Pituitary 5: 185–196, 2002

Current Status and Future Opportunities for Controlling Acromegaly

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Abstract. **Growth-hormone (GH) secreting adenomas, including acromegaly, account for approximately one-sixth of all pituitary adenomas and are associated with mortality rates at least twice that of the general population. The ultimate goal of therapy for acromegaly is normalization of morbidity and mortality rates achieved through removal or reduction of the tumor mass and normalization of insulin-like growth factor I (IGF-I) levels. Previously published efficacy results of current treatment modalities (surgery, conventional radiation, and medical therapy with dopamine agonists and somatostatin analogs) are often difficult to compare because of the different criteria used to define cure (some of which are now considered inadequate). For each of these modalities, pooled data from a series of acromegaly studies were reviewed for rates of IGF-I normalization, a currently accepted definition of cure. The results showed overall cure rates of approximately 10% for bromocriptine, 34% for cabergoline, 36% for conventional radiation, 50–90% for surgery for microadenomas and less than 50% for macroadenomas, and 54–66% for octreotide. These cure rates based on IGF-I normalization are generally less than those reported for cure based solely on GH levels. Novel new therapies for acromegaly include the somatostatin analog, lanreotide, Gamma Knife radiosurgery, and pegvisomant, the first in its class of new GH receptor antagonists. Although it does not appear that Gamma Knife radiosurgery results in significantly higher cure rates or fewer complications, it does provide a notable improvement in delivery compared with conventional radiation. Early studies have reported IGF-I normalization in 48% of lanreotide-treated patients and up to 97% of pegvisomant-treated.**

Key Words. **pituitary adenoma, acromegaly, lanreotide, octreotide, Gamma Knife, pegvisomant**

I. Incidence and Prevalence of Pituitary Tumors

Occult pituitary adenomas are common and have been observed in 10% of normal volunteers studied by magnetic resonance imaging (MRI) of the pituitary gland [1]. Most pituitary adenomas remain asymptomatic and do not require treatment, and clinically significant tumors are relatively rare. In a Canadian epidemiological study, the overall incidence rates for intracranial neoplasms have been estimated to be 10.2 and 10.8 per 100,000 for men and women, respectively [2]. Community and hospital-based studies have shown pituitary adenomas to be the third most common primary intracranial tumor following astrocytoma and meningioma [2–4]. The incidence of pituitary adenoma in Sweden, excluding growth hormone (GH)-secreting adenomas (acromegaly) and adrenocorticotrophic-hormone (ACTH)-secreting adenomas (Cushing's disease), rose from approximately 5–10/million/year in the 1950s and 1960s to approximately 10–15/million/year in the 1990s. This increase in incidence was observed for both men and women and was probably due to better diagnostic skills and awareness. More recently, a population study in the UK estimated the overall incidence of pituitary adenomas to be 2.5/100,000/year [4].

A retrospective review of 2,230 patients who underwent surgery for a pituitary adenoma between 1969 and 1993 showed prolactinomas to be the most common type of adenoma (39%), followed by non-functioning adenomas (27%), GH-secreting adenomas (16%), and Cushing's (15%) [5]. ACTH-secreting adenomas causing Nelson's syndrome and thyrotropin (TSH)-releasing adenomas are rare (<3%) [5]. Population-based studies in the UK, Sweden, Ireland, and Spain estimated the incidence of acromegaly to be 3–6 new cases/million/year (prevalence of 38–69/million) [3,4,6–8] (Table 1).

The frequency of pituitary adenomas varies greatly according to age and sex. Overall, more men than women are diagnosed with pituitary adenomas and have a peak incidence between 55 and 65 years of age [9]. A non-functioning adenoma and acromegaly occur equally

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Table 1. *Incidence and prevalence of acromegaly*

	Number of cases	Incidence per million	Prevalence per million	Percent (%) male
Alexander et al., 1980	164	2.8	38	–
Bengtsson et al., 1988	166	3.3	69	46
Ritchie et al., 1990	131	4	63	–
Etxabe et al., 1993	74	3.1	60	35

in men and women and have peak incidences in the older age groups (fourth to eighth decades), whereas prolactinoma and Cushing's occur more frequently in women and have peak incidences between the second and fifth decades of life [5,10]. The greatest discrepancy of gender distribution occurs at the time of peak incidence for each tumor type [5]. When distributed by tumor size, men are significantly more likely than women to have a macroadenoma (tumor size >10 mm) [11]. Overall, macroadenomas occur more frequently in acromegaly, as well as for non-functioning adenomas, whereas microadenomas are more common for prolactinomas and Cushing's.

