

# Acromegaly: an update

4th Annual European Meeting on the Management of Acromegaly  
Rome, Italy, 25–26 October 2013



This issue of *ESE News* is the first to provide you with insights into the latest endocrine developments from a recent conference, in this case on the topical issue of acromegaly.

The 4th Annual European Meeting on the Management of Acromegaly took place in Rome, Italy, on 25–26 October 2013. The event was initiated and sponsored by Pfizer, as part of their 'Endocrinology FIRST' programme. It attracted more delegates than in previous years – 224 attendees from 25 countries, a truly global representation.

Roy Gomez (Medical Director for Endocrine Care Europe, Pfizer) welcomed delegates to the meeting. Christian Strasburger (Berlin) then introduced the event on behalf of the faculty and the Scientific Planning Committee (comprising Christian Strasburger, Felipe Casanueva (Santiago de Compostela), Ezio Ghigo (Turin) and AJ van der Lely (Rotterdam)).

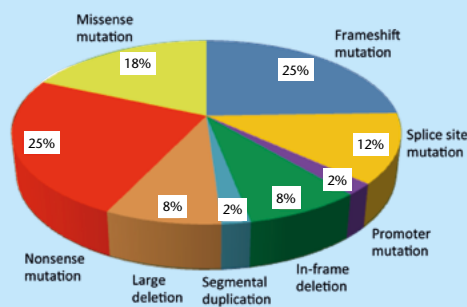
**'It is striking that 40% of patients are still poorly controlled'**

**Sebastian Neggers**

The independent programme was designed to discuss the latest information on the medical treatment of acromegaly, including sharing the perspectives of various countries, a debate on the use of cabergoline, acromegaly in pregnancy, and new treatment modalities.

## Genetics of acromegaly

Lawrence Frohman (Chicago) described genetic causes of acromegaly during the opening plenum. About 5% of pituitary tumours have a familial/genetic origin. They may occur as part of a mixed pattern, in MEN-1, MEN-4, McCune-Albright syndrome and the Carney complex. As regards isolated familial pituitary tumours, a breakthrough publication in 2006 (Vierimaa *et al.* 2006 *Science* **312** 1228–1230) described mutations in the *AIP* gene, which is believed to have a tumour suppressor role, in families in northern Finland with acromegaly and prolactinoma. Some 70 mutations of this gene have been described to date.



Types of mutation of the *AIP* gene: 70 mutations have been described to date (modified from Ozfirat & Korbonits 2010 *Molecular and Cellular Endocrinology* **326** 71)

Typically, somatotrophinoma patients with the *AIP* mutation:

- are diagnosed earlier
- have larger and more aggressive tumours
- are cured by surgery in only 25% of cases
- have a higher requirement for surgery to be repeated
- are more likely to be resistant to somatostatin analogues (SSAs)
- show poorer control after 12 months' therapy

Thus, these patients need to be watched particularly carefully. Their family members also need to be tested for gene mutations (as should those with a family history of pituitary tumour or gigantism).

## Breakout session

In discussions, the groups agreed that young patients (age at first symptoms below 30 or 40), giants, those with a family history of acromegaly or other endocrine tumours and patients with large and aggressive tumours that were resistant to medical treatment should have their genetic profiles investigated.

The groups also agreed that there were clinical benefits in diagnosing genetic causes of acromegaly:

- for the patient, since tumours with genetic causes of acromegaly tend to respond less well to surgery and medical treatment, so doctors caring for them would be more ready to treat the tumours aggressively and to follow them up more frequently; doctors would also search for other tumours in these patients
- for the relatives, as they have the opportunity for genetic counselling and testing, which would improve their clinical care and be useful for those who want children



## Cabergoline in acromegaly – a debate

The first scientific session saw a debate on the use of the dopamine agonist (DA) cabergoline in acromegaly, moderated by John Wass (Oxford).

### In favour

Philippe Chanson (Paris) spoke for cabergoline, encouraging doctors to try the drug since ‘an old drug may not be so bad for you’. Its practical value has been overshadowed by the advent of the SSAs, he said.

A meta-analysis of 15 studies showed that cabergoline treatment normalised insulin-like growth factor-I (IGF-I) levels in 34% of patients. When cabergoline was added to SSA treatment, more than 50% of patients achieved IGF-I levels within the normal range. Similarly, in a prospective trial, the combination of low-dose cabergoline with low-dose pegvisomant gave significantly better normalisation rates than either monotherapy in SSA-resistant patients.

Cabergoline is comparatively cheap, is given orally and is well-tolerated. It is no less effective than SSAs and the ‘usual’ dose of pegvisomant, and deserves to be tried in acromegaly patients.

### Against

The case against cabergoline was put by Diego Ferone (Genoa). Numerous studies have demonstrated the efficacy of SSAs as first-line therapy in newly diagnosed

patients with acromegaly, he said. By contrast, high quality studies are not available for efficacy of cabergoline.

Dr Ferone challenged Dr Chanson’s interpretation of the meta-analysis of the place of cabergoline, saying that some of the studies included were of poor quality. The meta-analysis could not be used to guide therapy. He concluded that cabergoline was viable therapy only for patients with minimally active disease.

