Endocrine, *vol. 20, no. 3, 299–305, April 2003* 0969–711X/03/20:299–305/$20.00

Comparison of Efficacy and Tolerability of Somatostatin Analogs and Other Therapies for Acromegaly

Morton G. Burt and Ken K. Y. Ho

Department of Endocrinology, St Vincent's Hospital and Garvan Institute of Medical Research, Sydney, NSW, Australia

Medical therapy plays an important role in the management of acromegaly. Dopamine agonists and somatostatin analogs are two classes of drugs approved for this purpose worldwide. Pegvisomant, a growth hormone receptor antagonist, has recently been evaluated in clinical trials. Somatostatin analogs have been the mainstay of medical treatment during the last 10 yr with their acceptability enhanced by the development of depot preparations. Somatostatin analogs improve symptoms and signs of acromegaly in the majority, normalize IGF- 1 in up to 60%, and result in tumor shrinkage in up to half of patients. Dopamine agonists have modest efficacy and limited tolerability. They are more effective in mixed GH/prolactin-secreting tumors. Newer agonists with D2 receptor specificity have fewer side effects but are less efficacious than somatostatin analogs. The addition of a dopamine agonist to somatostatin analog therapy can result in greater biochemical control than with individual agents. Pegvisomant is the most effective drug treatment for acromegaly, but it is likely to have a major adjuvant role as its mechanism of action is not directed at the tumor. The availability of more effective and better tolerated drug therapies offers greater flexibility and individualization of therapy that will lead to improved patient care and disease control.

Key Words: Acromegaly; dopamine agonist; somatostatin; insulin-like growth factor-1; surgery; radiotherapy.

Introduction

Surgery is currently regarded as first-line treatment for acromegaly. However, medical therapy is claiming an increasing role in the management of this difficult disease brought about by significant advances in drug development. Over the last 30 yr, three different classes of drugs have been introduced: dopamine agonists, somatostatin analogs, and a growth hormone (GH) receptor antagonist. Bromocriptine, a dopamine agonist, was introduced in the early 1970s; somatostatin analogs approx 10 yr later; and pegvisomant, a GH receptor antagonist, just in the last 2 yr.

Acromegaly is associated with both significant morbidity and increased mortality. Good biochemical control reduces excessive mortality from acromegaly and therefore is a critical consideration in assessing the efficacy of different treatment modalities. This principle was underscored in the recent consensus statement defining guidelines for assessment of biochemical response to treatment in acromegaly *(1)*. Remission was defined as normalization of GH output, with reduction of insulin-like growth factor-1 (IGF-1) levels to within the age-adjusted range. Cure is recognized when neuroregulation of GH secretion is also restored, as documented by the attainment of normal GH suppression after a glucose load. Other treatment goals should include alleviation of symptoms; prevention of cardiovascular, respiratory, and metabolic complications; eradication of tumor mass or control of its growth; and preservation of anterior pituitary function.

Mortality in acromegaly is increased, by 1.6–3.0 times that of the general population, predominantly from cardiovascular and respiratory disease *(2,3)*. Overall survival in acromegaly is reduced by 10 yr, and this reduction is predicted by the level of residual biochemical disease *(4)*. The presence of either hypertension or cardiac disease is associated with increased mortality. Good biochemical control as defined by GH <2.5 ng/mL, or normalization of IGF-1, reduces mortality to that of the general population *(4–6)*.

In this article we review experience using somatostatin analogs, dopamine receptor agonists, and the GH receptor antagonist pegvisomant in acromegaly and, where possible, directly compare somatostatin analogs with other medical therapies. We also define the roles of medical and surgical therapies in acromegaly. The assessment of efficacy focuses on biochemical control given its association with reducing the excessive mortality associated with acromegaly. Control of tumor growth and incidence of side effects are also important components of effective therapy.

Somatostatin Analogs

Somatostatin analogs have been the medical treatment of choice for acromegaly over the last decade. Two somato-

Received December 27, 2002; Revised January 13, 2003; Accepted January 13, 2003.