Pituitary tumors are associated with decreased life expectancy [9]. The mortality rate associated with acromegaly has been estimated to be at least twice that in the general population, most commonly from cardiovascular, pulmonary, and neoplastic disease [3,6,12–14]. Patients suffering from a macroadenoma are more likely to have pituitary deficiency; therefore, the probable cause of increased mortality is the impairment of pituitary function, and not the pituitary tumor itself.

II. Current Management of Patients with Acromegaly

The morbidity and mortality of acromegaly are determined by the GH/insulin-like growth factor (IGF-I)-induced somatic impairments (e.g., cardiac hypertrophy, sleep apnea, arthropathy, risk of cancer development), mass effects of the tumor, and by the accompanying hypopituitarism. Whereas tumor mass effects and hypopituitarism can be treated with combined medical and surgical approaches, hormone hypersecretion is often of greatest difficulty to control. The previously employed cure criteria used to evaluate treatment for acromegaly, spontaneous GH < 2.5 μg/L and glucose-suppressed GH < 2 μg/L, have been recently thought to be inadequate [15–17]. Currently, biochemical cure is defined as serum GH concentrations <1 μg/L after oral glucose ingestion (using a chemiluminescent or immunoradiometric assay for GH) and, more importantly, the reduction of circulating IGF-I levels to normal (adjusted for age and sex) [15–17] (Fig. 1). Because of the changes in criteria used for defining cure

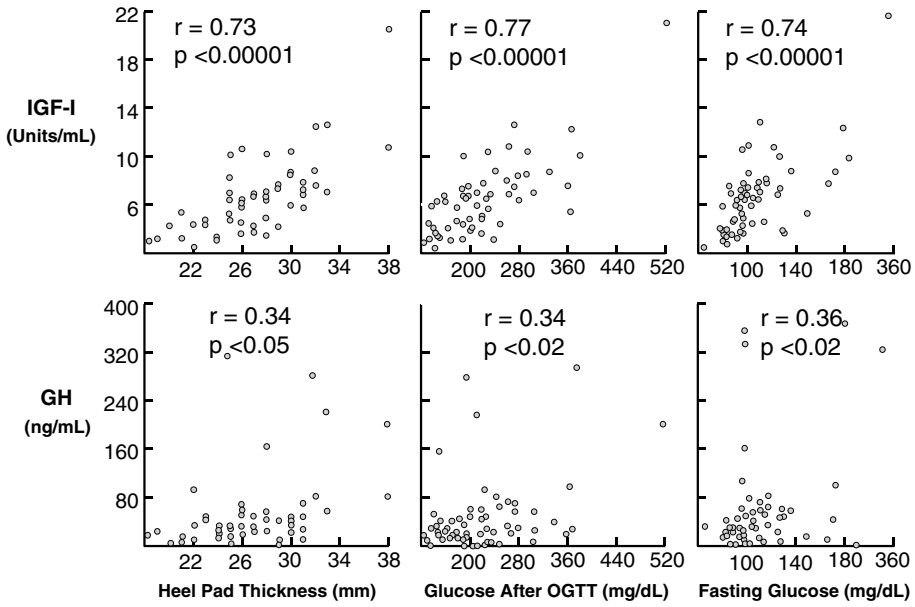

Fig. 1. *Linear regression analysis of the correlation between fasting IGF-I concentration or growth hormone concentration after glucose and heel pad thickness, blood glucose one hour after the oral administration of glucose (OGTT), and fasting blood glucose. Figure modified from D.R. Clemmons et al. NEJM 1979;301:1138–1142. Used with permission.*

