Comparative effectiveness review of treatment options for pituitary microadenomas in acromegaly

Clinical article

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Object. Acromegaly, a syndrome of excess growth hormone (GH) secretion typically caused by a GH-secreting pituitary adenoma, reduces life expectancy by approximately 10 years when left untreated. Treatment of acromegaly involves combinations of one or more discrete therapeutic modalities to achieve biochemical control. Unfortunately, data capable of informing decisions among alternate management strategies are presently lacking.

Methods. The authors performed a comparative effectiveness research (CER) review integrating efficacy, cost, and quality of life (QOL) analysis for treatment strategies comprising various combinations of surgery, radiotherapy, stereotactic radiosurgery, and pharmacotherapy in patients with acromegaly caused by a pituitary microadenoma. A management decision tree was used to identify 5 treatment strategies, each with up to 4 potential treatment steps. Efficacy was assessed using recent literature reports of biochemical control rates for each modality. Cost estimations were derived from wholesale drug prices and from the Healthcare Cost and Utility Project. Quality of life data were obtained from studies utilizing the Acromegaly Quality of Life Questionnaire.

Results. Individual treatment modalities were analyzed and ranked in each of 3 domains: highest rate of success, lowest cost, and highest QOL, and these scores were combined to facilitate comparison of overall effectiveness of each of the management strategies. These aggregate effectiveness scores were used to compare the 5 strategies from the decision tree, and a novel strategy was also proposed.

Conclusions. The choice of management strategy must be individualized for each patient with acromegaly. This CER analysis provides a comprehensive framework to inform clinical decisions among alternate management strategies in patients with GH-secreting pituitary microadenomas.

Key Words • acromegaly • pituitary adenoma • microadenoma • comparative effectiveness research • efficacy • cost • quality of life • pituitary surgery

ACROMEGALY is a syndrome of excess GH, most commonly caused by a GH-secreting pituitary adenoma, that results in organ overgrowth and physical deformity. The annual incidence in the US is estimated at 3–4 cases per million, with a worldwide prevalence of 40–130 million cases.41 Prognosis is determined by the pattern and extent of organ system involvement.58 Untreated acromegaly reduces life expectancy by approximately 10 years, and death commonly results from cardiovascular, cerebrovascular, metabolic, and respiratory comorbidities.58

Treatment goals in a patient with acromegaly include control of GH and IGF-1 secretion and tumor growth, relief of compressive effects on CNS and vascular structures if present, preservation or restoration of pituitary hormone function, and treatment of comorbidities and elimination of premature, excess mortality.58 There is no uniform standard of care for acromegaly, and alternate management strategies require variable durations of therapy to achieve biochemical control. Common treatment options include surgery, radiotherapy, SRS, and pharmacotherapy using somatostatin analogs or a GH receptor antagonist, which represent the mainstays of medical management. Multiple clinical investigations have assessed the efficacy of each of these therapies individually, but comprehensive comparisons among alternate treatment modalities remain uncommon. Quality of life considerations are also critical to the appropriate management of acromegaly, because the disease can influence patient self-image and overall well-being.73 Similarly, the high costs associated with the treatment of acromegaly

Abbreviations used in this paper: AcroQoL = Acromegaly Quality of Life Questionnaire; AWP = average wholesale price; CER = comparative effectiveness research; GH = growth hormone; HCUP = Healthcare Cost and Utility Project; IGF-1 = insulin-like growth factor–1; LAR = long-acting repeatable; SRS = stereotactic radiosurgery.

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mandate that cost-effective treatment delivery be considered when selecting a specific management strategy for this disease. Integrating data from these 3 domains into a comprehensive treatment plan to manage patients with acromegaly would be useful. In this review, we present a logical framework to approach as well as analyze the existing data from each domain.

Comparative effectiveness research is an analytical discipline that is well suited to the task of integrating efficacy data with cost and QOL data to inform clinical decisions regarding alternate treatment modalities. In addition to informing clinical decisions and improving health care delivery, CER analyses also help limit cost while maintaining appropriate standards of care. In recognition of the potential value of investigations utilizing the CER approach, the US government recently allocated $1.1 billion to develop a national CER enterprise designed to achieve these objectives.

This CER review of the management of acromegaly combines 3 domains—efficacy, QOL, and cost—to analyze the overall effectiveness of several common treatment strategies for this disease. The purpose of this review is to help inform clinical management decisions regarding alternate management strategies for patients with acromegaly from GH-secreting pituitary microadenomas.

Methods

Three Domains

Three domains were chosen on which to evaluate each treatment strategy: clinical efficacy, estimated lifetime cost, and QOL after treatment. Analysis of these 3 domains is consistent with and is fundamental to the methodology of CER. None of the 3 domains was weighted more heavily than the others during the research or evaluation process. All means and averages reported in the text and tables represent nonweighted arithmetic means.

Choice of Treatment Strategies

A management decision tree was constructed based on current treatment recommendations and on data regarding efficacy and prevalence for several therapeutic modalities commonly used in the management of acromegaly caused by a pituitary microadenoma (Fig. 1). Based on this tree, 5 unique strategies, each consisting of up to 4 potential steps, were selected for further analysis (Table 1). For each strategy, proceeding to a subsequent step is only necessary if and when the previous modality fails to produce biochemical remission. None of the therapeutic modalities was attempted a second time after initial failure, even if failure occurred in a delayed fashion. Microadenomas were chosen for analysis, since the results in all domains are clearest for this group of tumors; similar analyses can be conducted for noninvasive macroadenomas or for invasive adenomas, although the need for multiple treatment strategies would confound the analyses substantially.

Efficacy

We used Ovid Medline and PubMed to perform a comprehensive review of published literature evaluating the most commonly used treatment strategies for acromegaly, including transsphenoidal surgery (microscopic or endoscopic), SRS, conventional radiotherapy, and pharmacotherapy with somatostatin analogs (lanreotide [Somatuline Depot, Tercica], octreotide [Sandostatin, Novartis], GH receptor agonists (pegvisomant [Somavert, Pfizer]), or a combination thereof. Reports involving 5 or fewer patients were excluded, resulting in inclusion of 41 studies reporting on the efficacy of various treatment strategies or therapeutic modalities (Tables 2–6).

Because differing efficacies, including equivalence, have been suggested, lanreotide and octreotide were considered as separate treatment modalities and were investigated individually. The sustained-release preparation of lanreotide is not available in the US. All studies from which data were obtained occurred within the past 14 years.

When available, the results for patients with microadenomas were analyzed separately from those for patients with macroadenomas. Each modality was evaluated for overall treatment efficacy, and additional outcome measures for which data were available were also considered. In addition to efficacy, surgery was analyzed for remission criteria, side effects, and recurrence. Radiosurgery and radiotherapy were analyzed for dose, remission criteria, time to remission, and patients affected by hypopituitarism. Lanreotide was analyzed for dose, normalized GH, normalized IGF-1, and side effects. Octreotide was analyzed for dose, normalized GH, normalized IGF-1, tumor shrinkage, and side effects. Pegvisomant was analyzed for dose, normalized IGF-1, and side effects. Mean efficacies were calculated for each treatment when 5 or more studies were included in the analysis.

Cost

Few data have been published regarding the cost (in US dollars) of alternate treatment strategies for acromegaly, so it is impractical to obtain cost data from the peer-reviewed literature. Instead, current cost data were obtained from various publicly available sources, including online pharmacies, insurance company drug plan data, and government databases. The AWP of lanreotide and octreotide was obtained from the Department of Pharmacy Services at the Fallon Community Health Plan (Worcester, MA). The AWP of pegvisomant was supplied by Walgreens Health Initiatives. We emphasize that prices paid by patients with private insurance, those in state-financed programs, and those paying out of pocket are likely to differ; for this reason, we have chosen AWP. All of these prices were confirmed, through additional online resources, to be current. All costs for transsphenoidal surgery (ICD-9-CM 07.62) and SRS (ICD-9-CM 92.32), including inpatient hospital stays, physician fees, and other factors, were considered in aggregate and were obtained from 2008 data made available through the United States Agency for Healthcare Research and Quality’s (AHRQ) HCUPnet, a division of the HCUP (http://www.ahrq.gov/data/hcup).

