MANAGEMENT OF ENDOCRINE DISEASE

Individualised management of acromegaly

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Abstract

Acromegaly is a rare and challenging disease calling for management in highly specialised multidisciplinary teams (MDTs). Untreated disease has severe morbidity and a clearly increased mortality. Major attainments have been gained over the latest decades, and therefore, the aim of this review is to discuss recent achievements in modern multimodal therapy of acromegaly performed by MDTs, with an emphasis on individualised, proactive management from the time of diagnosis to long-term outcome. Treatment by surgery is the only potential curative treatment, however, even with modern techniques still with modest cure rates, leaving the patients to often long-term medical treatment. Treatment strategies have changed dramatically in the Western world over recent years, implying a more proactive treatment algorithm often with a shorter or longer pre-surgical treatment period with somatostatin receptor ligands (SRLs). Not all patients will however respond to primary treatment with conventional SRLs and there has recently been a development of potential biomarkers for response that has been implemented in the clinical routine. By today, multimodal treatment can bring every patient in remission, but still almost a third of all patients are undertreated according to large, international registries. On the other hand, it might be a challenge not to over treat thereby bringing the patient into a state of relative or absolute growth hormone deficiency. Clinical series published during the last decade on treatment of patients with acromegaly have indicated a normalisation of mortality, most probably reflecting the proactive and individualised modern treatment. In conclusion, modern, multimodal treatment seems to have normalised mortality, but still the patients suffer from a high multi-organ morbidity and often multi-pharmacy. Every patient should receive an individualised, proactive treatment in order to improve long-term outcome and to reduce costs for the society.

Invited Author’s profile

Jens Bollerslev is head of the Section of Specialized Endocrinology, Oslo University Hospital and Professor in Endocrinology at the University of Oslo, Norway. His special interest is within clinical and translational endocrinology, and in particular, in classical endocrine diseases, such as acromegaly and Cushing’s, often studying bone as target tissues for clinical activity. A major topic has been clinical management of acromegaly, and especially searching for biomarkers for responsiveness to medical therapy. Prospectively collected data of newly diagnosed patients with acromegaly has been the background for current studies of individualised, multimodal and transdisciplinary treatment.
**Introduction**

Acromegaly is a chronic systemic disease produced by excessive secretion of growth hormone (GH) and consecutively increased levels of insulin-like growth factor I (IGF-I). The GH excess is almost always caused by a benign, GH-secreting (somatotroph) pituitary adenoma (1). Acromegaly is recognised as a rare disease, with prevalence far below the definition of orphan diseases as defined by the European Union (European Medicines Agency – Overview – Orphan designation). Thus, management of patients with acromegaly is recommended to be centralised to tertiary referral centres with special expertise applying a transdisciplinary approach and performing individualised and most often multimodal treatment (1). Transphenoidal surgery is the only true curative treatment, however, with a disappointing low cure rate when performed as primary treatment (2, 3, 4, 5, 6), because the tumours often are large and invasive at the time of diagnosis. In order to improve therapeutic outcomes for patients and the society (cost effectiveness), new treatment algorithms have been developed during the last decades (4, 6, 7). These algorithms include a special focus on increasing the so far modest operative cure rate by stressing treatment to be performed in highly specialised multidisciplinary teams (MDTs) with a high experience in pituitary diseases (1, 8), and expert surgeons with special interest for and a broad experience in pituitary surgery and thereby a documented better operative cure rate (9). Moreover, pre- and postoperative medical treatment should be considered, in order to secure long-term postoperative normality of GH levels and action in target tissues (1, 10), with the aim to improve morbidity and mortality for a debilitating disease but also reduce the need for complicated and costly long-term medical therapy. Although, cure by surgery is obviously the most cost-effective treatment, newer studies have shown that preoperative SRLs treatment of macroadenomas not only achieves a significant improvement of the surgical outcomes, but seems also to be cost-effective (11, 12).

The aim of this review is to discuss recent achievements in modern multimodal therapy of acromegaly performed by MDTs, with an emphasis on an individualised, proactive management from the time of diagnosis to long-term outcome.

**Epidemiology**

Acromegaly has an estimated prevalence of 28–137 cases/million inhabitants and the incidence vary between 2 and 11 cases/million per year (13, 14). The clinical manifestations of acromegaly are broadly divided in signs and symptoms caused by the local tumour extension (headache, visual-field defects, cranial-nerve palsy and hypopituitarism) and systemic manifestations related to the prolonged exposure to GH/IGF-I excess. Recent data from the largest international acromegaly database, Liège Acromegaly Survey (>3000 patients), indicated a high prevalence of comorbid conditions at the time of diagnosis: diabetes mellitus in 28%, arterial hypertension in 29%, sleep apnoea syndrome in 26% and cardiac hypertrophy in 16% of the patients. Serious cardiovascular comorbidity was uncommon at the time of diagnosis, whereas osteoporosis was present in 12% (15).