### The audience’s view

- It would be difficult to conduct a placebo-controlled trial, since we already have effective agents
- Cabergoline has weak efficacy, which disappears with time
- We live in an era of individualisation of patient care. Intervention with cabergoline is benign and secures an answer very rapidly; it can be helpful in individual patients
- Tailoring of therapy makes sense since patients have different types of tumour

### The vote

The case for cabergoline was carried by 50 votes to 17.

## Maxillofacial surgery

The surgical procedures that may be used to correct facial anatomy in acromegaly were described by Rutger Schepers (Groningen). The facial characteristics are prominent brow, cheekbones and jaw; separation of the teeth; vertical enlargement of the lower third of the face; and thickening of the skin of the forehead. Patients are asked to bring photographs to the surgeon to trace the evolution of their face over the course of the disease.

- Due to late diagnosis, many patients have irreversible craniofacial malformations
- These malformations can be corrected to balanced proportions with skeletal and soft tissue procedures
- Psychological counselling is very important, partly to make sure that expectations are realistic
- The aim is to balance the features, though coarsened facial aspects must be accepted
- The patient’s disease must be stable before surgery can be considered

## Breakout session

Participants were asked how they managed acromegaly in pregnancy. First, if the patient wants to become pregnant, medication might be discontinued. Are drug treatments for acromegaly safe during pregnancy? They probably are, but pregnant women are reluctant to take drugs. In an ideal world, doctors would prefer to discontinue drug treatment and to monitor the patients’ symptoms, but the decision would depend on tumour size, how aggressive the disease was, and on biochemical control. Most felt happier with DAs than SSAs, but others preferred SSAs, especially if the patient had visual defects. If the patient is well controlled on pre-pregnancy medication then that should not be changed.

## Pregnancy

Philippe Chanson (Paris) reviewed what we do and don’t know about acromegaly and pregnancy. Research from France considered 46 pregnant women with active acromegaly (Caron *et al.* 2010 *Journal of Clinical Endocrinology and Metabolism* **95** 4680–4687): they produced 64 healthy babies, all but 4 born at term, only 2 with macrosomia, and no major birth defects. Those patients whose growth hormone (GH) and IGF-I were not controlled before conception were more likely to have gestational diabetes and hypertension. The pituitary tumour volume was stable in 81% of cases, and increased in just 3 women.

GH levels are variable in pregnant women; GH is secreted by the placenta but pituitary GH secretion may or may not be altered. Most pregnancies that occurred in women taking SSAs or DAs at the time of conception were uneventful, and those who took SSAs during pregnancy all delivered normal newborns.

- Ovarian dysfunction occurs in two-thirds of women with acromegaly
- Acromegaly is not a contra-indication to pregnancy
- Changes in GH and IGF-I are variable, so routine monitoring is not mandatory if the pregnancy is uneventful
- No major malformations were observed
- Rebound clinical symptoms may occur postpartum
- Breastfeeding is not contra-indicated

## Acromegaly – perspectives from different European countries

Data from Germany were presented by Christof Schoefl (Erlangen). There are about 80 million people in Germany. On average, 100 new cases of acromegaly are recorded in the register each year, which equates to about 3–5 new cases per million population per annum, compatible with data from other countries.

An analysis of 1344 patients from the German Acromegaly Register (Schöfl *et al.* 2013 *European Journal of Endocrinology* **168** 39–47) looked at long-term outcome in patients with acromegaly; the survey was conducted approximately 8.6 years post-diagnosis. Of these patients, 38.8% were controlled by surgery alone, and 65.2% of medically treated patients were controlled. There was a significant improvement in long-term outcome when patients were operated on by surgeons with a higher pituitary surgery caseload.

In all, 72% of patients had normalised IGF-I levels, and one-fifth of patients were not controlled as defined by GH and IGF-I levels. Thus there is room to up-titrate medical therapy, and indeed 47% of patients with elevated IGF-I were receiving no medical therapy.

Doctors were asked to complete a questionnaire to describe their reasons for not commencing or up-titrating medical treatment in patients with uncontrolled disease. In order, these were:

- the patient refuses treatment
- IGF-I levels were variable
- compliance
- drug holiday
- non-responders
- side effects
- cost

Ernesto De Menis (Montebelluna) gave some insights into the picture in Italy. There is inadequate provision of neurosurgery in some regions, he said. No national register of all patients is available, but an increased prevalence of acromegaly has been reported in a highly polluted area (Messina).

He presented findings of a recent Italian survey on predictors of morbidity and mortality in acromegaly, which included 1512 participants (about 45% of Italian acromegalics) (Arosio *et al.* 2012 *European Journal of Endocrinology* **167** 189–198). The mean diagnostic delay was 70 months, a figure which has not changed significantly over the past 20 years. Dr De Menis called for greater efforts to increase awareness of acromegaly in other specialities, such as rheumatology and orthopaedics. Diabetes was seen in 16% and hypertension in 33% of patients; these correlated with age and IGF-I level at diagnosis.