Author to whom all correspondence and reprint requests should be addressed: Ken K. Y. Ho, Pituitary Research Unit, Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia. E-mail: k.ho@garvan.org.au

Table 1
Major Trials of Somatostatin Analogs in Acromegaly

Somatostatin analog/reference	Study design	No. of patients	Duration of treatment (mo)	Normal IGF-1 (%)	GH < 2.5 ng/mL (%)	Tumor shrinkage (%)[a]
Octreotide *(27)*	Open	58	6	NA[b]	22	47
Octreotide *(12)*	Randomized double-blinded	115	6	68 (250 μg) 55 (750 μg)	NA[b]	19 (250 μg) 37 (750 μg)
Octreotide LAR *(14)*	Open	151	12	66	70	NA[b]
Octreotide LAR *(50)*	Open	14	18	64	64[c]	36
Lanreotide SR *(51)*	Open	22	36	63	27	15
Lanreotide SR *(30)*	Open	118	24	63	77	22 primary 6 secondary[d]

[a]Percentage of patients who had reduction in tumor size while taking somatostatin analog.
[b]NA, not available.
[c]< 2 ng/mL.
[d]Primary are previously untreated patients while secondary are patients who had prior surgery and/or irradiation.

statin analogs are available for clinical use—octreotide and lanreotide. Octreotide was the first introduced with open trials indicating benefit since 1984 and the first randomized clinical trial reporting efficacy in 1990 *(7)*. Incorporation of octreotide into microspheres of biodegradable polymer has led to the development of the depot preparation octreotide LAR. Lanreotide (available in depot formulation lanreotide SR) has subsequently been released in Europe and the United States. Native somatostatin exerts its clinical effect by binding to somatostatin receptors, of which five subtypes have been identified. Octreotide and lanreotide bind to somatostatin receptor subtypes 2 and 5 with greater affinity than native somatostatin *(8)*. These receptor subtypes are expressed more frequently in GH-secreting pituitary tumors *(8)*. The presence of somatostatin receptors in the GH-secreting tumor is a requisite for clinical effect.

Biochemical Efficacy

All major long-term trials of somatostatin analog therapy have shown consistent clinical benefit with normalization of serum IGF-1 in >50% of patients (Table 1). This level of disease control has been attained with octreotide administered subcutaneously three times per day, octreotide LAR administered every 28 d, and lanreotide SR administered every 10–14 d. Patients with a higher initial GH level are less likely to develop a normal IGF-1 level during treatment *(9,10)*. Suppression of GH following a single dose of octreotide predicts successful long-term response, since tachyphylaxis does not occur *(11)*. When administered three times daily, efficacy appears to be maximal with a dose of 100 μg *(12)*. Increasing the dosage does not improve control, which may, however, be improved if the frequency of administration is increased or if octreotide is administered as a continuous sc infusion *(13)*.

Depot preparations may improve efficacy because of the stable and continuous drug levels that they provide, but also improved compliance and acceptability. In an open multicenter study of 48 wk of treatment with octreotide LAR, IGF-1 was reduced into the normal range in approximately two-thirds of patients *(14)* (Table 1). A review of six published trials of octreotide LAR found suppression of GH of <2.5 ng/mL in 56% and normalization of IGF-1 in 66% of patients *(15)*. However, caution should be exercised in extrapolating these data to routine clinical practice because the majority of patients were preselected by prior response to treatment with sc octreotide.

Experience with lanreotide SR suggests a similar level of biochemical efficacy to octreotide. A review of 12 trials of lanreotide SR revealed GH suppression of <2.5 ng/mL in 49% of patients and normalization of IGF-1 in 48% *(15)*. Heterogeneity in patient selection does not allow direct comparison of efficacy between lanreotide SR and octreotide LAR. In particular, 90% of patients in the trials of octreotide LAR were preselected for octreotide responsiveness compared with 10% in the trials of lanreotide SR *(15)*. A new formulation of lanreotide (lanreotide autogel) that will allow dosing every 28 d has efficacy similar to lanreotide SR *(16)*.

There are limited data directly comparing octreotide LAR with lanreotide SR. Two trials have transferred patients from lanreotide SR to octreotide LAR and reported improved IGF-1 suppression on octreotide LAR *(17, 18)*. However, these trials used a fixed dosing regimen and therefore do not compare optimal dosages. Only two small, randomized controlled trials have compared octreotide LAR and lanreotide SR. IGF-1 was normalized in 12 of 18 patients (67%) after three doses of octreotide LAR and in 8 of 11 (73%) patients after five doses of lanreotide SR *(19)*. Following 24 mo of therapy, IGF-1 was in the normal range in 8 of 12