Before the millennium, mortality was reported to be increased in patients with active acromegaly by two- to three-fold compared to the general population. However, during the last decades overall mortality rates have declined markedly towards the general population, a fact ascribed to modern, multimodal therapy (16), but still a matter of discussion and still with severe morbidity.

The most recent study on acromegaly from the Swedish Pituitary Registry found an overall standard mortality rate (SMR) of 1.33 (95% CI: 1.17–1.52). However, the mortality was only increased during the first time period (1987–1995) suggesting a decrease of mortality over time (13) (Erratum published in January 2019 https://doi.org/10.1530/EJE-18-0015e). Of interest, in a modern Danish cohort, overall mortality risk was still increased, but only with about 30% compared to the background population, again primarily due to an increased cardiovascular mortality (17). Conversely, in the French Registry of Acromegaly, life expectancy was close to the general population, SMR 1.05 (95% CI: 0.70–1.42), and cancer occurred just in 10% of patients, but most deaths were related to malignancies (18). Lastly, a recent systematic review and meta-analysis, showed that mortality was increased in the studies published before 2008, but did not differ from the general population (SMR: 1.35 (95% CI: 0.99–1.85)) in studies published after 2008. Cancer had become the leading cause of death in patients with acromegaly in the last decade (14).

Thus, these multicenter national registry data on mortality differ depending on time, geography and probably registry quality and completeness. The most recent studies might have a power problem due to short observation time (5–8 years) and, of importance, treatment was not defined and individualised in these cohorts.
Changing strategies

Treatment of acromegaly in modern time involves in principle three different modalities, surgery, medical treatment and radiotherapy, and it is well acknowledged that surgery is the only potentially curative option (1, 4, 19, 20, 21, 22). When looking at the numerous international recommendations and guidelines for management of acromegaly over the past two decades, it is of interest how little the general recommendations have changed for the central role of transsphenoidal surgery, taking the major achievements of other modalities into account (1, 4, 6, 19, 21, 22, 23), and the modest cure rate for primary surgery in the daily clinic, not only for macroadenomas (2, 9, 24, 25, 26, 27), as will be discussed in detail below.

The first study to focus on the change in treatment strategies based on national registries (Table 1) was published in this journal 10 years ago (2). The study described 418 patients with acromegaly included in the AcroBel Registry and focused on ‘real-life outcomes’ as opposed to reports from highly specialised centres with potential biases and lack of transparent inclusion and exclusion criteria. Sex distribution was almost equal, with a mean age at diagnosis for the total population of around 44 years. Totally, 79% of the tumours were macroadenomas. At the time of the investigation, 68% of the patients had undergone surgery, either as monotherapy or in combination with other modalities. Radiotherapy had been used in 34% of the patients, mostly following unsuccessful primary surgery. Primary medical therapy was given to 23% of patients and most of the included patients (78%) had been treated with medical therapy either primarily or as an adjuvant (2). The paper describes the change in treatment strategy over four periods, from before the 1980s to after the millennium.

Not surprisingly, the proportion of patients receiving radiotherapy decreased markedly over the period, from almost 70% before the eighties to only 8% after the millennium. Since the eighties, the overall percentage of patients undergoing surgery decreased from 84 to 61%. Of interest, primary medical therapy increased gradually to almost 40% of all patients diagnosed after year 2000 (2), most of the patients (81%) receiving SRLs alone or in combination with dopamine agonists (DAs).

Similar trends have been published from the Spanish Acromegaly Registry (REA) (28). REA spans the same time period as the AcroBel study and included totally 1658 patients. Macroadenomas were seen in 75% of the patients. The study described the first treatment received over time. Surgery topped as first-line therapy in the 80s, where about 68% of the patients underwent surgery as primary therapy declining to about a third after the year 2000. In the same period (2000–2009), the use of medical therapy as first-line treatment increased and was received by two-thirds of the patients. After the millennium, more than 80% of the patients had ever received surgery and medical therapy, and only about 12% had been treated by radiotherapy (28).

The Mexican Acromegaly Registry was established in 2009, the only non-European national registry and, so far, the largest including more than 2000 patients diagnosed after 1990 (29). In this series, there was a female preponderance (59%), the mean age at diagnosis was lower than that seen in the above mentioned registries (41 years), and macroadenomas comprised 74% of all tumours, as in most other series (Table 1). Surgery was the primary treatment in 72% of the patients, whereas 26% received medical treatment as first-line (81% SRLs). As this registry only spans less than a decade, no change in primary strategy over time was presented (29).

Table 1  Patient characteristics and distribution of treatment modalities in registries presenting data overtime.