The cost for each treatment modality was applied to the 5 selected treatment strategies, and the estimated cost to treat and obtain a cure in 100 patients with each...
strategy (as well as the average cost per patient) was calculated. The lifetime cost for each medical treatment was determined by multiplying the annual cost of that therapy by the number of years of treatment required, which was taken as the number of years of expected survival after the initiation of treatment. The average age at diagnosis of acromegaly was taken as 40 years, and 78.3 years was used as the mean life expectancy in the US (https://www.cia.gov/library/publications/the-world-factbook/geos/us.html). While the life expectancy of patients with untreated, persistent, or recurrent acromegaly may be decreased by as much as 10 years, normalization of IGF-1 and lowering of serum GH levels to less than 2.5 μg/L can normalize mortality rates. Accordingly, for the purpose of cost analysis, we assumed that each modality was effective and so we did not reduce the published mean US life expectancy based on this logic. All costs used in this analysis reflect 2010 US dollars.

Quality of Life

The AcroQoL is a 22-item questionnaire designed specifically to assess QOL in patients suffering from acromegaly. It is divided into physical and psychological domains, the latter of which is further subdivided into appearance and personal relations subscales. However, because this survey has only recently been translated from Spanish, many English-language studies have continued to rely on nonspecific QOL questionnaires. Data obtained regarding QOL of treated patients with acromegaly from either source were quantified whenever possible to make a comparison among studies regarding the impact of specific treatments on QOL.

Results

Efficacy

Transsphenoidal Surgery. The transsphenoidal approach is used in more than 90% of all surgeries for pituitary adenomas. The goal of surgery is to resect the tumor while preserving normal pituitary function. Surgical success rate is dependent on tumor size, magnitude of hypersecretion, degree of invasion, and experience level of the surgeon. Assuming technically adequate surgical technique and using the normalization of serum IGF-1 as the remission criterion, the efficacy of surgery is estimated to be 72%–95% for intrasellar microadenomas and 40%–68% for noninvasive macroadenomas. The complication rate is less than 5%, with the most common complications including hyponatremia, CSF leak, infection, and diabetes insipidus. The surgical mortality is estimated at 0.1%. Recurrence rates are not consistently documented and are variable across studies but are estimated at approximately 6% for all pituitary tumors treated with transsphenoidal surgery that have been resected completely. The rate of hypopituitarism after transsphenoidal surgery is estimated at 2%–3% (Table 2).

In patients with GH-secreting pituitary adenomas, pretreatment with somatostatin analogs for a 3-month period prior to surgery may improve surgical outcomes. However, other data have shown no significant improvement in surgical remission rate when somatostatin analogs are administered, so the overall efficacy of this practice remains uncertain and is therefore not included here.

Conventional Radiotherapy. Radiation therapy is rarely a first-line modality and is usually reserved for treatment of recurrent or residual tumor after primary medical or surgical therapy. Remission rates after conventional radiotherapy are reported in modern series at 5%–75% (mean 45%) with a mean time to remission of 8.7 years (Table 3). This broad range is at least partially attributable to variability in the definition of “remission.”

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st surgery</td>
<td>surgery</td>
<td>surgery</td>
<td>SA</td>
<td>SA</td>
<td>SA</td>
</tr>
<tr>
<td>2nd SA</td>
<td>SRS</td>
<td>surgery</td>
<td>peg</td>
<td>SRS</td>
<td></td>
</tr>
<tr>
<td>3rd peg</td>
<td>SA</td>
<td>SRS</td>
<td>surgery</td>
<td>peg</td>
<td></td>
</tr>
<tr>
<td>4th SA + peg</td>
<td>peg</td>
<td>peg</td>
<td>SA</td>
<td>surgery</td>
<td>peg</td>
</tr>
</tbody>
</table>

* peg = pegvisomant; SA = somatostatin analog.
used in these studies. Most use a serum GH level less than 2.5 µg/L and normal IGF-1 as the criteria for remission and report efficacy in the 40%–70% range, although some with more stringent criteria report remission rates as low as 5%.4

The principal disadvantage to conventional radiotherapy is a latency period of up to 10 years before biochemical remission, during which patients must receive ongoing medical therapy.58 The average rate of hypopituitarism after conventional radiotherapy is 49% (Table 3). Secondary tumors as a result of the radiation are rare, occurring in about 1% of patients.60

Stereotactic Radiosurgery. Like conventional radiotherapy, SRS (for example, Gamma Knife surgery and CyberKnife radiosurgery) is typically not considered a first-line treatment for acromegaly. It is recommended for patients who have received surgical or medical treatment and have residual or recurrent tumors smaller than 3 cm in diameter that are distant from the optic tract.58 Biochemical remission rates following SRS for acromegaly range from 17% to 96%, with higher rates usually observed when less stringent criteria (GH < 5 ng/ml rather than < 2.5 ng/ml) are used to define “remission.” It should be noted that few studies have evaluated results using the 2010 consensus criteria.39,89 The mean time to remission after SRS is estimated at 3.3 years, with 14.5% of patients reporting hypopituitarism (Table 4).2,21,43,49,55,71,76,84,89 It is likely that higher rates of hypopituitarism will be seen with longer follow-up in SRS cohorts, and that the rates will be similar to those seen over the long term with fractionated radiotherapy, or at least similar to those reported by Pollock et al.71 and Sheehan et al.,86 of 33%–34%.20,26,77 However, at present it is more difficult to quantify these results with respect to CER analyses.20,26,77

Somatostatin Analogs. Somatostatin analogs are a common first-line therapy for acromegaly and are also indicated when surgical success is not technically feasible, after subtotal resection of secretory adenomas, or immediately following radiotherapy during the latency period. The somatostatin analogs used in the US to treat acromegaly are octreotide (Sandostatin) and lanreotide (Somatuline). Octreotide is available in an LAR form that is injected every 4 weeks. Lanreotide is available in a sustained-release form that is injected intramuscularly every 7–21 days (this form is not available in the US) and in an extended-release form (Autogel) that is injected subcutaneously every 4–6 weeks. The most prominent side effects of lanreotide are cholelithiasis/gall bladder sludge (one-third of patients, although the majority are asymptomatic and no therapy will be needed), abdominal pain (one-quarter of patients), and transient diarrhea. Patients treated with octreotide experience similar symptoms, with the exception of cholelithiasis, which should be approximately equivalent for both octreotide and lanreotide, and the addition of temporary hair loss.

Efficacy rates for both drugs range from 40% to 85%, with varying criteria being used to assess remission.33 Lanreotide has been found to produce normal serum GH in 56%–85% of patients and normal serum IGF-1 in 43%–60%, while octreotide normalizes GH and IGF-1 in

### TABLE 2: Recent studies investigating efficacy of transsphenoidal surgery*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts (micro/macro)</th>
<th>Remission Criteria</th>
<th>Remission % (no. w/ micro/macro)</th>
<th>Most Common Complication (%)</th>
<th>% Recurrence</th>
<th>Mean No. of Yrs to Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abosch et al., 1998</td>
<td>254 (17/173)</td>
<td>GH &lt; 5 ng/ml w/in 30 days</td>
<td>76 (75/71)</td>
<td>hyponatremia (6), CSF leak (2), meningitis (2), hypopituitarism (2)</td>
<td>5</td>
<td>3.3</td>
</tr>
<tr>
<td>Swearingen et al., 1998</td>
<td>162 (33/129)</td>
<td>OGTT &lt; 2, normal IGF-1</td>
<td>57 (91/48)</td>
<td>sinusitis (3), CSF leak (1)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Freda et al., 1998</td>
<td>115 (25/90)</td>
<td>GH &lt; 2, OGTT &lt; 2, normal IGF-1</td>
<td>61 (88/53)</td>
<td>none long term</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Biermasz et al., 2000</td>
<td>59 (9/42)</td>
<td>GH &lt; 2.5 µg/L, normal OGTT, normal IGF-1</td>
<td>61 (67/57)</td>
<td>NS</td>
<td>19</td>
<td>w/in 10</td>
</tr>
<tr>
<td>Laws et al., 2000</td>
<td>117 (NS)</td>
<td>GH &lt; 2.5, OGTT &lt; 1, normal IGF-1</td>
<td>67 (87/51)</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Kreutzer et al., 2001</td>
<td>57 (19/38)</td>
<td>GH &lt; 2.5 ± OGTT &lt; 1 ± normal IGF-1</td>
<td>70 (NS)</td>
<td>DI (&lt;1), nasal septal perforations (&lt;2)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Beauregard et al., 2003</td>
<td>103 (22/52)</td>
<td>GH &lt; 2.5 µg/L</td>
<td>54 (82/60)</td>
<td>death from op (1), hypopituitarism (3)</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>De et al., 2003</td>
<td>90 (29/61)</td>
<td>GH &lt; 2.5 µg/L, OGTT &lt; 1 µg/L, normal IGF-1</td>
<td>63 (79/56)</td>
<td>meningitis (3), CSF leak (7), DI (15)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nomikos et al., 2005</td>
<td>506 (142/354)</td>
<td>GH &lt; 2.5, OGTT &lt; 1, normal IGF-1</td>
<td>57 (75/51)</td>
<td>meningitis (&lt;2), CSF leak (&lt;1)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Trepp et al., 2005</td>
<td>94 (6/85)</td>
<td>GH &lt; 2.5, OGTT &lt; 1, normal IGF-1</td>
<td>37.5 (80/27)</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td></td>
<td></td>
<td>60 (80/53)</td>
<td></td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