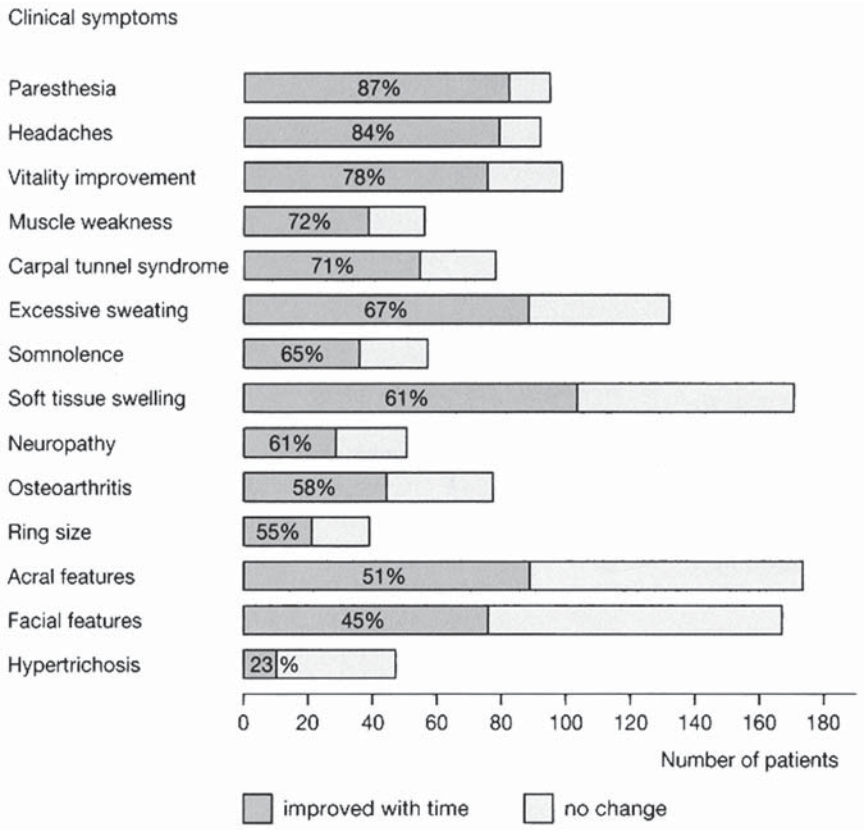

Fig. 1. Reduction in symptoms of acromegaly in patients taking octreotide.

(67%) patients treated with lanreotide SR and 4 of 8 (50%) patients treated with octreotide LAR *(20)*. The numbers of patients in these trials are too small to draw any specific conclusions. Given that both drugs have similar properties and a similar mechanism of action, there is no reason to expect a difference in efficacy.

Symptoms and Signs

Somatostatin analog therapy effectively reduces symptoms from acromegaly in up to 90% of patients, as reported in a large multicenter study of 178 patients (Fig. 1) *(21)*. Headache from acromegaly responds rapidly to octreotide therapy, suggesting that there may be a direct analgesic effect *(21)*. Paresthesia, muscle weakness, sweating, and soft-tissue swelling improve in the majority of cases. Somatostatin analog therapy improves cardiovascular, respiratory, articular, and metabolic consequences of acromegaly. A marked improvement in cardiac function has been reported following octreotide therapy, including a dramatic clinical improvement in three patients with severe heart failure *(22)*. Sleep apnea improves following treatment with both octreotide *(23)* and octreotide LAR *(24)* but may persist despite normalization of IGF-1. Somatostatin analogs have also been shown to improve glucose tolerance in the long term and reduce joint thickening *(25,26)*.

Effects on Tumor Mass

Both somatostatin and lanreotide reduce tumor mass in a proportion of patients (see Table 1). Tumor shrinkage is most commonly seen in macroadenomas. Tumor shrinkage with octreotide was reported in 47% of macroadenomas with a quarter of tumors decreasing in volume by >50% *(27)*. In a large multicenter study comparing the efficacy of two doses of octreotide (300 vs 750 μg/d), the higher dose resulted in a greater frequency of tumor shrinkage (37 vs 19% on lower dose) but no added biochemical or clinical benefit *(12)*. Direct comparison between trials is again limited by heterogeneity of patient population, prior treatment with surgery or radiotherapy, preselection for octreotide responsiveness, and the availability of tumor size data in only a subset of patients. Overall, approx 30% of patients with acromegaly demonstrate tumor shrinkage, usually of 20–50%.