<table>
<thead>
<tr>
<th>Registry</th>
<th>Number of patients</th>
<th>Female (%)</th>
<th>Age</th>
<th>Macro/micro adenoma^ (ratio)</th>
<th>Surgery* (%)</th>
<th>Primary medical treatment (%)</th>
<th>Radiotherapy* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcroBel Registry (2)</td>
<td>418</td>
<td>49</td>
<td>F: 46 (17–80); M: 42 (8–81)</td>
<td>330/65 (5.1)</td>
<td>68</td>
<td>23</td>
<td>34</td>
</tr>
<tr>
<td>Spanish Acromegaly Registry (28)</td>
<td>1658</td>
<td>61</td>
<td>46 (35–55)</td>
<td>1244/414 (3.0)</td>
<td>84</td>
<td>42</td>
<td>36</td>
</tr>
<tr>
<td>Mexican Acromegaly Registry (29)</td>
<td>2057</td>
<td>59</td>
<td>41 ± 25 **</td>
<td>1136/388 (2.9)</td>
<td>96</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>French Registry (18)</td>
<td>1034</td>
<td>54</td>
<td>F: 49 (37–58); M: 43 (34–53)</td>
<td>672/362 (1.9)</td>
<td>80</td>
<td>50</td>
<td>18</td>
</tr>
<tr>
<td>Swedish Registry (13)</td>
<td>1089</td>
<td>53</td>
<td>52 ± 15 **</td>
<td>NA</td>
<td>64</td>
<td>NA</td>
<td>13</td>
</tr>
</tbody>
</table>

^Number of patients; *at any time; **mean±S.D.; †median (range); ‡mean (IQR); F, female; M, male.
The French Registry also published recently in this journal (18), described in principle the same changes in treatment pattern over time. A total of 1034 patients were included, women being significantly older than men (median age 49 vs 43 years). Surgery was performed in 80% of the patients, but did not change over the time period (1977–2012), whereas the proportion of patients undergoing radiotherapy fell gradually over time. Primary medical therapy was performed in almost half of the patients, rising from 30% before 2001 to 54% in the period 2007–2012. The authors stress that 63% of the patients receiving primary medical therapy underwent a subsequent neurosurgical procedure. Of interest, the use of first-line medical treatment was not associated with the size but with lateral extension of the tumour (18).

The most recent registry, from Sweden, described 1089 patients diagnosed between 1987 and 2013 (13). The distribution between micro- and macroadenomas was not given, and medical treatment pattern was only available for a subgroup of 338 patients diagnosed after 2005. The study described a more active surgical approach over the time period, increasing from 58% in patients diagnosed in the period before 1995 to 72% after 2005 (P<0.001), with no change in the proportion of patients undergoing radiotherapy (from 10 to 15%, P=0.12). Most importantly, the proportion of patients developing hypopituitarism decreased significantly over the period (from 41 to 23%, P<0.001), ascribed as the most important factor for the improved patients prognosis (13).

The above mentioned registries present every day clinical practice in the management of acromegaly over several decades (2, 28, 29) and indicate a treatment strategy deviating from the international recommendations and evidence-based guidelines at the time of inclusion of the study patients (19, 23), but also in relation to the most recent recommendations (1, 4, 6). The series also indicate a change in strategy, especially reflecting the initial steps of management after the diagnosis of acromegaly has been made, as given in a recent short review (7). These registry data indicate an active and highly specialised competence of the treating MDTs taking the most recent achievements into account, but also reflect local therapeutic potential and tradition. These aspects were described in a survey performed in relation to an international expert meeting on management of acromegaly showing differences in initial treatment between European and US experts, European experts being more prone to use primary medical therapy (mostly SRLs) (20).

### Treatment modalities

#### Primary surgery

Surgical resection of the pituitary adenoma is recommended where possible and represents the best opportunity for cure. However, all the guidelines support the use of SRLs as first-line therapy in selected patients, if the majority of the tumour is not resectable and in patients without optic chiasm compression or those who are poor surgical candidates (1, 6, 19, 30). It is well accepted that the surgical outcome depends first and foremost on the surgeon’s experience and patient load of the neurosurgical centre and on the tumour extension into the cavernous sinus (9). Other factors that may increase the remission rate are older age at diagnosis and lower GH levels preoperatively. Both the microscopic and the endoscopic techniques give similar remission and complication rates and the choice lays on the surgeon’s acquaintance with these techniques (31). The variability of published remission rates depends also on whether the assessment is made early vs late postoperatively and on the biochemical criteria used (GH, IGF-I or both). Overall remission rates vary between 34 and 85%, with better rates in microadenomas between 75 and 90% and more modest results in macroadenomas 45–70%. However, these data should be interpreted with caution since the chance of publication bias is high. Accordingly, centres that present results on less than 30 patients describe remission rates that vary between 34 and 73%, whereas those presenting data on more than 100 patients have an overall remission rate slightly higher, ranging between 52 and 72% (31). Remission rates improve following establishment of a specialist surgical service from 27 to 67% underlining the importance of a dedicated surgeon (9). Moreover, studies presenting one surgeon experience, in which all surgeries are performed by the same surgeon, show higher remission when compared with studies by more than a single surgeon (71 vs 47%) (32). But, even if the operations are performed by experienced surgeons who operate more than 200 pituitary adenomas every year, the remission rate is still disappointingly low for macroadenomas (56%) (33).