Table 2. *Efficacy of therapeutic modalities in the treatment of acromegaly*

	Percent of patients with normalized IGF-I*	Adverse events	Comments	References
Surgery	67% overall 78% microadenomas; 57% macroadenomas		Immediate effect	[18–27]
Conventional radiation	36%	Hypopituitarism, visual disturbances, neurological damage and necrosis, secondary brain tumors	Slow response Serious complications	[30–41]
Dopamine agonists				
Bromocriptine	10%	Nausea, constipation, vomiting, indigestion, dyspepsia, orthostatic hypertension, anorexia, dry mouth, nasal stuffiness, digital vasospasm, and drowsiness	Convenient Frequent though generally mild to moderate side effects	[45–81]
Cabergoline	34%	Nausea, constipation, vomiting, indigestion, dyspepsia, orthostatic hypertension, anorexia, dry mouth, nasal stuffiness, digital vasospasm, and drowsiness	Convenient Less frequent gastrointestinal side effects than with bromocriptine	[82–88]
Somatostatin analogs				
Octreotide sc	54%	Nausea, abdominal pain, diarrhea, gallstones and/or biliary sludge	Frequent daily self-administered injections	[55,90–123]
Octreotide LAR	66%	Nausea, abdominal pain, diarrhea, gallstones and/or biliary sludge	Deep intragluteal injections at 1–6 week intervals	[124–132]

*Percentages are based on the total number of patients with available IGF-I data as taken from the cited references.

or control of acromegaly, the efficacy results of previously reported treatment are often difficult to compare. Current treatment modalities used in the management of acromegaly (surgery, radiotherapy, and medical therapy with dopamine agonists and somatostatin analogs) are discussed below with a focus on using the criteria of IGF-I normalization as the standard of cure or adequate control (Table 2).

II.A. Surgery

Transsphenoidal surgery for the removal of pituitary tumors remains the cornerstone of acromegaly therapy. When surgery is performed by an experienced surgeon, mortality rates are less than 1%, and 80–90% of microadenomas and up to 50% of macroadenomas may be completely removed [18–20]. In several recently reported studies (1995–2001), the surgical outcomes of 818 patients who had undergone transsphenoidal surgery for pituitary adenoma were reviewed based on recent criteria for biochemical cure (normalized IGF-I, random GH < 2.5 μg/L, and glucose-suppressed GH $<$ 1–2 μg/L) [18–27]. In these studies, the majority of patients were followed for 1–5 years post surgery (mean range, 3 months to 16 years). Transsphenoidal surgery resulted in normalized IGF-I levels in 67% of patients, random GH < 2.5 μg/L in 58% of patients, and normal glucose-suppressed GH levels in 66%. Simultaneous normalization of GH and IGF-I were reported in 72% of patients at follow-up. Patients with microadenomas had the highest rate of IGF-I normalization of 78%, while, as expected, patients with macroadenomas fared significantly worse—they achieved biochemical cure in only 57% of cases [19,20,22–24, 26]. One study reported normalized IGF-I levels in only 20% of patients with macroadenomas greater than 20 mm in size [23]. Patients with noninvasive tumors had an overall cure rate of 85% compared to only 37% of patients with invasive tumors. Long-term (mean follow-up of >5 years) recurrence rates ranged from 0 to 19% [19,21,24–26]. Surgical experience is yet another important determinant of the outcome. In one retrospective review [20], an improvement in surgical cure rates by a single surgeon was observed over time, from 45% following surgery performed prior to 1987 to 73% between 1991 and 1996. Serious surgical complications occur in approximately 1.5% of patients and mortality is rare ($<1\%$) [25]. For most patients, surgical management of acromegaly safely provides an immediate and effective treatment, and may be definitive therapy in some patients. However, differences in tumor size and invasiveness, as well as in surgical expertise, dramatically affect surgical outcome. A significant proportion of patients with acromegaly require medical therapy or radiation for biochemical control of acromegaly.

II.B. Conventional radiation

Conventional radiation has been employed as a treatment in patients with acromegaly for many years. Currently, conventional radiotherapy of a pituitary tumor is generally delivered in fractionated doses of 160–180 cGy 4–5 times/week over a 5–6 week period so as to administer 45–50 Gy (4500–5000 rads) [28]. Multiple studies of radiation have reported declines in GH levels for up to 20–25 years, with an ultimate cure rate of between

70–90% (cure defined as GH < 5 μg/L) [29]. A review of existing data, however, using current criteria for the cure of acromegaly, has demonstrated that radiation therapy is much less effective than previously thought. Radiation has been associated with the reduction of tumor size, and has been shown to normalize serum IGF-I levels in only about one-third of all patients.