* DI = diabetes insipidus; macro = macroadenoma; micro = microadenoma; NS = not specified; OGTT = oral glucose tolerance test; pt = patient.
50%–79% and 33%–68% of patients, respectively (Table 5). Direct comparisons of octreotide LAR with sustained-release lanreotide demonstrate that octreotide LAR is more effective in reducing serum GH and IGF-1 levels. However, more recent investigations suggest that this may only be true in patients receiving somatostatin analogs as a second- or third-line therapy and that primary treatment with lanreotide Autogel produces remission rates comparable to those observed after treatment with octreotide LAR. Similarly, comparable remission rates have been demonstrated when comparing the efficacy of somatostatin analogs used as a primary versus secondary treatment, where GH and IGF-1 normalization rates are 70% and 68% for primary and 61% and 62% for secondary treatment, respectively.

Additionally, several studies have examined the impact of second-line somatostatin analog therapy after surgical debulking. Karavitaki et al., evaluating strictly macroadenomas, found that GH levels were normalized in 30.7% of patients receiving lanreotide only and 69.2% of patients receiving it as a secondary treatment after surgical debulking. The IGF-1 levels were normalized in 42.3% and 88.5% of the patients in the 2 groups, respectively.

**Pegvisomant.** Pegvisomant (Somavert) is the only GH receptor antagonist currently available in the US for the treatment of acromegaly, and it is currently indicated to treat uncontrolled IGF-1 levels following maximum therapy with other modalities. Doses of 15–16.5 mg/day were reported to achieve IGF-1 normalization in 75%–76% of patients, while doses of 20 mg/day resulted in a slightly higher control rate of 82% (Table 6). Higher efficacy rates have been reported in a study of patients treated for longer than 12 months, although this rate may be influenced by the 19% of patients (30 of 160) excluded from final analysis because of adverse effects or lack of efficacy. The efficacy of pegvisomant appears to be maximized in patients who were previously treated with surgery, and pretreatment with radiotherapy improves the potency but not the overall efficacy of pegvisomant. This strategy reduces the average daily dose required for IGF-1 normalization by 3.3 mg, but it does not increase the drug’s overall efficacy. Pegvisomant can also be used as a therapeutic adjunct in patients who do not achieve IGF-1 normalization with somatostatin analog therapy alone. Here, the addition of pegvisomant at a dose of 60 mg/week to a standard somatostatin analog regimen results in biochemical control in 95% or more of patients (Table 6).

Pegvisomant was initially suspected to cause tumor expansion, but this was observed in only 2%–3% of patients, none of whom exceeded the expected tumor increase in untreated patients with acromegaly. Conversely, measurable reductions in tumor volume have been observed in 12%–19% of patients effectively treated with pegvisomant. Side effects of pegvisomant are rare and most often include elevated liver enzymes. This is more

### TABLE 3: Recent studies investigating efficacy of conventional radiotherapy

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts</th>
<th>Total Dose (Gy)</th>
<th>Remission Criteria</th>
<th>Remission (%)</th>
<th>Time to Remission (yrs)</th>
<th>% Pts w/ Hypopituitarism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barkan et al., 1997</td>
<td>38</td>
<td>46</td>
<td>GH &lt;5 ng/ml, normal IGF-1</td>
<td>5</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Powell et al., 2000</td>
<td>47</td>
<td>47.4</td>
<td>normal IGF-1</td>
<td>70</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Biermasz et al., 2000</td>
<td>36</td>
<td>40</td>
<td>normal OGTT, IGF-1</td>
<td>75</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Barrande et al., 2000</td>
<td>128</td>
<td>52</td>
<td>GH &lt;2.5 µg/L</td>
<td>53</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>Cozzi et al., 2001</td>
<td>49</td>
<td>46</td>
<td>GH &lt;2.5 µg/L, normal IGF-1</td>
<td>10</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Jenkins et al., 2006</td>
<td>884</td>
<td>45</td>
<td>GH &lt;2.5 µg/L, normal IGF-1</td>
<td>60</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>Jallad et al., 2007</td>
<td>89</td>
<td>50</td>
<td>GH &lt;2.5 µg/L, normal IGF-1</td>
<td>36–47</td>
<td>6</td>
<td>47</td>
</tr>
<tr>
<td>mean</td>
<td>45</td>
<td>8.7</td>
<td>49.2</td>
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</tbody>
</table>