Assessment of tumor shrinkage when somatostatin analogs are employed as primary therapy eliminates the effects of previous therapies. A modest reduction in tumor size was found in 6 of 13 (46%) patients receiving octreotide as primary therapy *(28)*. However, Colao et al. *(29)* reported a greater benefit following 24 mo of octreotide LAR, with a reduction in tumor size in 12 of 15 (80%) *de novo* patients, and a mean reduction in diameter of 30%. In their trial, the

Table 2
Common Side Effects of Medical Therapy

Agent	Side effects
Somatostatin analogs	Diarrhea
	Abdominal discomfort
	Nausea
	Headache
	Dizziness
	Injection site pain
	Cessation therapy
Dopamine agonists	Constipation
	Nausea
	Postural hypotension
	Headache
	Fatigue
	Mood change
GH receptor antagonist	Diarrhea
	Injection site reactions
	Acute hepatitis

Table 3
Efficacy of Dopamine Agonists in Normalizing Circulating IGF-1 in Acromegaly

Study	Dopamine agonist	Number	Normal IGF-1 (%)
Jaffe et al. *(32)*	Bromocriptine	Meta-analysis of 31 trials	10
Abs et al. *(33)*	Cabergoline	64 patients	39
Colao et al. *(34)*	Quinagolide	16 patients	44
	Cabergoline	11 patients	0
	Bromocriptine LAR	7 patients	0

reduction in tumor size was similar in *de novo* patients and those with prior surgical treatment. There was no correlation between reduction in tumor mass and control of GH excess. After 2 yr of follow-up, lanreotide SR resulted in a higher rate of tumor shrinkage in *de novo* patients than in patients who had prior surgical and/or irradiation therapy (Table 1) *(30)*. However, the patients were not randomized, and this may account for the difference between the two groups. In a small randomized trial, no difference in tumor shrinkage was observed comparing octreotide LAR and lanreotide SR *(20)*.

Tolerability

Somatostatin analogs are generally well tolerated. The most common side effects (see Table 2) are gastrointestinal (GI) symptoms such as diarrhea, abdominal discomfort, and nausea. Early side effects occur in approx 50% of patients but improve with time and generally persist in <10% of patients. During long-term octreotide therapy, 58% (66/114) reported diarrhea in the first 18 mo of treatment, 44% (50/114) had abdominal discomfort, and 30% (34/114) reported nausea *(9)*. When assessed after 18 mo, the incidence of these side effects fell to 16, 13, and 6% respectively. New gallstones were found in 24 of 102 (24%) patients, with biliary sludge developing in a further 21 patients. However, after a mean follow-up of 24 mo no patient had developed acute cholecystitis. Gallstones have been reported to develop in 20–30% of patients on somatostatin analogs and can be managed similarly to gallstones in the general population *(31)*.

The effect of somatostatin analogs on glucose homeostasis is minor and variable, and dependent on glycemic status before treatment. Improvement tends to occur in those with impaired glucose tolerance while a mild deterioration may occur in those without impaired glucose tolerance *(10)*. Although somatostatin analogs inhibit thyroid-stimulating hormone (TSH) secretion, thyroid function is not perturbed during somatostatin analog treatment *(10)*. Somatostatin analogs are discontinued in <5% of cases, usually because of GI side effects *(15)*.

Dopamine Receptor Agonists

Dopamine receptors are widely distributed in the central nervous system and the GI tract and exist as two subtypes, D1 and D2. Binding of dopamine agonists to D2 receptors leads to stimulation of GH secretion in normal individuals but, paradoxically, inhibits secretion in patients with a GH-secreting adenoma. Dopamine agonists (bromocriptine, cabergoline, quinagolide) have the advantages of oral administration and being inexpensive when compared with other medical therapies for acromegaly.

Efficacy

Bromocriptine (a nonselective dopamine agonist) was the first dopamine agonist introduced for the treatment of acromegaly. The efficacy of bromocriptine in controlling acromegaly, however, is disappointing. A meta-analysis of 31 studies of bromocriptine revealed that IGF-1 is normalized in only 10% of patients *(32)*. Tumors that cosecrete prolactin (PRL) are more likely to respond to bromocriptine *(32)*. Some trials report an improvement in symptoms out of proportion to the biochemical response. Bromocriptine therapy only occasionally results in tumor shrinkage, usually when good biochemical control is achieved *(32)*.