In a series of 12 studies conducted between 1988 and 2001, and including a personal communication from Dr. Phillippe Jaquet from Marseille, France, 560 patients with acromegaly were treated with radiotherapy and followed for an average of 4 to 13 years [30–41]. The overall frequency of normalization of IGF-I in these patients was 36%. Patients with a mean or median follow-up of no more than 7 years had a efficacy rate of 29% compared to 45% in patients followed longer than 10 years. However, because of an increasing number of patients lost to follow-up over time, and the greater likelihood that "lost" patients died prematurely, this long-term rate of efficacy is most likely inflated. Side effects related to conventional radiation commonly include radiation-induced hypopituitarism (up to 50–60% of patients), and rarely, damage to the optic pathways, neurological damage and complications, and secondary brain tumors [29,42]. In addition, because of the slow biochemical response to radiation, the morbidities of acromegaly persist for several years following treatment unless adjunctive medical therapy is successfully used [29]. As radiation technology improves, the risks of optic and neurological damage may be further minimized, but whether there exists causal factors other than radiation predisposing these patients to secondary brain tumors has yet to be determined [43,44].

II.C. Dopamine agonists (bromocriptine and cabergoline)

Dopamine agonists suppress GH release through negative coupling of dopamine receptors with adenylate cyclase resulting in direct suppression of GH release [45]. Dopamine agonists are advantageous in that they have the convenience of an oral route of administration; however, published data have shown only limited effectiveness in the treatment of acromegaly. Of the numerous dopamine agonists developed and used in the management of patients with acromegaly, bromocriptine is the most widely investigated and has been used since the early 1970s. Bromocriptine is generally administered orally several times daily for a total dose ranging between 7.5 and 80 mg/day. Few patients have exhibited any benefit at dose levels greater than 20–30 mg/day and side effects at higher doses can be significant [46–48].

In a review of 34 studies between 1975 and 1990, 616 patients received bromocriptine (7.5–80 mg/day). Approximately 21% of these patients achieved plasma GH < 5 μg/mL, but only 10% of achieved normalization of IGF-I levels [46–79]. Treatment with bromocriptine has been generally found to be ineffective with regard to tumor shrinkage, with an incidence of only between 10% and 20% [45]. Frequent side effects include gastrointestinal disorders (nausea, constipation, vomiting, indigestion, and dyspepsia), orthostatic hypertension, anorexia, dry mouth, nasal stuffiness, digital vasospasm, and drowsiness [80]. Most symptoms resolve with continued use of the drug; however, side effects continue in a significant number of patients [81].

Compared to bromocriptine, a newer orally administered dopamine agonist, cabergoline, has a more specific D2 receptor-binding activity and a prolonged duration of action. Effective dose levels of cabergoline for the treatment of acromegaly range between 1 mg administered twice weekly and 0.5 mg administered daily (total weekly dose range of 2–3.5 mg). Doses higher than 3.5 mg/week have not been shown to improve efficacy, but rather, result in decreased tolerability [82]. Cabergoline, however, has been mainly used in the treatment of hyperprolactinemic disorders, and its use in the treatment of acromegaly has been studied significantly less extensively than has bromocriptine. In a series of six studies conducted between 1988 and 1998, 112 patients received cabergoline 0.3–7.0 mg/week [82–87]. Normal IGF-I was achieved in a total of 34% of patients. Although it appears that cabergoline may be more effective than bromocriptine, it must be noted that, in addition to the limited data currently available, the range of efficacy in these studies varied between 0% and 100%. Side effects have been reported less frequently during treatment with cabergoline than with bromocriptine [88].

II.D. Somatostatin analogs (immediate- and slow-release octreotide)

The natural hormone somatostatin exerts numerous physiological effects including suppression of GH, glucagon, and insulin [89]. Somatostatin analogs, far more potent and longer-acting than natural somatostatin, are used in the treatment of acromegaly and have been shown to have a suppressive effect on both hormone hypersecretion and, in some cases, tumor size. Octreotide, administered by subcutaneous (sc) injection, has been studied extensively since the early 1980s. It is generally administered in 3 to 4 divided doses of 100–300 μg per day. The dosage may be initiated at 50 μg/day in order for patients to adapt to adverse gastrointestinal effects and titrated upward to achieve the desired effect [89].