### TABLE 4: Recent studies investigating efficacy of stereotactic radiosurgery

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts</th>
<th>Dose (Gy)</th>
<th>Remission Criteria</th>
<th>Remission (%)</th>
<th>Time to Remission</th>
<th>% Pts w/ Hypopituitarism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Izawa et al., 2000</td>
<td>29</td>
<td>22</td>
<td>endocrinological normalization</td>
<td>41</td>
<td>NS</td>
<td>0</td>
</tr>
<tr>
<td>Zhang et al., 2000</td>
<td>68</td>
<td>31</td>
<td>GH &lt;5 ng/ml</td>
<td>96</td>
<td>24–36 mos</td>
<td>0</td>
</tr>
<tr>
<td>Attanasio et al., 2003</td>
<td>30</td>
<td>20</td>
<td>GH &lt;2.5 ng/ml, normal IGF-1</td>
<td>23</td>
<td>24 mos</td>
<td>10</td>
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<td>Castinetti et al., 2005</td>
<td>82</td>
<td>30</td>
<td>GH &lt;2 ng/ml, normal IGF-1</td>
<td>17</td>
<td>36 mos</td>
<td>16</td>
</tr>
<tr>
<td>Jezecková et al., 2006</td>
<td>96</td>
<td>35</td>
<td>OGTT &lt;1 ng/ml, normal IGF-1</td>
<td>44</td>
<td>60 mos</td>
<td>NS</td>
</tr>
<tr>
<td>Pollock et al., 2007</td>
<td>46</td>
<td>25</td>
<td>GH &lt;2 ng/ml, normal IGF-1</td>
<td>50</td>
<td>36 mos</td>
<td>33</td>
</tr>
<tr>
<td>Vik-Mo et al., 2007</td>
<td>53</td>
<td>25</td>
<td>normal IGF-1</td>
<td>17</td>
<td>NS</td>
<td>13</td>
</tr>
<tr>
<td>Losa et al., 2008</td>
<td>83</td>
<td>25</td>
<td>GH &lt;2.5 ng/ml, normal IGF-1</td>
<td>60</td>
<td>60 mos</td>
<td>10</td>
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<tr>
<td>Sheehan et al., 2011</td>
<td>130</td>
<td>24</td>
<td>normal IGF-1</td>
<td>53</td>
<td>30 mos</td>
<td>34</td>
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<tr>
<td>mean</td>
<td>44.6</td>
<td>3.3 yrs</td>
<td>14.5</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Authors &amp; Year</td>
<td>No. of Pts†</td>
<td>Study Design</td>
<td>Dose (%) of pts</td>
<td>Normal GH (%)</td>
<td>Normal IGF-1 (%)</td>
<td>Normal IGF-1 &amp; GH (%)</td>
</tr>
<tr>
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<tr>
<td>lanreotide</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Verhelst et al., 2000</td>
<td>66</td>
<td>slow-release lanreotide, 6 mos</td>
<td>30 mg/4 wks (100)</td>
<td>85</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Caron et al., 2002</td>
<td>107</td>
<td>lanATG, 3 mos</td>
<td>60 mg/4 wks (48), 90 mg/4 wks (32), 120 mg/4 wks (20)</td>
<td>56</td>
<td>48</td>
<td>39</td>
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<tr>
<td>Caron et al., 2004</td>
<td>130</td>
<td>lanATG, 12 mos</td>
<td>60 mg/4 wks (48), 90 mg/4 wks (15), 120 mg/4 wks (37)</td>
<td>68</td>
<td>60</td>
<td>52</td>
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<tr>
<td>Caron et al., 2006</td>
<td>14</td>
<td>lanATG, 3 yrs</td>
<td>60 mg/4 wks (54), 90 mg/4 wks (15), 120 mg/4 wks (31)</td>
<td>77</td>
<td>54</td>
<td>46</td>
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<tr>
<td>Chanson et al., 2008</td>
<td>57</td>
<td>lanATG, 11 mos</td>
<td>60 mg/4 wks (14), 90 mg/4 wks (6), 120 mg/4 wks (73)</td>
<td>85</td>
<td>43</td>
<td>38</td>
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<tr>
<td>mean</td>
<td>74</td>
<td></td>
<td></td>
<td>50</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>octreotide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newman et al., 1998</td>
<td>1°, 26; 2°, 81</td>
<td>octreotide, 3 yrs</td>
<td>100–1750 µg/day SC as needed</td>
<td>1°, 70; 2°, 61</td>
<td>1°, 68; 2°, 62</td>
<td>1°, 3/13 had &gt;25% shrinkage</td>
</tr>
<tr>
<td>Colao et al., 2001</td>
<td>36</td>
<td>octLAR, 12–24 mos</td>
<td>10 mg/4 wks (5), 20 mg/4 wks (39), 30 mg/4 wks (31), 40 mg/4 wks (22)</td>
<td>69</td>
<td>61</td>
<td>80% of 1° pts</td>
</tr>
<tr>
<td>Bevan et al., 2002</td>
<td>15 (9/5)</td>
<td>octLAR, 48 wks</td>
<td>20 mg/4 wks (60), 30 mg/4 wks (20), 20/30 mg/4 wks (13)</td>
<td>79</td>
<td>53</td>
<td>73% had &gt;30% tumor shrinkage</td>
</tr>
<tr>
<td>Jenkins et al., 2004</td>
<td>6 (4/2)</td>
<td>octLAR, 6 mos</td>
<td>20 mg/4 wks (50), 30 mg/4 wks (50)</td>
<td>50</td>
<td>33</td>
<td>100% of 1° pts; mean shrinkage 47%</td>
</tr>
<tr>
<td>Jallad et al., 2005</td>
<td>80 (75/5)</td>
<td>octLAR, 6–24 mos</td>
<td>10 mg/4 wks (4), 20 mg/4 wks (37), 30 mg/4 wks (59)</td>
<td>74</td>
<td>41</td>
<td>76% of de novo pts had &gt;25% shrinkage</td>
</tr>
<tr>
<td>mean</td>
<td>67</td>
<td></td>
<td></td>
<td>50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* GI = gastrointestinal; lanATG = lanreotide Autogel; octLAR = long-acting repeatable octreotide; SC = subcutaneously; 1° = primary treatment is octreotide; 2° = secondary treatment is octreotide after surgery and/or radiotherapy.
† Numbers in parentheses represent microadenomas/macroadenomas.
circumstances should be considered when deciding be-
period (Tables 1 and 3). 19 Pegvisomant, despite its high
rate of efficacy, has traditionally been used as a third- or
somatostatin analogs are considered the 2 primary options
for first-line treatment in our decision tree (Fig. 1), and
current treatment guidelines68,69 and individual clinical
circumstances should be considered when deciding be-
tween these options. Stereotactic radiosurgery is recom-
mended as a second- or third-line option and is preferable
to conventional radiotherapy, as it exhibits a similar rate
of efficacy, a more rapid decline in serum GH levels, and a shorter latency
of remission with a lower rate of hypopituitarism, a more
commonly observed when pegvisomant is used as an ad-
junct to somatostatin analog therapy, where elevations are
reported in 27%—34% of patients.63,65

Outline of Treatment Strategies

Based on this efficacy analysis, surgery and soma-
tostatin analogs are considered the 2 primary options
for first-line treatment in our decision tree (Fig. 1), and
current treatment guidelines68,69 and individual clinical
circumstances should be considered when deciding be-
tween these options. Stereotactic radiosurgery is recom-
mended as a second- or third-line option and is preferable
to conventional radiotherapy, as it exhibits a similar rate
of remission with a lower rate of hypopituitarism, a more
rapid decline in serum GH levels, and a shorter latency
period (Tables 1 and 3).68 Pegvisomant, despite its high
rate of efficacy, has traditionally been used as a third- or
fourth-line modality. This is attributable in large measure
to perceptions of high cost and mechanism of the action
associated with this drug, including lack of tumor shrink-

In any given course of treatment, if the first-line ther-
apy fails to produce biochemical remission, additional
treatments are used progressively from the levels below.
If additional modalities are also unsuccessful, subsequent
therapies may be chosen from the same level or levels be-
low, depending on factors unique to the patient, physician,
and clinical circumstances. This approach results in nu-
merous potential management strategies, and we selected
for comparative effectiveness review 5 of the most com-
mon approaches for treating acromegaly resulting from a
secretory pituitary microadenoma (Table 1).

Strategy 1: Surgery, Then Medical Management. Be-
cause of the high efficacy of surgery in treating pituitary
microadenomas, it is generally used as a first-line treat-
ment for acromegaly. If unsuccessful, somatostatin ana-
logs are a commonly used and widely available second-
line therapy. If this approach fails to achieve biochemical
control, pegvisomant can be used as an alternative. If bio-
chemical control is still not achieved, somatostatin analog
and pegvisomant therapy can be used in combination in
an attempt to further improve control. Stereotactic radio-
surgery was not included in this treatment regimen.

Strategy 2: Surgery, SRS, and Then Medical Manage-
ment. Again, surgery is used as the first-line treatment. If
unsuccessful, SRS can be used in an attempt to avoid life-
long pharmacotherapy. If unsuccessful, medical therapy
of somatostatin analog and then pegvisomant, if neces-
sary, can be implemented.

Strategy 3: Initial Medical Management, With Surgi-
Salvage. In the setting of patient preference against
surgery, lack of an experienced neurosurgeon, or a low
probability of a surgical success, pharmacotherapy with
somatostatin analogs may be considered as an initial

treatment option.6 If unsuccessful at producing biochemi-
control, surgery can be considered as a secondary inter-
tervention. Surgical remission rates after pretreatment with
somatostatin analogs are not different from remission
rates from surgery used as a primary treatment,25 al-
though tumor shrinkage with pretreatment may shorten
hospital stay postoperatively. If unsuccessful, somatosta-
tin analogs may be administered again. As previously
shown, patients with microadenomas treated with soma-
tostatin analogs after surgical debulking who were ini-
tially nonresponsive to somatostatin analogs as a primary
treatment demonstrate responsiveness at rates similar to
overall rates of efficacy with somatostatin analogs.44 If
somatostatin analogs again fail to produce control, pegvi-
somatostatin analogs are given as the primary therapy. If any of the afore-
mentioned contraindications to surgery exist after initial
treatment failure, pegvisomant can be administered as a
secondary modality. If unsuccessful, surgical treatment
should be considered at this point. After surgery, a com-