Newer dopamine agonists have greater specificity for the D2 receptor. Pergolide and lisuride have undergone trials with small numbers of patients with acromegaly, but there is greater experience with cabergoline and quinagolide. Cabergoline and quinagolide appear to have greater efficacy than bromocriptine in acromegaly (see Table 3). In an open trial using cabergoline as either primary or secondary treatment, normalization of IGF-1 was observed in 25 of 64 (39%) patients with acromegaly *(33)*. Lower pretreatment IGF-1

Table 4
Comparison of Dopamine Agonist and Somatostatin Analog Therapy in Acromegaly

Study	Duration	Efficacy definition	Number	Bromocriptine (%)	Octreotide (%)	Combination (%)
Lamberts et al. *(39)*	Single dose	GH < 5 ng/mL	17	29	59	NA[c]
Halse et al. *(37)*	8 wk	GH < 2 ng/mL	11	18	33	NA[c]
		IGF-1 normal		36	67	
Flogstad et al. *(41)*	42-d crossover	GH % of pretreatment[a]	12	64	23	16
Li et al. *(42)*	56-d crossover	GH < 5 mU/L[b]	16	12.5	31	50

[a]Refers to area under curve from 15 GH collections.
[b]≅< 2.5 μg/mL.
[c]NA, not available.

and cosecretion of PRL were predictors of adequate biochemical control. Tumor shrinkage was seen in 13 of 21 (62%) patients and was generally between 20 and 50%, but >50% reduction was achieved in five tumors that cosecreted PRL. Colao et al. *(34)* showed that quinagolide normalized IGF-1 in nearly half of patients *(34)*. In their study, cabergoline and a long-acting depot bromocriptine were ineffective in normalizing IGF-1. In two studies using quinagolide and five with cabergoline for acromegaly, IGF-1 was normalized in 43 and 34%, respectively *(35)*. The overall data suggest that dopamine agonists achieve good biochemical control and modest tumor shrinkage in a minority of patients. They are more efficacious in tumors that cosecrete PRL.

Tolerability

In the substantial dosage usually needed to treat acromegaly, the nonselectivity of bromocriptine leads to poor tolerability in many patients with GI, hypotensive, and central side effects. Frequently experienced side effects include nausea, headache, postural hypotension, and constipation. Side effects may be reduced by taking bromocriptine in the evening together with a small meal and gradual escalation of dosage. They often decrease with time but lead to discontinuation of therapy in a substantial proportion of patients. Up to 12% of patients receiving bromocriptine for hyperprolactinemia are unable to tolerate therapeutic doses *(36)*. During treatment of 13 acromegalic patients with bromocriptine for 8 wk, one patient discontinued the drug following a hypotensive reaction and one patient required dose reduction because of postural hypotension *(37)*. Therefore, poor drug tolerance may contribute to the low efficacy of bromocriptine in the treatment of acromegaly.

D2-selective dopamine agonists are better tolerated than bromocriptine in the treatment of hyperprolactinemia, for which they have been used more extensively than for acromegaly *(36,38)*.

Side effects such as nausea and vomiting were significantly less frequent and severe for patients taking cabergoline, with 3% of women discontinuing treatment as compared with 12% taking bromocriptine *(36)*. Two of 64 patients with acromegaly discontinued cabergoline therapy because of nausea, but no serious adverse effects were reported *(33)*. Four of 16 (25%) patients reported nausea while taking quinagolide but all patients were able to continue treatment *(34)*. Hence, improved patient tolerability may be an important component of the greater efficacy of D2-selective dopamine agonists in acromegaly.

Direct Comparisons of Somatostatin Analogs and Dopamine Agonists

A small number of trials have directly compared somatostatin analog therapy to dopamine agonists in acromegaly (see Table 4). Most data indicate that somatostatin analogs are more efficacious. Two trials have shown that a single dose of octreotide resulted in greater GH suppression than bromocriptine with combination therapy sometimes resulting in further GH suppression *(39,40)*. A single dose of octreotide (50 μg) suppressed GH to <5 ng/mL in 10 of 17 (59%) patients with acromegaly, whereas 2.5 mg of bromocriptine achieved equivalent GH suppression in only 5 of 17 (29%) *(39)*. Five of seven (71%) unresponsive patients did not suppress plasma GH with combination therapy, but two patients who were insensitive to either agent alone achieved significant GH suppression with combination therapy, although GH level remained >5 ng/mL. Note that the doses used of both drugs are lower than those usually required to achieve GH control.

In a randomized controlled trial of 26 patients with acromegaly treated for 8 wk, octreotide resulted in a greater reduction in IGF-1 than did bromocriptine *(37)*. In another trial comparing the effect of 5 mg of bromocriptine and 200 μg of octreotide, both administered twice daily, greater suppression of GH and IGF-1 occurred with octreotide but the greatest suppression was observed with combination therapy *(41)*. Another small study of acromegaly found that octreotide was more effective than bromocriptine with no added benefit from combination therapy *(42)*. The combination of cabergoline and lanreotide SR was assessed in 10 patients with inadequate GH and IGF-1 suppression with

octreotide and lanreotide as single agents *(43)*. Combination therapy achieved increased suppression of both GH and IGF-1 with GH <2 ng/mL in four patients and normalization of IGF-1 in 5 patients. The limited data indicate that improved biochemical control may be achieved by the addition of dopamine agonist therapy to a somatostatin analog.