In a series of 35 studies conducted between 1985 and 1995, 978 patients received octreotide sc at dose levels between 100 μg and 1500 μg/day [55,90–123]. Of these patients, 54% achieved plasma GH < 5 μg/mL, and 54% achieved normalized IGF-I. Doses greater than 100 μg t.i.d. (300 μg/day) seldom resulted in any additional benefit [96,119]. Although some patients have responded favorably to doses as high as 800 μg/day, the frequency of octreotide dosing may be more important than the total daily dose [104].

A slow-release dosage form, octreotide LAR, has been developed which reduces the need for frequent daily administration while maintaining all of the clinical and pharmacological characteristics of the

immediate-release formulation. Clinically, it is typically given as a once monthly injection. Octreotide LAR, administered by intragluteal injection at 1- to 6-week intervals at doses of 10–40 mg, was administered in 303 patients in a series of 9 studies conducted since 1995 [124–132]. About 63% of patients achieved GH < 2.5 μg/L and 66% achieved normal IGF-I. Tumor reduction of more than 20% following octreotide therapy was recorded in 100% of previously untreated patients ($n = 4$), and 62% of patients ($n = 42$) previously treated with medical therapy or surgery had a reduction of tumor size between 20% and 100% [125,126]. It should be noted, however, that in nearly all of these studies that report efficacy, the patients had been treated with short-acting octreotide and had been shown to respond with lowering of GH before they were treated with the long-acting formulation. Thus, inherent somatostatin nonresponders were excluded from participating in the long-acting protocols, thereby artificially inflating the efficacy of these preparations.

The most common side effects of octreotide therapy are gastrointestinal, specifically nausea and abdominal pain, which generally appear at the onset of therapy and decrease in frequency over time [124]. The incidence of diarrhea appears to be dose-related [124]. Radiographically demonstrated gallbladder abnormalities, especially stones and/or biliary sludge, develop in 18% of patients on chronic octreotide therapy [124].

III. New Therapeutic Opportunities in the Management of Acromegaly

Major advances have been made over the last 30 years in our ability to treat acromegaly, namely, improvement in surgical results and the development of dopamine agonists and short- and long-acting forms of the somatostain analog, octreotide. Several other novel therapies for acromegaly are under development, and are as yet not approved by the Food and Drug Administration (FDA) or are not well recognized in the literature. These include short- and long-acting forms of a relatively new somatostatin analog, lanreotide, the new GH receptor antagonist, pegvisomant, and Gamma Knife radiosurgery.

III.A. Long-acting somatostatin analog, lanreotide

Lanreotide, a somatostatin analog, has been used for 7 years in the treatment of acromegaly and is clinically available in several European countries but has not yet been approved for use in the United States. It is structurally similar to somatostatin but has better affinity for the specific somatostatin receptors considered to be responsible for GH inhibition and, like octreotide, has a longer duration of action. The shorter-acting form of lanreotide is provided as a sustained-release microparticle formulation and has a duration of action of several weeks [133]. For optimal efficacy, it must be administered by intramuscular injection at a dose of 30 mg at intervals ranging from every 7 to 14 days [134]. However, optimal drug intervals may be as much as 21 to 28 days due to the marked variability in individual patient responses [135]. In contrast, the longer-acting form of lanreotide (Autogel) is administered by deep subcutaneous injection in an aqueous base every 28 days at a dose of 60 to 120 mg, and, therefore, may improve the acceptability of treatment for patients requiring long-term therapy [136]. Adverse reactions related to lanreotide treatment (either formulation) are predominantly gastrointestinal and most commonly include diarrhea, abdominal pain, and nausea. These effects are generally mild and transient. The most potentially important side effect is the tendency for reduced gall bladder motility, hence increased incidences of gallstones and sludge in 5 to 10% of patients during prolonged treatment. Therefore, periodic gall bladder echography evaluations are recommended. If gallstones do occur, they are generally asymptomatic. Other common side effects include constipation and flatulence.