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts</th>
<th>Study Design</th>
<th>Daily Dose of Peg (% pts)</th>
<th>Normal IGF-1 (%)</th>
<th>GH Level</th>
<th>Side Effect (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trainer et al., 2000</td>
<td>112</td>
<td>randomized double blind, 12 wks</td>
<td>placebo (29), 10 mg (23), 15 mg (23), 20 mg (25)</td>
<td>At Any Point: 10, 54, 81, 89</td>
<td>−0.8 ng/ml, +2.7 ng/ml, +9.2 ng/ml, +14.4 ng/ml</td>
<td>injection site reaction</td>
</tr>
<tr>
<td>van der Lely et al., 2001</td>
<td>160</td>
<td>observational at 6, 12, &amp; 18 mos</td>
<td>6 mos, 14.7 mg, 12 mos, 18.0 mg, 18 mos, 19.6 mg</td>
<td>Normal: NS, At End: 97, 92</td>
<td>+12.5 µg/L, +12.5 µg/L, +14.2 µg/L</td>
<td>injection site reaction (33), headache (26), pain (23), flu-like Sx (21), peg antibodies (17)</td>
</tr>
<tr>
<td>Schreiber et al., 2007</td>
<td>229</td>
<td>observational 6–24 mos</td>
<td>mean 16.5 mg</td>
<td>Normal: NS, At End: 76.3</td>
<td>NS</td>
<td>injection site reaction (7), elevated liver enzymes (9), increased tumor vol (5), headaches (2)</td>
</tr>
<tr>
<td>Feenstra et al., 2005</td>
<td>19</td>
<td>SA + peg</td>
<td>60 mg/wk &amp; 30 mg octLAR or 120 mg lanATG</td>
<td>Normal: NS, At End: 95</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Naggers et al., 2007</td>
<td>32</td>
<td>SA + peg</td>
<td>60 mg/wk &amp; 30 mg octLAR, 120 mg lanATG</td>
<td>Normal: NS, At End: 100</td>
<td>NS</td>
<td>elevated liver enzymes (34)</td>
</tr>
</tbody>
</table>

* Sx = symptoms.
bination of somatostatin analogs and pegvisomant can be administered.

**Strategy 5: Medical and Radiosurgical Management Without Surgery.** When a patient refuses surgery or when surgery is absolutely contraindicated, therapy is limited to pharmacotherapy and/or radiotherapy. In this scenario, the patient is given a somatostatin analog as a first-line treatment. If unsuccessful at controlling GH and IGF-1 levels, SRS is administered as a secondary modality. The order of the primary and secondary modalities in this strategy is debatable, as there are few data on whether pretreatment with radiosurgery improves efficacy of somatostatin analog or vice versa. Regardless, if the first 2 modalities fail to achieve biochemical control, pegvisomant can be administered as tertiary therapy. Finally, the combination of somatostatin analog/pegvisomant can be administered if all other modalities have been unsuccessful.

**Cost**

**Procedures.** Costs to the patient for procedures, such as surgery and SRS, are generally time limited, while costs for medical therapies are lifelong, as continued administration is required to maintain biochemical control. The HCUPnet database (http://www.ahrq.gov/data/hcup) reported the median hospital charges to patients undergoing transsphenoidal resections of pituitary tumors in 2008 at $39,311 (mean $55,014 ± $6822 [SE]) (Table 7), with a median length of stay in the hospital of 3.0 days (mean 4.0 days). The HCUPnet reported median hospital charges to patients undergoing multisource (stereotactic) radiosurgery on pituitary tumors in 2008 at $56,356 (mean $67,224 ± $8882 [SE]), with a median length of stay in the hospital of 1.0 day (mean 3.2 days).

**Pharmacotherapy.** The annual costs of somatostatin analogs were provided by the Department of Pharmacy Services of the Fallon Community Health Plan.31,32 Given in price per dose, 10-, 20-, and 30-mg doses of octreotide (injected every 4 weeks) cost $1866.29, $2335.79, and $3453.07, respectively. Doses of 60, 90, and 120 mg of lanreotide (injected every 4 weeks) cost $2052.00, $2481.60, and $3668.40, respectively. The mean dose of octreotide administered is 24 mg/4 weeks, while the mean dose of lanreotide is 103 mg/4 weeks.16 The cost of each drug was then calculated based on specific dose prices and multiplied by the number of doses per year (13 doses in a 52-week period) to determine annual cost. The mean annual cost for octreotide is therefore calculated as $43,526, and the mean annual cost for lanreotide is $41,216 (Table 7).

The cost of pegvisomant (Somavert), injected daily, is $937.75, $1406.62, and $1875.50 for 10-, 15-, and 20-mg visals, respectively.16 Using 20 mg as the standard dose,80 the annual cost of pegvisomant is $68,438 (Table 7). The cost of combination somatostatin analog and pegvisomant therapy was calculated similarly, using 120 mg lanreotide per 4 weeks and 60 mg pegvisomant per 1 week as the standard doses.34,65 and is calculated at $67,189 (Table 7).

Estimates of the lifetime costs of each pharmacological treatment strategy were determined by multiplying the annual cost of the drug by the anticipated duration of treatment. The anticipated duration of treatment was taken as the anticipated length of survival after diagnosis and initiation of pharmacotherapy. For patients with acromegaly, the average age at diagnosis is 40 years,48 and the life expectancy for patients achieving biochemical control has been shown to be similar to that of the normal population49 at 78.3 years in the US (https://www.cia.gov/library/publications/the-world-factbook/geos/us.html). Accordingly, the anticipated duration of treatment for lifelong pharmacotherapy for acromegaly is estimated to be 38.3 years. Using this multiplier, the lifetime cost of octreotide, lanreotide, pegvisomant, and somatostatin analog plus pegvisomant therapies are $1,667,052; $1,578,567; $2,620,833; and $2,573,339, respectively (Table 7). Due to the uncertain nature of determining whether a medication, once off patent protection, will face competition in the marketplace, and how this will alter prices, it has not been possible to factor this into the calculations, although lower prices may make certain formulations or combinations of therapeutic strategies more attractive in the future.

From the costs and the approximate efficacy for each strategy, the average cost of treatment for a patient with a pituitary microadenoma can be estimated for each of the 5 strategies outlined above. Because of equivalent efficacy of lanreotide and octreotide in the treatment of acromegaly (see Efficacy), it is assumed that physicians will prescribe them equally when choosing to treat with somatostatin analog. Therefore, the estimated lifetime cost for somatostatin analog used in the calculation was their average ($1,622,597).

**Overall Costs**

The average expected cost to a patient can be estimated by first determining the total cost to treat 100 patients with a specific approach or strategy, and then dividing that cost by 100. This strategy corrects for the fact that the cost of each treatment in the approach is not incurred by all 100 patients. Instead, the cost of Steps 2–4 is only incurred by those patients in whom a cure was not achieved by the previous treatment in the approach. These costs, in turn, can be calculated using the efficacies of each modality to estimate the fraction of 100 patients who would need to be treated with each modality. The lifetime cost of medical therapy (somatostatin analog or pegvisomant) is only considered if it is the curative step in a patient’s treatment and would therefore need to be continued indefinitely. If medical therapy fails to produce a cure and the patient undergoes successful surgery or SRS, no lifelong medical therapeutic costs are included. The details of this cost analysis are summarized in Table 8.

**Quality of Life**

Acromegaly has been shown to diminish patient-perceived QOL. Joint pain and other musculoskeletal problems impact everyday physical comfort, while soft-tissue overgrowth affecting areas such as the spine, hands, and most notably the face can impair self-image and psycho-
logical well-being. Additional studies of QOL in patients with acromegaly have demonstrated psychological symptoms independent of excess GH secretion, including loss of initiative, mood swings, disruption in interpersonal relations, and social withdrawal anxiety.69

A self-administered questionnaire, the AcroQoL, quantitatively measures QOL in patients with acromegaly using 22 statements to which patients assign an agreement rating of 1–5. It is divided into physical and psychological scales, the latter being further divided into appearance and personal relations subscales. Lower scores on Acro-QoL indicate impairments in QOL. The most impacted area of QOL in patients with acromegaly is the appearance subscale, where patients with active disease scored 47 ± 23 and patients with inactive disease scored 55 ± 22. Both were significantly lower than obese controls, who scored 60 ± 19.66 Personal relationship QOL scores are actually higher for patients with acromegaly, regardless of disease control, compared with obese controls. Patients with controlled disease have higher overall (65 ± 18) QOL.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Efficacy (%)</th>
<th>Cost/Yr, Cost/Occurrence ($)</th>
<th>Duration of Treatment</th>
<th>Lifetime Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>transsphenoidal resection</td>
<td>80</td>
<td>39,311</td>
<td>1 time</td>
<td>39,311</td>
</tr>
<tr>
<td>SRS</td>
<td>45</td>
<td>56,356</td>
<td>1 time</td>
<td>56,356</td>
</tr>
<tr>
<td>octreotide (24 mg/4 wks)</td>
<td>60</td>
<td>43,526</td>
<td>38.3 yrs</td>
<td>1,667,052</td>
</tr>
<tr>
<td>lanreotide (103 mg/4 wks)</td>
<td>60</td>
<td>41,216</td>
<td>38.3 yrs</td>
<td>1,578,567</td>
</tr>
<tr>
<td>peg (20 mg/day)</td>
<td>80</td>
<td>68,438</td>
<td>38.3 yrs</td>
<td>2,620,833</td>
</tr>
<tr>
<td>SA + peg (120 mg lan/4 wks, 60 mg peg/wk)</td>
<td>95</td>
<td>67,189</td>
<td>38.3 yrs</td>
<td>2,573,339</td>
</tr>
</tbody>
</table>