#### Surgical debulking and responsiveness to SRLs

Surgical debulking is a practical alternative for invasive tumours when the chance for remission following surgery is low. In addition to a decrease of tumour burden, the goal of surgery for large tumours is to decompress the optic

https://eje.bioscientifica.com
apparatus and the pituitary gland, thereby optimising a potential radiosurgery target. Moreover, surgical debulking of GH-secreting pituitary adenomas improves the postoperative control by SRLs (34, 35, 36, 37). The first study that assessed if debulking surgery improved the post-surgical outcome of SRLs given postoperatively showed that GH normalisation was achieved in 29% patients preoperatively and rose to 54% after debulking, whereas the effect on IGF-I was more impressive, rising from 46 to 78% with postoperative medical therapy (37). Similarly, in another cohort of unselected patients with active acromegaly who received lanreotide LAR prior to surgery, the biochemical control of disease as estimated by GH <2 mUI/l (<0.6 µg/L) was 31% and increased to 69% following surgery, whereas normal IGF-I was achieved in 42% before and in 89% after surgery. One of two patients who were not controlled before surgery became controlled when lanreotide was re-introduced following the operation (36). Similar results were obtained by a recent observational study (35).

Pre-surgical treatment with SRLs

Efficacy rates of SRLs treatment

The overall biochemical control rates achieved by treatment with first-generation SRLs (i.e. octreotide or lanreotide) in acromegaly was 56% for mean GH and 55% for IGF-I normalisation (38). However, remission or cure rates vary widely from 30 to 60%, depending on primary treatment vs adjuvant therapy, definition of endpoints (including composite endpoints) and, not the least, dose adjustment (39, 40, 41). A significant reduction in tumour volume (≥20%) can be observed in 63–79% of cases, with median tumour volume shrinkage of 27–39% (42, 43). Of interest, treatment-naïve patients experience a better response compared with those previously treated with surgery or radiotherapy.

A prospective, randomised, double-blind study performed in treatment-naïve patients showed a higher biochemical control (composite endpoint of GH <2.5 µg/L and IGF-I normalisation) with pasireotide LAR compared with octreotide LAR (31.3 vs 19.2%; P=0.007) (44). No benefit was observed on tumour volume reduction for pasireotide compared to octreotide. Of notice for this study were the low biochemical control efficacy rates obtained by octreotide, suggesting a suboptimal dosage and the fact that more patients in the pasireotide group developed glucose metabolism abnormalities (with impact on IGF-I). The frequency of hyperglycaemia-related adverse events in patients with acromegaly treated with pasireotide varied between 57 and 67% (44, 45).

A randomised, controlled study (PAOLA Study) showed that switching patients with non-controlled acromegaly by first-generation SRLs to pasireotide was followed by an increase in biochemical control of 15% of the patients in the pasireotide 40mg group and 20% patients in the pasireotide 60mg group after 24 weeks, using a composite GH and IGF-I criteria as endpoint, compared to no further effect of conventional SRLs (46). However, a recent retrospective study performed in patients resistant to first-generation SRLs treatment showed a higher biochemical control rate (54%) as assessed by IGF-I in patients switched to pasireotide, with 63% experiencing glucose control deterioration (47). Pasireotide is a pharmacological treatment option in selected patients inadequately controlled by first-generation SRL and a need for control of tumour size. In the PAOLA study, 15% of the patients experienced a tumour volume reduction more than 25% (46). Further, pasireotide seems to be efficient in the treatment of patients with intractable headache and could be considered as a treatment option in such cases (48).

Increase surgical cure rate by primary SRLs therapy

It has been debated whether preoperative treatment with SRLs could have a potential benefit on the post-surgical remission rate in newly diagnosed acromegaly. The Norwegian Neuro-Endocrine Working Group performed the first clinical randomised study on preoperative medical treatment in patients with acromegaly (POTA) (49, 50) and showed that the early remission rate was improved in macroadenomas with no obvious benefit for microadenomas (Table 2). Long-term postoperative cure rates at 1- and 5-year visits were not significantly different between the groups, but this could be due to the low number of patients (51). Accordingly, when presenting data combined with the long-term results reported by another randomised study (52), the results were very similar, with a trend for increased cure of macroadenomas by pre-treatment and a doubled cure rate in the pre-treated group (51). Furthermore, the results are supported by another two prospective randomised studies showing an advantage of preoperative SRLs treatment by doubling the remission rate and a higher remission for tumours with cavernous sinus invasion (53, 54). However, when discussing the improvement of surgical cure rate by pre-treatment with SRLs in the above mentioned randomised studies, the very low cure rates by direct surgery should be taken into account (49, 52, 53, 54). Interestingly, two retrospective
Table 2 Postoperative treatment outcome in patients pre-surgically treated with SRLs as compared to patients directly operated.