GH Receptor Antagonists

Pegvisomant is the most recent addition to and exciting development in the medical treatment of acromegaly. It is an analog of GH, genetically engineered to prevent dimerization of the GH receptor, an event necessary for cellular activation *(44)*. It is conjugated to polyethelene glycol to reduce renal clearance and immunogenecity. Pegvisomant is available but has not yet been approved for use by medical authorities in the United States or Europe. Because pegvisomant does not lead to a reduction in GH secretion, IGF-1 levels must be used to assess efficacy of treatment. The first major trial randomized 112 patients to 12 wk of one of three daily doses of sc pegvisomant (10, 15, and 20 mg) or placebo *(45)*. This resulted in normalization of IGF-1 in 54 (14/26), 81 (21/26), and 89% (25/28) of treated patients, respectively, compared with 10% (3/31) in the placebo group. Pegvisomant improved symptoms in all treatment groups. Longer-term data from 160 patients receiving up to 18 mo of open treatment confirm the efficacy of pegvisomant, with 97% (87/90) of patients achieving a normal serum IGF-1 concentration *(46)*. While there are no trials directly comparing pegvisomant to other medical agents, many subjects in the cited studies had previously failed other medical therapy *(45,46)*. There have been a number of reports of normalization of IGF-1 with pegvisomant in resistant acromegaly, either alone *(47,48)* or in combination with somatostatin analog therapy *(49)*. Therefore, these data indicate that pegvisomant is more effective than other medical therapies in achieving a normal serum IGF-1. The long-term implications of a normal IGF-1 with ongoing high GH levels will require further investigation.

Pegvisomant is well tolerated. Of 160 patients, only 3% (5/160) withdrew because of lack of efficacy and 6% (9/160) because of treatment related adverse events including two with reversible hepatic dysfunction *(46)*. One patient was rechallenged and the drug induced a further rise in transaminases. Because pegvisomant does not act directly on the tumor, concern has been raised that loss of negative feedback mechanisms may lead to an increased rate of tumor expansion. However, there was no increase in mean tumor size among 160 patients receiving pegvisomant over a 12-mo period of observation *(46)*. Although significant tumor expansion was reported in two patients, both had large macroadenomas and neither had previously received radiotherapy. While there is no evidence that pegvisomant induces tumor growth, the drug would not protect against this risk in nonirradiated patients with aggressive tumors. Concurrent treatment with octreotide arrested tumor progression in one patient *(49)*.

Medical Therapy in Management of Acromegaly

Medical therapy in the management of acromegaly is increasing with widening choice and improved efficacy and tolerability of drugs. The success of medical therapy with prolactinomas has supplanted surgery as first-line therapy and offers hope that similarly effective treatments will be found for acromegaly. Surgical resection is still considered the treatment of choice for acromegaly, although the cure rate is sufficiently low in patients with large or invasive tumors that additional therapy such as medical or radiotherapy is inevitable.

The question of whether somatostatin analogs could be considered as primary treatment has been raised by a recent study in which octreotide was as effective in a group of previously untreated patients as in a group previously treated with surgery and/or radiotherapy *(28)*. However, the patients were not randomized and the results may have been affected by selection bias. Moreover, a significant proportion of patients in the secondary therapy group were previously unresponsive to octreotide, and debulking may have rendered acromegaly easier to control medically. Despite these caveats, this observation calls into question the current practice of surgery regardless of the likelihood of cure and supports somatostatin analog therapy as primary treatment, particularly when the likelihood of surgical cure is low. The feasibility of primary medical therapy clearly calls for a prospective randomized evaluation.

Conclusion

Major strides have been made in recent years in the medical treatment of acromegaly. Three classes of drug that target the disease at different levels are now available (see Table 5). Somatostatin analogs are a major advance in the drug therapy of acromegaly. The availability of depot preparations has improved acceptability, which, together with efficacy and tolerability, has resulted in an enhanced complementary role to surgery and has possibly challenged surgery as primary treatment in some circumstances. They are superior to dopamine agonists in terms of efficacy and tolerability. The GH receptor antagonist pegvisomant is an exciting advance and is more effective than somatostatin analogs. As its mode of action is not directed at the tumor it is unlikely to be used as primary treatment but will have a major adjuvant role in disease control. Acromegaly remains a challenging disease and many patients may require the three modes of surgical, medical, and irradiation therapy to achieve tight control. The availability of more effective and better-tolerated drug therapies offers greater flexibility and individualization of therapy.