* lan = lanreotide.
† The cost per year is given for continuous strategies, and the cost per occurrence is given for one-time treatments.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Strategy 1</th>
<th>Strategy 2</th>
<th>Strategy 3</th>
<th>Strategy 4</th>
<th>Strategy 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>surgery</td>
<td>surgery</td>
<td>SA</td>
<td>SA</td>
<td>SA</td>
</tr>
<tr>
<td>Step 2</td>
<td>SA</td>
<td>SRS</td>
<td>surgery</td>
<td>peg</td>
<td>SRS</td>
</tr>
<tr>
<td>Step 3</td>
<td>peg</td>
<td>SA</td>
<td>SA</td>
<td>surgery</td>
<td>peg</td>
</tr>
<tr>
<td>Step 4</td>
<td>SA + peg</td>
<td>peg</td>
<td>peg</td>
<td>SA + peg</td>
<td>SA + peg</td>
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<tr>
<td>pts w/ cure or control by each step</td>
<td>80/100</td>
<td>80/100</td>
<td>60/100</td>
<td>60/100</td>
<td>60/100</td>
</tr>
<tr>
<td>Step 1 (of 100 pts)</td>
<td>12/20</td>
<td>9/20</td>
<td>32/40</td>
<td>32/40</td>
<td>18/40</td>
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<tr>
<td>Step 2 (of remaining)</td>
<td>6/8</td>
<td>7/11</td>
<td>5/8</td>
<td>6/8</td>
<td>18/22</td>
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<tr>
<td>Step 3 (of remaining)</td>
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<td>3/3</td>
<td>2/2</td>
<td>4/4</td>
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<td>99</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<tr>
<td>total no. w/ cure</td>
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<td>100</td>
<td>40</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>no. of pts requiring treatment</td>
<td>12</td>
<td>7</td>
<td>65</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>surgery</td>
<td>8</td>
<td>4</td>
<td>3</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>SA (lifetime)</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>peg (lifetime)</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
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<tr>
<td>SRS</td>
<td>3,931,100</td>
<td>3,931,100</td>
<td>1,572,440</td>
<td>314,488</td>
<td>0</td>
</tr>
<tr>
<td>SA</td>
<td>19,471,169</td>
<td>11,358,182</td>
<td>105,468,834</td>
<td>97,355,847</td>
<td>97,355,847</td>
</tr>
<tr>
<td>peg</td>
<td>20,966,666</td>
<td>7,862,500</td>
<td>6,709,333</td>
<td>83,866,663</td>
<td>47,174,998</td>
</tr>
<tr>
<td>SRS</td>
<td>0</td>
<td>1,127,120</td>
<td>0</td>
<td>0</td>
<td>2,254,240</td>
</tr>
<tr>
<td>SA/peg</td>
<td>5,146,677</td>
<td>0</td>
<td>0</td>
<td>5,146,677</td>
<td>10,293,355</td>
</tr>
<tr>
<td>cost of treatment ($)</td>
<td>49,500,000</td>
<td>24,300,000</td>
<td>113,800,000</td>
<td>186,700,000</td>
<td>157,100,000</td>
</tr>
<tr>
<td>mean cost/pt/lifetime (US $)</td>
<td>495,156</td>
<td>242,789</td>
<td>1,137,506</td>
<td>1,866,837</td>
<td>1,570,784</td>
</tr>
</tbody>
</table>
scores compared with those with active disease (56 ± 20), but patients in sustained remission still exhibit a QOL lower than normal controls, due to irreversible changes caused by excess GH.13,86

Several studies have attempted to determine the impact of specific treatments on QOL (summarized in Table 9).13,42,52,55,64,73,79 In a study of 118 patients with controlled disease who were treated with various methods, the highest AcroQoL scores were observed in patients who were treated with surgery alone.13 Using additional QOL questionnaires, the same investigation found that radiotherapy negatively impacted energy levels and physical scores despite achieving adequate control. Additional studies have verified these results,32,73 although one study suggested that this QOL reduction may be attributable to the longer interval to remission observed in patients treated with radiotherapy.73 Adding pegvisomant to treatment with somatostatin analog in patients with controlled disease was shown to increase overall QOL and physical QOL compared with patients with controlled disease receiving somatostatin analog only.64

Discussion

Overview

This comparative effectiveness review was designed to integrate efficacy, cost, and QOL data for individual treatment modalities for acromegaly in an effort to inform clinical decisions regarding specific treatment regimens for patients with acromegaly resulting from a GH-secreting pituitary microadenoma. The 5 strategies examined represent common clinical approaches to managing patients with acromegaly over time.

Selection of Efficacy Data

We recognize that patients with macroadenomas, and especially those with tumors that invade the cavernous sinus, have outcomes different from (and often inferior to) those with microadenoma and are likely to require multimodality therapy at the initiation and for the duration of treatment (and, at the present time, throughout the remainder of their lives). These circumstances require more complex—and, potentially, more subjective—assessment of the therapies to be used as well as the morbidities and excess mortality associated with the disease and its treatment.39,51,58,68,77 For this reason, we have focused this initial CER on noninvasive, GH-secreting microadenomas.

We recognize that criteria for disease control or cure, in view of improvements in treatments and in biochemical assays (both static and dynamic), have changed over the last 15 years. This may influence the utility of older studies in which biochemical criteria for cure or control were less stringent, especially when compared with the latest consensus statement published in 2010: an IGF-1 level in the age-adjusted, normal range plus either a random GH of less than 1 μg/L in patients treated medically or glucose-suppressed GH less than 0.4 μg/L in patients treated with other modalities, except pegvisomant, where only IGF-1 levels are used.37–39 Notwithstanding, because few investigations of either mono- or polytherapy completely satisfy the 2010 consensus criteria, we have included data from older as well as more recent periods to conduct a comprehensive, contemporary CER review that integrates clinical and health economics data. The results and conclusions of this review should therefore be considered in the context of the evolving definitions of disease control and cure, and future CER studies can be adjusted as more studies with Class I evidence, which fully satisfy the 2010 criteria, are published.

Efficacy Versus Effectiveness

Multiple therapeutic options exist for the treatment of acromegaly, and various combinations of modalities have been used in response to specific clinical circumstances. Efficacy is a major determinant of the initial and subsequent therapeutic modalities. As discussed in detail above, our primary literature review demonstrates efficacy rates for treating GH-secreting pituitary microadenomas of approximately 80% for transsphenoidal resection, 80% for pegvisomant therapy, 60% for somatostatin analog therapy, 45% for stereotactic radiosurgery, and 95% for combined somatostatin analog and pegvisomant therapy (Table 10). However, determining the most effective treatment strategy or combination of strategies involves combining considerations of efficacy with those related to the cost of therapy and to the QOL associated with each of the potential treatment strategies.

Cost

The lifetime cost for pharmacotherapy is between 29 and 41 times the cost of SRS and 41 and 59 times that of surgery, depending on the drug (or drugs) used to achieve remission. When considering the 5 management strategies described earlier, those that incorporated surgery at some point in the management algorithm had significantly lower mean costs than strategies involving pharmacotherapy alone. Using surgery earlier in the management algorithm reduces costs versus waiting until secondary or tertiary steps for surgical intervention. Similarly, incorporation of SRS into the treatment strategies also reduces cost relative to strategies using pharmacotherapy alone. Conversely, strategies beginning with medical therapy had significantly higher costs, each with an average lifetime cost exceeding $1 million per patient (Table 8).