In a multicenter study conducted in Europe [137], 23 patients previously treated with lanreotide 30 mg every 14, 10, or 7 days for at least 3 months then received 60 mg, 90 mg, and 120 mg of lanreotide Autogel, respectively. After 4 months of treatment with the Autogel formulation, the dose was adjusted as necessary (minimum 60 mg, maximum 120 mg) according to GH levels (increased if GH > 2.5 μg/mL, decreased if GH < 1 μg/mL). Before changing to lanreotide Autogel, 39% of patients had a GH level < 2.5 μg/mL and 30% had a normal age-adjusted IGF-I, which improved after 8 months of treatment with lanreotide Autogel to 52% and 61% of patients, respectively. No differences in gall bladder status or in incidence of side effects were observed. In another multicenter European study, 107 patients were changed from short-acting lanreotide to a comparable dose of long-acting Autogel for 3 months [138]. The once-a-month formulation reduced serum GH to < 2.5 μg/mL in 56% of patients, normalized IGF-I in 48%, and reduced both GH and IGF-I in 39%. It was shown to be at least as effective in controlling GH hypersecretion as intramuscular injections of lanreotide 30 mg every 7 to 14 days (Fig. 2). Clinical symptoms of acromegaly—headaches, night sweats, asthenia, swelling of extremities, and joint pain—occurred in 21 to 38% of patients treated with lanreotide Autogel but, with the exception of headache, there was an improvement in each symptom compared to intramuscular lanreotide (Fig. 3). Diarrhea, abdominal pain, and nausea occurred less frequently in Autogel-treated patients than in patients treated with lanreotide 30 mg (29%, 17%, and 9% vs. 38%, 22%, and 18%, respectively.)

III.B. Growth hormone receptor antagonist, pegvisomant

Pegvisomant is a novel, genetically engineered analog of human GH which functions as a highly selective GH receptor antagonist. In contrast to existing

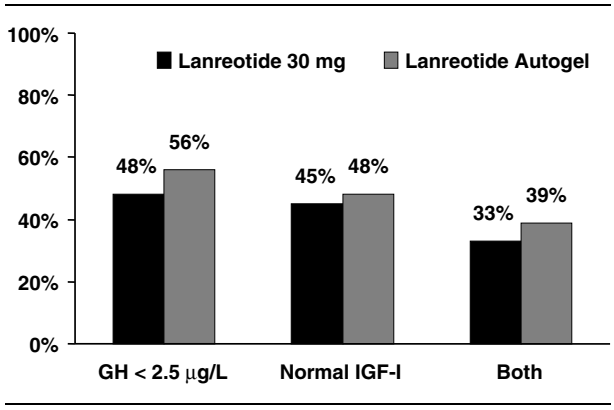

Fig. 2. *Lanreotide 30 mg vs. Lanreotide Autogel—biochemical response in 107 patients.*

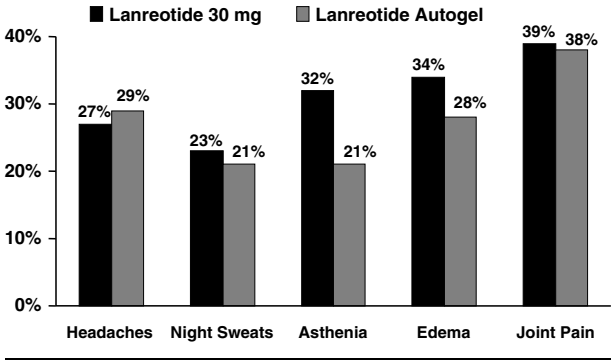

Fig. 3. *Lanreotide 30 mg vs. Lanreotide Autogel—symptom improvement in 107 patients.*

medical treatments which inhibit GH secretion, pegvisomant specifically inhibits the *action* of GH [139,140]. In effect, it prevents generation of IGF-I at the cellular receptor level by binding to GH receptors and interfering with growth hormone receptor mediated signal transduction [141] (Fig. 4). The targeted effect is to lower IGF-I; therefore, serum GH is not lowered. Unlike somatostatin analogs, which require the presence of subtype-specific somatostatin receptors on the tumor to inhibit GH secretion (lacking in an estimated 10 to 15% of patients with acromegaly), the action of pegvisomant is independent of tumor receptor status [142,143]. Treatment of acromegaly with pegvisomant is by daily subcutaneous injection that is self-administered, and the dose can be titrated to between 10 and 30 mg/day to reach optimal effect (i.e., decreased IGF-I concentrations).