Table 5
Efficacy and Tolerability of Somatostatin Analogs, Dopamine Agonists, and GH Receptor Antagonists in Acromegaly

Medical therapy	Normal IGF-1 (%)	Tolerability	Tumor reduction (%)	Primary treatment
Somatostatin analogs	50–60	Side effects 50%, persist in 10%	30	Efficacy similar to secondary treatment
Dopamine agonists	10–40	Bromocriptine—poor Cabergoline—well tolerated	10–15	Unlikely to be of benefit
GH receptor antagonists	95	Well tolerated	No reduction	Not assessed

References

1. Giustina, A., Barkan, A., Casanueva, F. F., et al. (2000). *J. Clin. Endocrinol. Metab.* **85,** 526–529.
2. Orme, S. M., McNally, R. I., Cartwright, R. A., and Belchez, P. E. (1998). *J. Clin. Endocrinol. Metab.* **83,** 2730–2734.
3. Bates, A. S., Van't Hoff, W., Jones, J. M., and Clayton, R. N. (1993). *Q. J. Mol.* **86,** 293–299.
4. Rajasoorya, C., Holdaway, I. M., Wrightson, P., Scott, D. J., and Ibbertson, H. K. (1994). *Clin. Endocrinol.* **41,** 95–102.
5. Abosch, A., Tyrell, J. B., Lamborn, K. R., Hannegan, L. T., Applebury, C. B., and Wilson, C. B. (1998). *J. Clin. Endocrinol. Metab.* **83,** 3411–3418.
6. Swearingen, B., Barker, F. G. II, Katznelson, L., et al. (1998). *J. Clin. Endocrinol. Metab.* **83,** 3419–3426.
7. Fredstorp, L., Harris, A., Haas, G., and Werner, S. (1990). *J. Clin. Endocrinol. Metab.* **71,** 1189–1193.
8. Lamberts, S. W. J., Van Der Lely, A. J., De Herder, W. W., and Hofland, L. J. (1996). *N. Engl. J. Med.* **334,** 246–254.
9. Newman, C. B., Melmed, S., Snyder, P. J., et al. (1995). *J. Clin. Endocrinol. Metab.* **80,** 2768–2775.
10. Ho, K. Y., Weissberger, A. J., Marbach, P., and Lazarus, L. (1990). *Ann. Intern. Med.* **112,** 173–181.
11. Colao, A., Ferone, D., Lastoria, S., et al. (1996). *J. Clin. Endocrinol. Metab.* **81,** 2356–2362.
12. Ezzat, S., Snyder, P. J., Young, W. F., et al. (1992). *Ann. Intern. Med.* **117,** 711–718.
13. Christensen, S. E., Weeke, J., Orskov, H., et al. (1987). *Clin. Endocrinol.* **27,** 297–306.
14. Lancranjan, I., Atkinson, A. B., and Sandostatin LAR Group. (1999). *Pituitary* **1,** 105–119.
15. Freda, P. U. (2002). *J. Clin. Endocrinol. Metab.* **87,** 3013–3018.
16. Caron, P. H., Beckers, A., Cullen, D. R., et al. (2002). *J. Clin. Endocrinol. Metab.* **87,** 99–104.
17. Chanson, P., Boerlin, V., Ajzenberg, C., et al. (2000). *Clin. Endocrinol.* **53,** 577–586.
18. Turner, H. E., Vadidale, A., Kennan, J., and Wass, J. A. (1999). *Clin. Endocrinol.* **51,** 275–280.
19. Jenkins, P. J., Akker, S., Chew, S. L., Besser, G. M., Monson, J. P., and Grossman, A. B. (2000). *Clin. Endocrinol.* **53,** 719–724.
20. Amato, G., Mazziotti, G., Rotondi, M., et al. (2002). *Clin. Endocrinol.* **56,** 65–71.
21. Harris, A. G. (1996). *Acromegaly and its management.* Lippincott-Raven: Philadelphia.
22. Chanson, P., Timsit, J., Masquet, C., et al. (1990). *Ann. Intern. Med.* **113,** 921–925.
23. Grunstein, R. R., Ho, K. K. Y., and Sullivan, C. E. (1994). *Ann. Intern. Med.* **121,** 478–483.