Quality of Life

While QOL studies lack a common structure or a standardized metric, their results paint a general picture of how treatment regimens affect QOL in patients with acromegaly. Patients undergoing curative surgery had the highest QOL of all treated patients. Radiotherapy was associated with lower QOL in several studies, and it has been suggested that this is related to delayed remission. Although not specifically considered in this study, SRS also has the highest incidence of hypopituitarism (14.5%) of all treatment options, and GH deficiency in patients who previously had acromegaly has been shown to decrease QOL.87 These findings suggest that SRS has a less favorable QOL profile than surgery and may be associated with comparable or lower QOL than medical management strategies.
<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts</th>
<th>Study Design</th>
<th>Disease Status (%)</th>
<th>AcroQoL Total Score</th>
<th>Physical Performance</th>
<th>Psychological Well-Being</th>
<th>Appearance</th>
<th>Personal Relations</th>
<th>Relationship of GH/IGF-1 w/ QOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biermasz et al., 2004</td>
<td>118</td>
<td>cross-sectional; all treatments examined</td>
<td>cont</td>
<td>68.3 ± 16.9</td>
<td>64.0 ± 21.2</td>
<td>70.7 ± 16.8</td>
<td>63.1 ± 22.1</td>
<td>78.3 ± 14.9</td>
<td>longer active disease duration correlates w/ lower scores</td>
</tr>
<tr>
<td>Note: Surgery only produced a higher QOL on physical, pain, &amp; energy related subscales (AcroQoL).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rowles et al., 2005</td>
<td>80</td>
<td>evaluation of accuracy of AcroQoL</td>
<td>cont (34), uncont (66)</td>
<td>59.4 ± 26.9</td>
<td>59.3 ± 30.6</td>
<td>59.5 ± 27.4</td>
<td>48.5 ± 27.8</td>
<td>70.6 ± 30.6</td>
<td>no correlation</td>
</tr>
<tr>
<td>Note: Previous radiotherapy is associated w/ lower overall QOL, but that may be due to longer duration of disease in people treated w/ radiotherapy.</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hua et al., 2006</td>
<td>52</td>
<td>cross-sectional; effect of lanreotide</td>
<td>cont (58)</td>
<td>63.85</td>
<td>60.88</td>
<td>65.42</td>
<td>56.78</td>
<td>74.48</td>
<td>no correlation</td>
</tr>
<tr>
<td>Note: No association btwn radiotherapy &amp; AcroQoL score.</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matta et al., 2008</td>
<td>93</td>
<td>cross-sectional; all treatments examined</td>
<td>cont (39)</td>
<td>58.8 ± 17.9</td>
<td>63.8 ± 16.5</td>
<td>70.4 ± 15.9</td>
<td>63.1 ± 20.0</td>
<td>77.9 ± 14.8</td>
<td>weak inverse correlation btwn appearance subscale &amp; IGF-1 value</td>
</tr>
<tr>
<td>Note: Surgery produced a higher appearance subscale score vs no surgery.</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neggers et al., 2008</td>
<td>20</td>
<td>prospective; effect of peg</td>
<td>cont</td>
<td>58.9 ± 18.6</td>
<td>65.0 ± 18.3</td>
<td>68.8 ± 15.7</td>
<td>56.3 ± 16.7</td>
<td>77.9 ± 17.0</td>
<td>no correlation btwn GH, IGF-1, &amp; QOL</td>
</tr>
<tr>
<td>Note: Treatment w/ SA + peg increased overall QOL &amp; physical subscale scores vs SA only &amp; vs SA + placebo, regardless of effect on IGF-1 levels.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pegvisomant was found to increase QOL when given in conjunction with somatostatin analogs, as opposed to the use of somatostatin analogs alone. Treatment with a somatostatin analog (lanreotide) alone actually lowered QOL in patients with controlled disease. This was not investigated in the reviewed QOL studies, but drug injections may play some role in the reduction in QOL. Studies in diabetic patients have shown that treatment with insulin pumps produces a higher QOL than treatment with multiple daily injections. While multiple daily injections are much more frequent and bothersome than monthly somatostatin analog injections, there may be some correlation between any type of required injection and QOL. However, pegvisomant is also an injection (daily), but it improves QOL, suggesting that this issue requires further investigation. Consider, for example, that differences in hypodermic needle sizes between types of injections—larger needles for intramuscular or deep subcutaneous injection versus smaller needles for superficial subcutaneous injection—may also have an impact when comparing monthly injections of LAR or Somatuline (intramuscular or deep subcutaneous) to daily, superficial subcutaneous injection of pegvisomant. We have not been able to find an objective consideration of such factors and so have not included it in this review.

Finally, we did not consider dopamine agonists, since they are generally not used as commonly or as consistently as either somatostatin analogs or pegvisomant (summarized by Katznelson 51). Bromocriptine normalizes IGF-1 levels only with high doses, which are poorly tolerated in about 10% of patients. Cabergoline, which appears to work best in patients with the most modest elevations of serum IGF-1, may normalize IGF-1 in slightly fewer than 40% of patients and in those with cosecretion of prolactin. Side effects of dopamine agonists are common, and the development of valve disease in patients on lifelong dopamine agonist treatment has limited their use to a minority of patients (as summarized by Katznelson 51). Dopamine agonists, then, tend to be used as an adjunct after multiple treatment failures, which would place them beyond Step 4 in most of the algorithms that we describe (Table 11).

Most importantly, no study found a strong correlation between QOL and biochemical control or remission status in patients receiving treatment for acromegaly. In other words, while treatment in general improves overall QOL for patients with acromegaly, successfully achieving biochemical control does not result in additional QOL benefit compared with strategies resulting in incomplete biochemical response. This strengthens the case for QOL being included as a separate parameter when evaluating the effectiveness of treatment modalities.

**Summary of Comparative Effectiveness Review**

The 4 individual therapies examined in this study were given relative categorical rankings (1–4) in each of the 3 domains: efficacy, cost, and QOL. In all categories, lower scores are more favorable. Giving all domains equal weight, a total rank score was assigned to each therapy, and an overall ranking was determined by ordering the modalities by ascending total rank score (Table 10). As
expected, surgery received the highest overall rank. Next was pegvisomant, which may seem unlikely because of its typical place as a last-choice therapy, often due to high cost. However, its high efficacy and association with high QOL improve its overall effectiveness. Somatostatin analogs and SRS received rankings of 3 and 4, respectively. Not included in the table is the option of a combined somatostatin analog and pegvisomant treatment. This modality actually has a higher efficacy than both somatostatin analog and pegvisomant treatment, while costing slightly less than pegvisomant therapy alone. This would suggest choosing the combination therapy using lower doses of pegvisomant over treatment with strictly higher doses of pegvisomant in the future.

A Novel Potential Regimen for Management of Acromegaly

Cost-effectiveness (which combines cost and efficacy data) of the 5 examined treatment regimens was presented as a mean cost for a patient treated by a certain regimen. Determining the mean QOL of a patient after a specific regimen, however, is more difficult in that QOL studies vary widely from each other regarding the control and experimental groups, even though many use the same AcroQoL questionnaire. Because delineating mean QOL for specific regimens is not feasible at this time, cost, efficacy, and QOL were evaluated for individual treatments, rather than overall regimens, to formulate independently a treatment strategy that seemed optimal when weighing each of the 3 domains (cost, efficacy, and QOL) equally.

The end result of this ranking system was a unique strategy not previously considered in either the decision tree (Fig. 1) or the 5 preselected treatment regimens (Table 10). It consisted of the following treatment choices (in order): surgery, pegvisomant, somatostatin analog, and SRS. While surgery is a widely accepted and used first-line therapy, pegvisomant is not commonly chosen as the first medical therapy in clinical practice, due in part to its perceived high cost, lack of tumor shrinkage, and the need to inject it daily. Its efficacy, however, ranks above the remaining options of somatostatin analogs and SRS, and QOL data show that patients treated with pegvisomant exhibit a higher QOL than those treated using somatostatin analog or SRS. Although pegvisomant is the most costly of the treatment options (a combination of its high cost per dose and lifetime use), its high efficacy prevents many treatment failures that other therapies (somatostatin analogs and SRS) allow—failures that would require subsequent treatments and, consequently, cause additional cost and potentially diminished QOL.