In a 12-week, double blind, multicenter study, 112 patients were randomized to receive either placebo or 1 of 3 doses of pegvisomant [144]. A significant decrease in mean serum IGF-I levels compared with baseline was evident in all groups within the first 2 weeks of therapy and was subsequently maintained thereafter until the end of the study. After 12 weeks of therapy, patients taking 10, 15, or 20 mg of pegvisomant had significant decreases in mean serum IGF-I levels compared to placebo of 27%, 50%, and 63%, respectively. Furthermore, IGF-I became normal in 54 to 89% of patients in a dose-related fashion (Fig. 5). A rise in GH levels, inversely correlated with the fall in IGF-I, was observed; however, the rise in GH was not accompanied by an increase in tumor volume. Treatment with either 15 or 20 mg/day of pegvisoment resulted in significant reductions in ring size and significant improvements in clinical symptoms of acromegaly, specifically energy level, sweating, and self-perceived soft tissue swelling. In the continuation of that study, 87 of 90 patients (97%) treated with pegvisomant for 12 to 18 months were found to have a sustained reduction from their initial IGF-I to the normal age-related IGF-I range [145]. Improvements in ring size and symptoms were also sustained. There was no evidence of tachyphylaxis.

Side effects of pegvisomant were similar to those receiving placebo, the most common of which were mild, self-limited injection site reactions and non-serious upper respiratory tract infections. Two patients developed transaminase elevations requiring withdrawal from therapy; in one case the effect was reversible with a return to normal transaminase levels upon cessation of the drug and the other patient was treated for autoimmune hepatitis. Two patients required treatment for progression in tumor size. Both had recent transsphenoidal surgery, and neither had received radiation. Patients

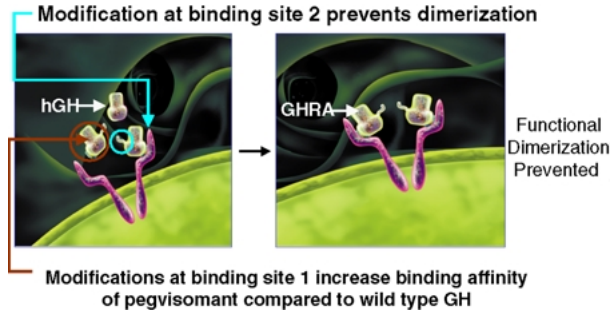

Fig. 4. *Pegvisomant's rational design. GHRA, growth hormone receptor antagonist; hGH, human growth hormone.*

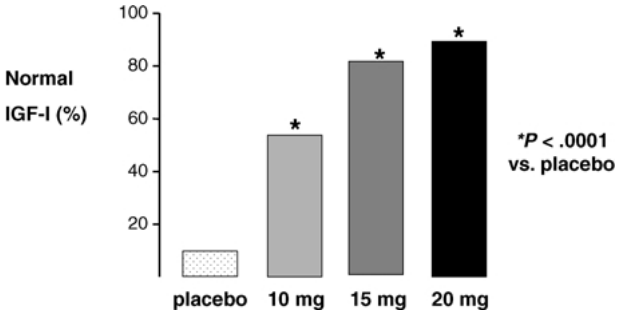

Fig. 5. *Percent of patients achieving normal IGF-I concentrations in a 12-week study of pegvisomant.*

who had been previously treated with radiation very *rarely* had an increase in the volume of their tumor while on pegvisomant therapy. Overall, there was no association between the duration of pegvisomant treatment and change in tumor volume irrespective of the patients' previous history of radiation therapy [146]. In contrast to other therapies for acromegaly, in which treatment outcome is inversely related to the initial concentration of the serum GH and IGF-I, this medication has proven effective in nearly all patients treated thus far.

