information on acromegaly, endocrinology and hormones please visit You & Your Hormones (www.yourhormones.info), the Society for Endocrinology's public information website.

More information on the UK Acromegaly Register can be found at the Society for Endocrinology website.

ABSTRACT

Control of growth hormone and IGF1 in patients with acromegaly in the UK: responses to medical treatment with somatostatin analogues and dopamine agonists

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Objective
We investigated the control of GH and IGF1 in acromegaly in routine clinical practice in the UK on and off medical treatment.

Design

The UK Acromegaly Register collected routine biochemical and clinical data on patients with acromegaly from 31 UK centres with GH data covering >30y.

Patients
We identified 2572 patients. Somatostatin analogues (SMS) were used in 40·6% and dopamine agonists (DA) in 41·4%.

Measurements
We identified 29,181 GH records linked to data on IGF1, surgery, radiotherapy and medical treatment and derived data on 9900 distinct Periods of Care including 4206 courses of medical treatment. We considered GH controlled when ≤2 µg/l.

Results
Control of GH and IGF1 improved over time, particularly on medical treatment. Control on medical treatment was better after prior surgery and/or radiotherapy. On long-term SMS, GH was controlled in 75%, IGF1 in 69% and both in 55%; on long-term DA, GH control was similar but IGF1 worse (77%/55%/45%). Responses to long-term treatment with octreotide LAR and lanreotide autogel were broadly similar, but we noted a failure to escalate SMS to maximal effective dose. Increasing precourse GH levels were associated with a decreasing proportion who achieved control, despite greater suppression from baseline.

Conclusions
Control of acromegaly in the UK is improving, but 'safe' GH levels are still only achieved in 75% on long-term medical treatment, with GH and IGF1 both normalized in no more than 55% on SMS and 36% on cabergoline. It remains unclear whether the control of GH, but not IGF1, observed in many patients is sufficient to restore long-term morbidity and mortality to normal.