<table>
<thead>
<tr>
<th>Reference/patient inclusion</th>
<th>Study type</th>
<th>Pre-surgical SRLs/total number</th>
<th>Pre-surgical SRLs treatment (months)</th>
<th>Remission criteria</th>
<th>Postoperative remission (months)</th>
<th>Patients in remission</th>
<th>Other criteria/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>(53) (2006–2010) PR</td>
<td>24/49</td>
<td>3</td>
<td>GH nadir OGTT &lt;1 µg/L and IGF-I &lt; ULN</td>
<td>3</td>
<td>46 vs 20.0 &lt; 0.05 All patients had macroadenomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(52) (2005–2006) PR</td>
<td>19/39</td>
<td>3</td>
<td>GH nadir OGTT &lt;1 µg/L and IGF-I &lt; ULN</td>
<td>3</td>
<td>32 vs 10 &lt; 0.13 All patients had invasive macroadenomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(54) (2004–2007) PR</td>
<td>49/98</td>
<td>4</td>
<td>GH nadir OGTT &lt;1 µg/L and IGF-I &lt; ULN</td>
<td>3</td>
<td>32 vs 5 0.025 Invasive adenomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(49) (1999–2004) PR</td>
<td>32/62</td>
<td>6</td>
<td>GH nadir OGTT &lt;1 µg/L and IGF-I ≤ ULN</td>
<td>3</td>
<td>32 vs 11 IGF-I criteria: all patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(51)*</td>
<td>31/61</td>
<td>6</td>
<td>GH nadir OGTT &lt; 2 mL/L and IGF-I ≤ ULN</td>
<td>1 year</td>
<td>39 vs 18 0.044 GH and IGF-I criteria: all patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(57) (1997–2007) Ret.</td>
<td>64/110</td>
<td>3–18 (med: 5)</td>
<td>GH nadir OGTT &lt;0.4 µg/L and IGF-I &lt; ULN</td>
<td>3</td>
<td>32 vs 27 0.63 GH and IGF-I criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(59) (2010–2016) Ret.</td>
<td>38/100</td>
<td>1–13 (med: 3)</td>
<td>GH nadir OGTT &lt;1 µg/L and IGF-I &lt; ULN</td>
<td>3</td>
<td>38 vs 24 0.27 Macroadenomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(58) (2009–2014) Ret.</td>
<td>81/358</td>
<td>3–36 (med: 4)</td>
<td>GH random &lt; 2.5 µg/L, or OGTT GH &lt;1 µg/L or IGF-I &lt; ULN</td>
<td>11 ± 11 (range: 3–53)</td>
<td>41 vs 30 0.79 IGF-I criteria: all patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(55) (1990–2003) Ret.CC</td>
<td>143/286</td>
<td>15 (±2)</td>
<td>GH nadir OGTT &lt;2 µg/L and IGF-I &lt; ULN</td>
<td>4–6</td>
<td>41 vs 31 0.45 GH and IGF-I criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(56)</td>
<td>24/48</td>
<td>3–6</td>
<td>GH nadir OGTT &lt;1 µg/L and IGF-I &lt; ULN</td>
<td>6weeks</td>
<td>41 vs 27 0.34 Macroadenomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(54) (2004–2007) Ret.CC</td>
<td>11 ± 11</td>
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<td></td>
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<tr>
<td>(55) (1990–2003) Ret.CC</td>
<td>56 vs 37</td>
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<tr>
<td>(56)</td>
<td>64 vs 57</td>
<td></td>
<td></td>
<td>6 ± 11</td>
<td>57 vs 32 0.39 IGF-I criteria: macroadenomas</td>
<td></td>
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<tr>
<td>(58) (2009–2014) Ret.CC</td>
<td>59 vs 45</td>
<td></td>
<td></td>
<td>6 ± 11</td>
<td>57 vs 32 0.39 IGF-I criteria: macroadenomas</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Presented long term data for patients described in Carlsten et al. (49).
OGGT, oral glucose tolerance test; PR, prospective randomized; Ret., Retrospective; Ret. CC, retrospective case control; med, median.
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case–control studies did not show any apparent beneficial effect of pre-surgical treatment (55, 56) (Table 2). There have been three recently published retrospective studies on the surgery outcome after preoperative SRLs treatment. All of these showed a favourable result with improved overall remission rate in one study (57) and an effect present just in invasive macroadenomas in two studies (58, 59) (Table 2). Despite the obvious disparate results published until now, it seems that primary SRLs treatment may have a benefit in carefully selected patients. Thus, stratification for individualised treatment is needed based on clinical work-up, in order to identify the patients who would benefit the most for primary treatment with SRLs (7).

Repeated surgery

The results of repeated surgery are generally less favourable than those in primary operations but still a 50–60% remission rate has been described in small and retrospective series (60, 61). This was accompanied by an increased rate of complications, such as transient diabetes insipidus and meningitis, but no increase in mortality. The choice to offer a second pituitary operation for persistent disease is based on a thought-out evaluation in the MDTs with respect to tumour remnant localisation and volume, compression of optic chiasm, the response to medical treatment with SRLs and patient preference.