III.C. Gamma Knife radiosurgery

Stereotactic radiotherapy for pituitary tumors using Leksell's Gamma Knife technique utilizes multiple beams of ionizing radiation from a Cobalt-60 source focused on the tumor [146]. With increased precision and accuracy, further enhanced by the use of MRI for radiological localization of the lesions [28], a high dose of radiation can be delivered in a single session while minimizing the risk of serious complications, specifically, damage to nearby optic pathways. In contrast, conventional radiotherapy of pituitary tumors is generally delivered in fractionated doses of 160–180 cGy 4–5 times per week over a 5- to 6-week period (45–50 Gy) [28]. Gamma Knife radiosurgery has been primarily employed in cases of incomplete surgical removal to treat recurrent tumors or small remnants of tumor that are at least 5 mm away from the optic chiasm. Dosing plans are determined by tumor size, the relationship of the tumor to adjacent critical structures, and past history of radiotherapy, and utilize multiple shots to deliver 50% of the maximum dose of radiation to the periphery of the tumor [28]. Marginal doses of between 20 and 35 Gy and maximum doses between 40–70 Gy have been reported for control of secreting adenomas [147].

Although stereotactic Gamma Knife radiosurgery has been used since 1973, data regarding the effectiveness of this form of therapy are meager. Few studies have employed the modern criteria for the cure of acromegaly, i.e., GH < 2.5 μg/L and a normal age-adjusted IGF-I. In a series of 11 studies in which IGF-I was the measure of efficacy, a review of 256 patients followed for at least 6 months after undergoing Gamma Knife radisurgery showed that 35% of patients achieved normalized IGF-I, an efficacy rate nearly identical to that of conventional radiation [28,34,35,38,148–154]. Using the strictest criteria for the cure of acromegaly (normal age-adjusted IGF-I and GH < 1 μg/L), Vance and colleagues have treated 85 patients with acromegaly not cured by surgery; 58 patients were evaluable (Vance ML, personal communication). In this as yet unpublished study, patients underwent Gamma Knife radiosurgery followed by medical therapy, including octreotide and lanreotide. Medical therapy was stopped every 6 months for an evaluation. At a mean of 27 months (range, 5–98 months), 17 of 58 (29%) evaluable patients had IGF-I that was normal for age. New onset hypopituitarism occurred in 29%.

With Gamma Knife radiosurgery, resolution of pituitary hypersecretion begins earlier than with conventional radiotherapy. In a study comparing conventional fractionated radiotherapy with stereotactic Gamma Knife radiosurgery in patients with acromegaly, the beneficial effects of Gamma Knife on excess GH and IGF-I occurred much earlier than fractionated radiation; the mean time to simultaneous normalization of both GH and IGF-I was 1.4 years in patients treated with Gamma Knife radiation and 7.1 years in those treated with fractionated radiation [155].

Early studies suggest that the side effects associated with the use of Gamma Knife technique are similar to that of conventional radiation but occur less frequently. Other benefits may be found in the use of focused radiosurgery for additional radiation effect following conventional radiation depending on the doses previously given and the proximity of the lesion to the optic chiasm. Further long-term study, however, is needed to determine the safety and effectiveness of Gamma Knife radiosurgery and other radiosurgical techniques as a treatment for acromegaly.

IV. Conclusions

The primary goals in the treatment of acromegaly are to alleviate tumor mass effects and normalize IGF-I in order to ultimately reduce the morbidity and mortality rates. Although surgery remains the initial treatment in most cases, adjunctive treatment with medical therapy and/or radiation is often necessary for optimal treatment, as a significant proportion of patients continue to have elevated IGF-I levels following any given treatment. With the improved delivery and efficacy of longer-acting dopamine agonists and somatostatin analogs, and the advent of a novel new class of GH receptor antagonist drugs such as pegvisomant, promising new therapeutic opportunities exist in the management of acromegaly. The use of radiation continues to be justified in patients whose tumors are unresponsive to medical therapy and may perhaps allow for eventual termination of medical therapy in some patients. How newer therapies will affect our treatment approaches to patients with acromegaly still remains to be determined.

Acknowledgments

This work was supported by an unrestricted educational grant from Pharmacia and is based on a symposium presented at the 2001 meeting of the Endocrine Society (ENDO 2001), 19 June 2001, Denver, Colorado.

The authors wish to acknowledge Mary Jean Matus, ELS and Sherri Bowen, ELS for their medical writing assistance.

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