Patients were treated with surgery (80%), medical therapy (75%), radiotherapy (18%) and radiosurgery (6%). Among medical therapies, three-quarters of patients received SSAs; 10% DAs; SSA and DA 12%; and GH antagonist 3%. (The regulatory rules concerning use of pegvisomant are very restrictive in some parts of the country, he said.) More than two-thirds of patients received two or more types of therapy. Controlled disease, as defined by normal GH and IGF-I levels, was seen in 65%, and control was correlated with initial GH levels.

Sixty-one deaths were recorded, giving a standardised mortality rate (SMR) of 1.13. Those with controlled disease

had an SMR of 0.59, whereas those with active disease had an SMR of 1.93. Predictors of mortality were age, IGF-I level at diagnosis, GH level at follow-up, neoplasia and radiotherapy.

In his personal view, medical treatment of acromegaly should aim for normalisation of GH and IGF-I in the shortest possible time.

Richard Ross (Sheffield) presented the UK experience. Data from the National Acromegaly Register Investigators describe 2572 patients with a median 7.2 years of observation. Of these patients, 70% have had surgery, 45% pituitary radiotherapy and 60% medical therapy. Control of GH levels has improved with time, from 21% pre-1990 to 61% in the 2000s: pre-treatment levels were similar, and the improved control reflects improvements in treatment, he said. The most recent figures suggest GH control in more than 75% of patients on SSAs. Similarly, the percentage of patients with control of both GH and IGF-I has risen to roughly 50%.

Clinicians are not up-titrating doses of SSAs: this is partly from ambivalence about the importance of getting GH and IGF-I to normal levels, partly because of concern about side effects, and partly because of cost. DAs are generally less effective in achieving control, though results with bromocriptine are better when treatment is started early.



## New treatments for acromegaly

Annamaria Colao (Naples) discussed the SSA pasireotide. Although SSAs remain the mainstay of medical treatment, only 50% of patients in the real world have adequate biochemical control. An improved medical option is needed with a good safety profile. Pasireotide has a higher affinity for some of the different somatostatin receptor subtypes than other SSAs and so has the potential to be more effective.

A large study published in 2012 (Colao *et al.* 2012 *Endocrine Abstracts* **29** OC1.1) enrolled 358 patients with medically naïve acromegaly. Its primary objective was to compare the effects of pasireotide and octreotide in normalising GH and IGF-I at 12 months. In all, 83% of patients completed 12 months of therapy. Pasireotide was significantly superior to octreotide: the primary end-point was achieved in 31% of pasireotide patients versus 19% of octreotide patients.

Diabetes and hyperglycaemia were more common with pasireotide but the hyperglycaemia appeared to be reversible when patients were switched to octreotide. During the extension phase of the trial, GH and IGF-I levels remained suppressed in both treatment groups.

A new formulation of octreotide for oral administration was described by Christian Strasburger (Berlin). Octreotide acetate is given with transient permeability enhancer, a combination of chemical excipients that enhances intestinal absorption via the paracellular route, opening the tight junctions in the gut wall. Toxicology studies in monkeys observed no adverse octreotide-related effects at 9 months, and four clinical studies conducted in healthy volunteers demonstrated similar pharmacokinetics in patients who had the oral and subcutaneous formulations.



A phase 3 study is ongoing in 13 countries, investigating patients who respond to parenteral SSAs. Duration of the core treatment phase is 7 months, with a 6-month extension phase for patients who successfully maintain a normalised IGF-I and are willing to continue treatment. Enrolment of 155 patients is complete: the core study should have completed by the end of 2013 and, to date, the majority of patients who completed the core phase have elected to enrol into the extension phase.

Martin Bidlingmaier (Munich) described work on 'antisense' drugs, molecules that target mRNA. They are termed 'antisense' because the base sequence of these oligonucleotides is complementary to the 'sense' sequence of mRNA. The antisense strand is taken up, combines with mRNA and then blocks the translation phase of protein production.

The drug ATL1103 (Isis Pharmaceuticals) is an antisense oligonucleotide specific for GH receptor mRNA. When this receptor is inhibited, the level of circulating IGF-I is reduced. Positive results have been seen in mice, monkeys and human volunteers, with reductions in IGF-I and GH receptor mRNA in the liver. A phase 1 clinical trial in 36 healthy men showed that the treatment was safe and generally well-tolerated. A phase 2 randomised, open-label trial is ongoing. The trial will recruit 24 patients from 11 European centres, who will be given two subcutaneous dosing regimes over a 13-week period. Results should be available in 2014.

## Breakout session

The new treatments and treatment modalities were discussed. When asked to select the most important therapeutic need that was unmet, participants found it difficult to decide. Their responses sum up their opinions of our current position regarding the diagnosis and management of acromegaly:

- earlier diagnosis
- reliable assays and assessment criteria
- an easy tool to assess clinical control
- improved knowledge of the relationship between biochemical control and patient well-being, quality of life, morbidity and mortality
- better medical and surgical treatment of acromegaly and its co-morbidities
- new tools to assess pituitary tumours
- a drug that actually cures the disease
- lower cost drugs
- for every patient to have access to the best management, wherever they live