Radiation therapy

Radiation therapy (RT) is generally considered a third-line option, when both surgery and medical treatment have failed (1, 19). RT is aimed both at obtaining biochemical disease control by decreasing GH and IGF-I and to gain tumour control. However, the role of RT in the management of acromegaly has decreased markedly, due to increasing range and effectiveness of medical therapy options and despite the use of highly targeted radiotherapy (i.e. stereotactic radiosurgery) instead of conventional fractionated radiotherapy (62). Both conventional fractionated RT and stereotactic RT/ radiosurgery can be utilised. Stereotactic radiosurgery allows a high radiation dose to be delivered with precision, in a single dose, being associated with lower irradiation doses to the neighbouring normal brain tissue. Although the obvious benefit, comparable outcome data show only marginally improved biochemical remission over conventional, fractionated RT, whereas safety data on long-term complications such as the development of a second intracerebral tumour, cerebrovascular disease and neurocognitive defects require further evaluation. The most common complication following RT is the development of hypopituitarism, which might be prevented by a better targeting of the remnant tumour and a decrease of maximum radiation dose administered to the pituitary and stalk tissue (62).

A recent meta-analysis showed that compared to conventional RT, stereotactic radiosurgery to patients with acromegaly was associated with a slightly increased remission rate at the latest follow-up period (52 vs 36%; P=0.14) and a significantly lower follow-up IGF-I level (63). Furthermore, in a cohort of 121 patients treated with stereotactic radiosurgery the cumulative remission rate at 6, 12, 24, and 60 months was 14, 23, 50 and 88%, respectively. The incidence of new cases with hypopituitarism was 25% after 8 years, and there was no evidence of radiographic tumour progression (64). Moreover, in another large cohort of 371 patients treated by stereotactic radiosurgery, the actual rates of initial and durable endocrine remission at 10 years were 69 and 59%, respectively. Interestingly, cessation of IGF-I-lowering medication prior to stereotactic radiosurgery was the only independent predictor of durable remission (65).

Recently, increased white matter signal abnormalities at the temporal lobes, the basal ganglia (insula) and the infratentorial regions, bilaterally were described by magnetic resonance image (MRI)/MR angiography (MRA) in a case–control study of patients with acromegaly who received RT compared to patients that did not receive RT. The small sample size of the study did not allow any conclusion on whether the findings were associated with time elapsed after RT or to the specific RT protocol applied (different radiation dose or regimens). The clinical and neurocognitive impact is however still unknown (66).

Prediction of response to medical treatment

First-generation SRLs

The response to treatment with first-generation SRLs varies substantially between patients and histological tumour subtypes (38, 50, 67). Adequate prediction of treatment response may improve the choice of initial treatment modality and post-surgical pharmacological control.

T2-weighted MRI signal intensity of the adenoma has been shown to correlate with granulation pattern and has also been proven to correlate directly with treatment response to first-generation SRLs (68, 69, 70, 106). If histological classification is not available, particularly if
preoperative pharmacological treatment is considered, T2 hypointensity is an indicator of first-generation SRLs efficacy. In contrast, in cases with adenoma showing T2 hyperintensity, other treatment options should be considered (Fig. 1).

Histological tissue characterisation by different markers has been shown to correlate with SRLs efficacy (3). Of obvious reasons, prediction relying on tissue sampling is only available for the prediction of postoperative SRLs treatment. Here, the most commonly used and commercially available biomarkers for clinical use will be discussed.

Among the markers available for routine immunohistochemical (IHC) assessment, granulation pattern assessed by anti-Cam5.2, somatostatin receptor (SSTR) status and Ki-67 are best studied and validated predictors of first-generation SRLs efficacy (6, 67, 71).

The terms densely and sparsely granulated adenomas were derived from an early electron microscopic (EM) characterisation by Yamada et al. (72). Adenomas with dense distribution (DG) of GH vesicles in the cytoplasm by EM were found to have Cam5.2 perinuclear staining pattern by IHC. All sparsely granulated (SG) adenomas had dot-like IHC (Cam5.2). The EM-nomenclature SG and DG has been kept in the present pathological WHO classification (73), although perinuclear pattern and dot-like pattern would be more correct when referring to anti-Cam5.2 staining pattern. The anti-secretory and anti-tumour effects of first-generation SRLs are most prominent in DG adenomas, while SG adenomas often have blunted response on SRLs or even resistance (67, 68, 71, 74, 75, 76). In patients with DG adenomas, first-generation SRLs should be considered as preferred pharmacological treatment among the available substances.

The somatostatin receptor subtype (SSTR) 2a is the direct pharmacological target of first-generation SRLs. Since the introduction of the specific monoclonal antibody (UMB-1), the predictive value of the SSTR2a receptor status has been confirmed in several large, independent cohorts (71, 74, 77) and has been proposed to be routinely included in the pathologic evaluation of somatotroph adenomas together with SSTR5 (78).