Strictly evaluating cost-effectiveness of the preselected and novel potential regimens, the novel strategy was found to rank above all but one (surgery, SRS, somatostatin analog, and pegvisomant) of the preselected strategies (Table 11). Directly comparing these 2 regimens in the third domain (QOL) could not quantitatively be performed, for aforementioned reasons. However, because pegvisomant has been found to bring about a significantly higher QOL than SRS, it can be inferred that a strategy using pegvisomant as a second-line option (our formulated strategy) would lead to a higher QOL than a strategy using SRS as its second-line option (the most cost-effective strategy). Therefore, while this regimen is less cost-effective than the previously described strategy, it would most likely produce a higher QOL in the patient after treatment. For this reason, pegvisomant use could be considered an optimal medical strategy to use when treating acromegaly, especially if QOL ranks equally with or higher than the domains of cost and efficacy, in the eyes of the physician and patient.

Summary

Our study suggests that surgery is the most efficacious first-line treatment option when treating a GH-secreting pituitary microadenoma, and this is in line with current treatment recommendations. Interestingly, our study produced results that suggest that pegvisomant may be the

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Average Cost/Pt ($)</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>surgery</td>
<td>SA</td>
<td>peg</td>
<td>495,156</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>surgery</td>
<td>SRS</td>
<td>peg</td>
<td>242,789</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>SA</td>
<td>surgery</td>
<td>peg</td>
<td>1,137,506</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>SA</td>
<td>peg</td>
<td>surgery</td>
<td>1,866,837</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>SA</td>
<td>SRS</td>
<td>peg</td>
<td>1,570,784</td>
<td>5</td>
</tr>
<tr>
<td>novel</td>
<td>surgery</td>
<td>SA</td>
<td>peg</td>
<td>387,390</td>
<td>2</td>
</tr>
</tbody>
</table>
Comparative effectiveness review of acromegaly treatment options

most efficacious second-line therapy (after surgery). Despite its high cost and required lifetime use, its rate of efficacy is significantly higher than that of the remaining treatment options (somatostatin analog and SRS), and the QOL produced after treatment with pegvisomant is also better than the QOL achieved after treatment with somatostatin analogs or SRS. In the past, cost has been a major deterrent to the use of pegvisomant as a therapy, but the high rate of success and high QOL associated with its use may outweigh the cost. It is appropriate to note that when using somatostatin analog or SRS as an early-line therapy, failure of treatment often results in the ultimate use of pegvisomant for a persistent biochemical remission in at least half of the patients; choosing pegvisomant as an early-line therapy may produce better results earlier in treatment.

Study Limitations

This comparative effective analysis is not intended to present firm recommendations, as each treatment strategy must be tailored to the unique clinical circumstances associated with a particular patient. Instead, the analysis that we have performed is designed to inform the decisions of physicians who may be confronted with several alternate strategies for treating a patient with acromegaly from a GH-secreting pituitary microadenoma. It does not consider all potential permutations possible, but rather analyzes typical strategies used in every day clinical practice. Therapeutic approaches for which inadequate efficacy or outcome data are available in the current literature have been excluded. For this reason, strategies including (but not necessarily limited to) initial management with dual, concurrent medical therapy, combined medical and radiosurgical therapy, and repeat surgery for delayed treatment failure have not been included in this review.25

As we noted earlier, we have focused our attention deliberately on GH-secreting microadenomas, since larger and more invasive tumors are inherently more complicated and typically require multimodality therapy from the start. This situation requires more subjectivity in choosing combinations of therapies and would have a more convoluted set of interactions due to the nature of morbidity and mortality related to disease, its duration, and its treatment.20,27,41,51,58,77

This analysis uses efficacy figures published in the primary medical literature, and thus the efficacy of each modality can only be estimated for clinical circumstances identical to the experimental conditions under which each modality was studied. Notwithstanding, this review discusses a multistep approach to management, and it is impossible to account fully for the potential effects of uncontrolled variables in the primary investigations, for potential cumulative effects of prior therapeutic interventions, or for variability in efficacy associated with chronological differences in the use of each modality. Additionally, factors including the length of follow-up in each study, population-specific characteristics, and institutional referral patterns and management preferences cannot be directly controlled. The relative effects of these potential confounding factors remain unknown, and clinicians interpreting this or any study based upon interpretation of primary literature should be aware of this potential source of unquantifiable bias.

The ranking system we use is semiquantitative in nature and assigns equal weights to efficacy, cost, and QOL. We recognize that the quantity of evidence available regarding the efficacy, cost, and QOL of each modality are variable and that a balanced scoring scheme does not account for this quantitative difference. We also recognize that this strategy of equal weighting may not be appropriate for all patients and that each domain may need to be more or less heavily considered in real-life situations. However, in the absence of any standardized approach to determining an appropriate strategy for weighting, we have elected to perform an equally weighted analysis, and we advise clinicians to consider the potential need for individualized weighting of each of the data domains when applying this analysis to real-life, clinical scenarios.

Estimation of costs in this study did not take into account the costs of treatment for comorbidities, income lost due to sick leave, or other, indirect costs that result from acromegaly, as there are no reliable data available for such calculations. Regarding SRS, treatment with somatostatin analogs often used during the latency period (mean 3.3 years) following administration of radiotherapy was not included, but would add to the overall cost of SRS. The treatment of possible side effects, most notably hypopituitarism, was not considered but could also contribute to increased overall costs. We limited our review to microadenomas; the necessary analyses for larger or invasive tumors would be more complex and less definitive but represent an area for future research. Finally, this review neither accounts for potential cost decrements due to technological advances nor loss of patent protection, nor does it include inflation over time, but rather it calculates cost in current dollars. Again, future changes in cost of medications is not easily modeled due to the complex nature of patent protection, entry into the generic market, and the size of the market. This dimension of cost analysis was excluded here, and changing drug costs may necessitate adjustment of this CER analysis in the years to come.

Quality-adjusted life years are the current method to evaluate the cost-effectiveness of treatments by determining cost per year of survival. Because survival is generally the same after each treatment, given that biochemical control is achieved, quality-adjusted life years were not directly applicable to this study. However, a study concentrating on length of survival posttreatment and AcroQoL data could use this measure. If this investigation were to be undertaken, it would have to consider that certain treatment strategies are chosen based on age of the patient; that is, SRS may be recommended to younger patients and would therefore be associated with a longer overall length of survival, or conversely the recommendation may be medical therapy in an older patient who is deemed not to be an optimal surgical candidate. Long-term (2–3 decades) effects of SRS on disease remission as well as alterations in morbidity and mortality due to disease control and treatment are still lacking for SRS.77

Despite the development of AcroQoL, QOL data as-
associated with individual treatment modalities remain limited. Additional QOL research may illuminate the QOL implications of each of the potential treatment strategies for acromegaly. Similarly, additional cost-effectiveness data from US health care markets are necessary to further clarify the detailed costs associated with various comprehensive treatment strategies for acromegaly.

Conclusions

Transsphenoidal surgery and lifetime pegvisomant therapy were the most efficacious modalities, followed by somatostatin analog therapy and then by SRS. One-time, curative procedures (surgery and SRS) were more cost-effective than lifelong medical therapy (somatostatin analog and/or pegvisomant). Quality of life data, while less quantitative in nature, suggested that early, curative surgery results in the highest patient QOL, followed by pegvisomant therapy, then by somatostatin analog therapy, and finally by SRS.

The novel potential treatment regimen proposed in this study is not meant to serve as a steadfast recommendation to physicians or to rank strategies above one another when deciding on a treatment regimen, but rather to inform clinicians faced with patients for whom several treatment modalities or strategies could be used. Each patient presents different challenges, and the domains that we weighted equally in our study (cost, efficacy, and QOL) may carry a different weight with the clinician and patient. This should be taken into account by the clinician, along with the data provided by this study, to choose the best strategy for the patient at hand.

Disclosure

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Author contributions to the study and manuscript preparation include the following, Conception and design: Marko, LaSota, Weil. Acquisition of data: Marko, LaSota. Analysis and interpretation of data: Marko, LaSota, Weil. Drafting the article: Marko, LaSota. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Marko. Statistical analysis: Marko, LaSota. Administrative/technical/material support: Weil. Study supervision: Hamrahian, Weil.

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