24. Ip, M. S. M., Tan, K. C. B., Peh, W. C. G., and Lam, K. S. (2001). *Clin. Endocrinol.* **55,** 477–483.
25. Ho, K. K. Y., Jenkins, A. B., Furler, S. M., Borkman, M., and Chisholm, D. J. (1992). *Clin. Endocrinol.* **36,** 271–279.
26. Colao, A., Marzullo, P., Vallone, G., et al. (1999). *Clin. Endocrinol.* **51,** 611–618.
27. Sassolas, G., Harris, A. G., and James-Dedlier, A. (1990). *J. Clin. Endocrinol. Metab.* **71,** 391–397.
28. Newman, C. B., Melmed, S., George, A., et al. (1998). *J. Clin. Endocrinol. Metab.* **83,** 3034–3040.
29. Colao, A., Ferone, D., Marzullo, P., et al. (2001). *J. Clin. Endocrinol. Metab.* **86,** 2779–2786.
30. Baldelli, R., Colao, A., Razzore, P., et al. (2000). *J. Clin. Endocrinol. Metab.* **85,** 4099–4103.
31. Melmed, S., Dowling, R. H., Frohman, L., et al. (1994). *Am. J. Med.* **97,** 468–473.
32. Jaffe, C. A. and Barkan, A. L. (1992). *Clin. Endocrinol. Metab* **21,** 713–735.
33. Abs, R., Verhelst, J., Maiter, D., et al. (1998). *J. Clin. Endocrinol. Metab.* **83,** 374–378.
34. Colao, A., Ferone, D., Marzullo, P., et al. (1997). *J. Clin. Endocrinol. Metab.* **82,** 518–823.
35. Newman, C. B. (1999). *Endocrinol. Metab. Clin. North Am.* **28,** 171–190.
36. Webster, J., Piscitelli, G., Polli, A., Ferrari, C. I., Ismail, I., and Scanlon, M. F. (1994). *N. Engl. J. Med.* **331,** 904–944.
37. Halse, J., Harris, A. G., Kvistborg, A., et al. (1990). *J. Clin. Endocrinol. Metab.* **70,** 1254–1261.
38. Verhelst, J. A., Froud, A. L., Touzel, R., Wass, J. A., Besser, G. M., and Grossman, A. B. (1991). *Acta Endocrinol.* **125,** 385–391.
39. Lamberts, S. W. J., Zweens, M., Verschoor, L., and Del Pozo, E. (1986). *J. Clin. Endocrinol. Metab.* **63,** 16–19.
40. Wagenaar, A. H., Harris, A. G., van der Lely, A. J., and Lamberts, S. W. (1991). *Acta Endocrinol.* **125,** 637–642.
41. Flogstad, A. K., Halse, J., Grass, P., et al. (1994). *J. Clin. Endocrinol. Metab.* **79,** 461–465.
42. Li, J. K., Chow, C. C., Yeung, V. T., et al. (2000). *Aust. NZ J. Med.* **30,** 457–461.
43. Marzullo, P., Ferone, D., Di Somma, C., et al. (1999). *Pituitary* **1,** 115–120.
44. Chen, W. Y., Chen, N., Yun, J., Wagner, T. E., and Kopchick, J. J. (1994). *J. Biol. Chem.* **269,** 20806–20811.
45. Trainer, P. J., Drake, W. M., Katznelson, L., et al. (2000). *N. Engl. J. Med.* **342,** 1171–1177.
46. van der Lely, A. J., Hutson, R. K., Triner, P. J., et al. (2001). *Lancet* **358,** 1754–1759.
47. Drake, W. M., Parkinson, C., Akker, S. A., Monson, J. P., Besser, G. M., and Trainer, P. J. (2001). *Eur. J. Endocrinol.* **145,** 451–456.
48. Herman-Bonert, V. S., Zib, K., Scarlett, J. A., and Melmed, S. (2000). *J. Clin. Endocrinol. Metab.* **85,** 2958–2961.
49. van der Lely, A. J., Muller, A. F., Jansen, J. A., et al. (2001). *J. Clin. Endocrinol. Metab.* **86,** 478–481.
50. Flogstad, A. K., Halse, J., and Bakke, S. (1997). *J. Clin. Endocrinol. Metab.* **82,** 23–28.
51. Caron, P., Morange-Ramos, I., Cogne, M., and Jaquet, P. (1997). *J. Clin. Endocrinol. Metab.* **82,** 18–22.