The widely used Ki-67 labelling index is a marker for aggressiveness in pituitary adenomas including somatotroph adenomas (73). High Ki-67 labelling index is associated with first-generation SRLs unresponsiveness, but there are conflicting results for the prognostic value of somatostatin responsiveness (74, 78, 79). Molecular profiling has become an emerging method to characterise a large variety of molecular markers. qPCR is widely used in research settings, but has not yet been established in a daily clinical diagnostic routine setting and validation in well characterised cohorts undergoing standardised SRLs treatment, with well-defined outcome parameters is warranted (38, 80).

In summary, granulation assessment by anti-Cam5.2 staining pattern, SSTR2a and Ki-67 are well-established IHC biomarkers for first-generation SRL responsiveness. In patients considered for preoperative pharmacological treatment, T2-wighted MRI signal intensity is associated with responsive (T2 hypointensity) or unresponsive (T2 hyperintensity) adenomas (Fig. 1).

Second-generation SRLs

Pasireotide has strong affinity to the SSTR5. As for first-generation SRLs and SSTR2a, it is reasonable to assume that SSTR5 receptor status is a predictor for pasireotide responsiveness. However, it seems that the SSTR2 status is a better predictor of pasireotide response in the clinic (81). So far evidence of the predictive value of SSTR5 status is limited, as pasireotide has not been used as long and extensively as the first-generation SRLs (78, 82).

Prediction of response to DAs

In a meta-analysis of cabergoline treatment in acromegaly, the pre-treatment prolactin levels did not predict IGF-I treatment response as expected, but tumour shrinkage was associated with baseline prolactin concentration (83). Patients with IGF-I elevation up to 1.5x of upper limit of normal (ULN) can expect IGF-I normalisation in about half of the cases according to the meta-analysis by Sandret et al. (83). Thus, cabergoline is a treatment option in patient with mild acromegaly with moderate elevated IGF-I levels (6).

Prediction of the optimal dose of GH receptor antagonist pegvisomant

For optimal dosing of the GH receptor antagonist pegvisomant, weight and BMI are the most consistent factors predicting the dose needed for IGF-I normalisation, whereas the presence of truncated exon 3 of GH receptor does not seem to have any impact. Further, pre-treatment IGF-I levels and younger age are associated with higher pegvisomant doses needed to obtain IGF-I control (84, 85).
Managing acromegaly

As previously mentioned, mortality rate in acromegaly has decreased and even normalised in studies published after 2008, most probably due to a better control of disease activity and comorbidities (14). However, it does not seem that an improved surgical outcome was the main determinant of the decrease in mortality rates since the surgical cure rates remained relatively unchanged during the last decades (31). Rather, the increased availability and use of combination medical therapy has lead to a better clinical outcome. Indeed, the UK Acromegaly Register presenting data from real-life management of acromegaly found evidence of overall improvement in GH levels and in the percentage control of biochemical parameters over time. However, the degree of control of GH and IGF-I actually achieved was only around 75% for ‘safe’ GH levels (random <2 μg/L or <0.4 μg/L during OGTT), and GH and IGF-I both normalised in no more than 55% by first-generation SRLs and 36% by cabergoline (86). Moreover, the analysis of patients enrolled in the ACROSTUDY showed that treatment patterns changed over the 10-year period, with an increase of combination therapy (SRLs and pegvisomant) from 20% in 2003 to 54% in 2012, and an overall IGF-I control of around 63% (10).

An improved disease control and a reduction of the proportion of patients with medically uncontrolled disease over time were also observed in the French Registry of Acromegaly (18). Registry data indicate that the proportion of patients who underwent radiotherapy as a second-line therapy decreased gradually over time, being replaced by medical therapy. The use of pegvisomant increased, whereas that of SRLs declined.

During the last years, the role of the second-generation multi-receptor ligand SRL (pasireotide) in the treatment of acromegaly has been described (87). In inadequately controlled patients treated with first-generation SRLs, treatment with pasireotide lead to a further increase in disease control in another 20% of patients, at the expense of increased hyperglycemic events (46). Moreover, the increased availability and use of combination medical therapy has lead to a better control of disease activity and comorbidities (14). However, it does not seem that an improved surgical outcome was the main determinant of the decrease in mortality rates since the surgical cure rates remained relatively unchanged during the last decades (31). Rather, the increased availability and use of combination medical therapy has lead to a better clinical outcome. Indeed, the UK Acromegaly Register presenting data from real-life management of acromegaly found evidence of overall improvement in GH levels and in the percentage control of biochemical parameters over time. However, the degree of control of GH and IGF-I actually achieved was only around 75% for ‘safe’ GH levels (random <2 μg/L or <0.4 μg/L during OGTT), and GH and IGF-I both normalised in no more than 55% by first-generation SRLs and 36% by cabergoline (86). Moreover, the analysis of patients enrolled in the ACROSTUDY showed that treatment patterns changed over the 10-year period, with an increase of combination therapy (SRLs and pegvisomant) from 20% in 2003 to 54% in 2012, and an overall IGF-I control of around 63% (10).

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switching well controlled patients treated with first-generation SRLs and pegvisomant to pasireotide and pegvisomant lead to controlled disease (IGF-I ≤1.2×ULN) in 77% of patients and an about 50% reduction in the cumulative pegvisomant doses (88).

The present clinical knowledge suggests that pasireotide could be of benefit in patients who are resistant/not controlled on first-generation SRLs and that present (87):

1. Clinical aggressive tumours (e.g. young patients) or tumours showing growth potential
2. Side effects on first-generation SRLs and intolerance to pegvisomant monotherapy
3. Complain of severe headache.

However, the beneficial effect of this new drug on the rate of disease control, reduction of comorbidities and mortality remains to be demonstrated.

Although a relative wide range of medical treatments, in addition to surgery, are available nowadays, the biochemical disease control in real clinical practice is still disappointingly low, ranging from 41 to 76% of the patients (18), definitely leaving room for further improvement.

Discussion, perspectives and conclusions

By definition acromegaly is an orphan disease and is a condition that warrants highly competent, specialised transdisciplinary teams for optimisation and individualising treatment algorithm. Despite major interests and efforts over the last decades, virtually since the introduction of SRLs in the 80s (89), little has happened with the diagnostic delay, still being up to 8–10 years (90, 91, 92). The diagnostic delay is directly correlated to long-term morbidity and also survival. As discussed in this review, multimodal therapy before and after surgery seems to have been successful, as the most recent series published within the last decade have demonstrated a normalisation of mortality by treatment which indeed is a major achievement. However, our patients still suffer from morbidity related to the disease and potentially also related to consequences of the treatment being excessive surgery or RT (93, 94, 95). Therefore, the first treatment stratification made by the MDTs is of outmost importance for the long-term prognosis of the patient (7). Pre-surgical treatment of newly diagnosed acromegaly has been regarded as controversial (Fig. 1), even though it is one of the areas in the context of treatment of acromegaly, where several investigator initiated randomised trials have been performed, with almost uniform results indicating a better outcome of surgery for macroadenomas and invasive tumours compared to direct surgery (51). Most of the hitherto performed studies on pre-surgical treatment have been based on unselected patients. The recent developments of biomarkers for responsiveness to SRLs (96, 97, 98, 99, 100, 101, 102) in newly diagnosed patients underlines the clinical interest in a proactive approach even before surgery (7). This is also illustrated by the change in strategies over the last decades, as discussed above and where medical treatment has become more prevalent as a first treatment option (2, 18, 28). By selecting patients for primary treatment based on biomarkers for responsiveness to SRLs, should further improve surgical outcome in these selected patients.

Residual active adenoma tissue following surgery is a challenge, as it is often difficult to identify the residual tumour by MRI. So far, modern amino-acid PET investigations for remnant tumours have had limited use in most centres, but is one of the areas to be developed further (103).

The overall goal should be to have as many patients cured by modern strict definition of the cure (5), leaving as few patients as possible for life long medical treatment. On the other hand, we do have the tools for bringing patients with active acromegaly under clinical and biochemical control. But, as illustrated above, even today up to a third of our patients are not sufficiently treated for remnant activity. Another point is not to over treat, inducing a state of GH deficiency to the patient (104). This aspect calls for further development of useful biomarkers for overall GH activity beyond GH itself and IGF-I (105).

In conclusion, acromegaly is an orphan disease to be managed in highly specialised MDTs. By modern, multimodal treatment, mortality seems to have normalised, but still the patients suffer from a high multi-organ morbidity and often multi-pharmacy. Every patient should have an individualised, proactive treatment plan in order to improve long-term outcome and to reduce costs for the society.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Acknowledgements

The authors thank Geir Ringstad, Department of Radiology and Nuclear Medicine, Oslo University Hospital, Rikshospitalet, Oslo, Norway for the assistance with the MRI pictures.

References


49 European Journal of Endocrinology. Review J Bollerslev and others Managing acromegaly 181:2 | R68


71 Casar-Borota O, Heck A, Schulz S, Nesland JM, Ramn-Pettersen J, Lekva T, Alafuzoff I & Bollerslev J. Expression of SSTR2a, but not of SSTRs 1, 3, or 5 in somatotroph adenomas assessed by monoclonal antibodies was reduced by octreotide and correlated with the acute and long-term effects of octreotide. Journal of Clinical Endocrinology and Metabolism 2013 98 E1730–E1739. (https://doi.org/10.1210/jc.2013-2145)


acromegaly following localisation by 11C-methionine PET co-registered with MRI. European Journal of Endocrinology 2016 175 485–498. (https://doi.org/10.1530/EJE-16-0639)


Received 25 February 2019
Revised version received 14 May 2019
Accepted 16 May 2019