0163-769X/02/$20.00/0
Printed in U.S.A.

Endocrine Reviews 23(5):623–646

doi: 10.1210/er.2001-0022

Growth Hormone Receptor Antagonists: Discovery, Development, and Use in Patients with Acromegaly

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An understanding of the events that occur during GH receptor (GHR) signaling has facilitated the development of a GHR antagonist (pegvisomant) for use in humans. This molecule has been designed to compete with native GH for the GHR and to prevent its proper or functional dimerization—a process that is critical for GH signal transduction and IGF-I synthesis and secretion. Clinical trials in patients with acromegaly show GHR blockade to be an exciting new mode of therapy for this condition, and pegvisomant may have a therapeutic role in diseases, such as diabetes and malignancy, in which abnormalities of the GH/IGF-I axis have been observed. This review charts the discovery and development of GHR antagonists and details the experience gained in patients with acromegaly. (*Endocrine Reviews* 23: 623–646, 2002)

I. Introduction

WITHIN 12 yr the GH receptor (GHR) antagonist has developed from a scientific concept to a commercially available product (pegvisomant) of proven efficacy.

GH is a protein that contains 191 amino acids with 2 disulfide bonds and 4 α-helices (Fig. 1). Its molecular mass is approximately 22,000 Da. By combining site-specific mutagenesis studies of the GH gene with the *in vivo* assay of the ability of GH analogs to regulate growth of transgenic mice, a GH antagonist was discovered (1–4). Glycine in the third α-helix of GH was found to be particularly important for GH's biological activity. If it is replaced with arginine, lysine, or with a variety of amino acids, GH is converted from a growth enhancer to a growth suppressor or a GH antagonist (4).

Subsequent observations describing the interaction of GH with two identical cell-surface receptors (5, 6) and a second confirmatory report describing generation of the GH antagonist by substituting human (h)GH glycine-120 with arginine (7) set the stage for the development of a GH antagonist for clinical uses.

Pegvisomant is a GH analog that includes a single-amino-acid substitution at position 120 that generates the antagonist. Additional changes include amino acid substitutions within binding site 1 and a further modification by the addition of polyethylene glycol moieties that increase the half-life and reduce the immunogenicity of the molecule.

Pegvisomant's development has been paralleled by increased awareness of the need for tight control of the GH/IGF-I axis in patients with acromegaly. Despite the best en-

Abbreviations: ALS, Acid labile subunit; bGH, bovine GH; CIS, cytokine inducible Src homology 2-containing protein; CRT, conventional, three-field, pituitary radiotherapy; GHD, GH deficiency; GHR, GH receptor; GHS-R, GH secretagogue receptor; hGH, human GH; 11β-HSD, 11β-hydroxysteroid dehydrogenase; IGFBP, IGF binding protein; JAK2, Janus-kinase 2; LDL, low-density lipoprotein; LFTs, liver function tests; mGHBP, mouse GH binding protein; mGHR, mouse GHR; PEG, polyethylene glycol; rhIGF-1, recombinant human IGF-I; SMS, somatostatin; SOCS, suppressors of cytokine signaling; SSTR, SMS-receptor; STAT, signal transducer and activator of transcription; TC, total cholesterol.

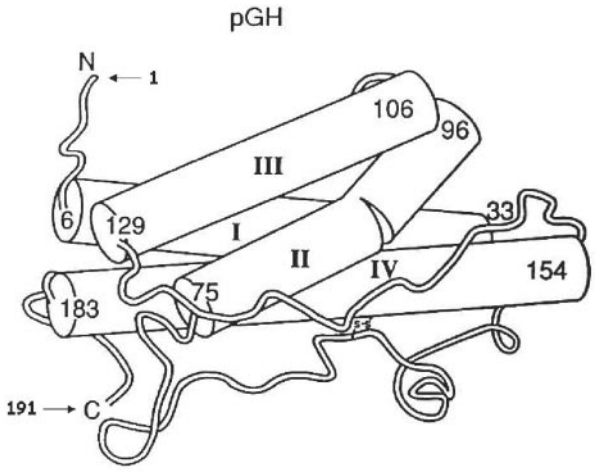

FIG. 1. Computer representation of porcine GH crystal structure. The four antiparallel α-helical bundles are represented as *cylindrical rods* and labeled with *Roman numerals I–IV*. The amino and carboxyl termini are indicated with an N and C, respectively. The *numbers* indicate amino acid positions at the N and C termini of each independent α-helix. [Adapted from S. S. Abdel-Meguid *et al.: Proc Natl Acad Sci USA* 84:6434–6437, 1987 (30).]

deavors of dedicated pituitary surgeons combined with dopamine agonist and somatostatin (SMS) analog therapy, a significant proportion of patients remain inadequately controlled and in need of additional treatment.

The evidence from early clinical studies indicates pegvisomant to be the most potent medical treatment for acromegaly, with serum IGF-I being reduced into the age-related reference range in excess of 90% of patients. A great deal more knowledge will be gained in terms of long-term effects of pegvisomant on both the metabolic consequences of acromegaly and on pituitary adenoma tumor growth as these clinical studies continue. Epidemiological and preclinical studies suggest pegvisomant may also have a role in the management of microvascular complications of diabetes mellitus and certain human malignancies, specifically those in colon, breast, and prostate. This review will not discuss these issues but will review and discuss the discovery, development, and clinical experience with pegvisomant.

II. GH

A. The GH gene family

GH is a member of a hormone family that includes PRL and the placental lactogens. The genes that encode these hormones are believed to have evolved over the last 350 million years via the duplication of a common ancestral gene (8). In this regard, the primary structure of GH shares a high degree of identity with both PRL and the placental lactogens (8–10). Further characterization of these three hormones has demonstrated that they are structurally (10, 11), genetically (8, 9), and functionally (10, 11) similar and clearly represent a distinct family of proteins. Based on structural studies, mouse proliferin, mouse proliferin-related protein, rat decidual PRL-like protein, and somatolactin have been identified as additional members of the GH gene family (12–16). These four helical bundle hormones have structural homology with other members of the class 1 cytokine family such as leptin and erythropoietin (11).

B. GH gene structure and regulation

The hGH gene is located on the long arm of chromosome 17 as part of a gene cluster composed of five closely related genes (17). This cluster spans 66.5 kb and is composed of the genes for GH, choriosomatomammotrope hormone L, choriosomatomammotrope hormone A, GH variant, and choriosomatomammotrope hormone B (17). The 5′ flanking area of the cluster contains a transcriptional control region consisting of the following *cis* elements (from 5′ to 3′): enhancer region, glucocorticoid responsive element, two copies of the pituitary-specific GH transcription factor (GHF-1 or pit-1), a cAMP responsive element, and a TATA box (18).

GH is synthesized and secreted by the somatotroph cells in the anterior lobe of the pituitary gland (8, 10). The GH gene is approximately 3 kb long, consists of 5 exons and 4 introns, and encodes a 217-amino-acid precursor protein (8). An amino-terminal signal peptide is subsequently removed by proteolytic cleavage yielding a mature single-chain polypeptide that contains 191 amino acids with a molecular mass of approximately 22 kDa (8, 10, 11, 19–21). A 20-kDa form of GH has also been found to be secreted by the pituitary and is produced by alternative splicing of the GH precursor mRNA (22).

It has been established that the synthesis and secretion of GH from somatotrophs is a calcium (Ca^+)-dependent event during which an increase in cytosolic Ca^+ is required for GH release (23). GH synthesis and secretion are regulated by at least two hypothalamic peptides, GHRH and SMS, via their

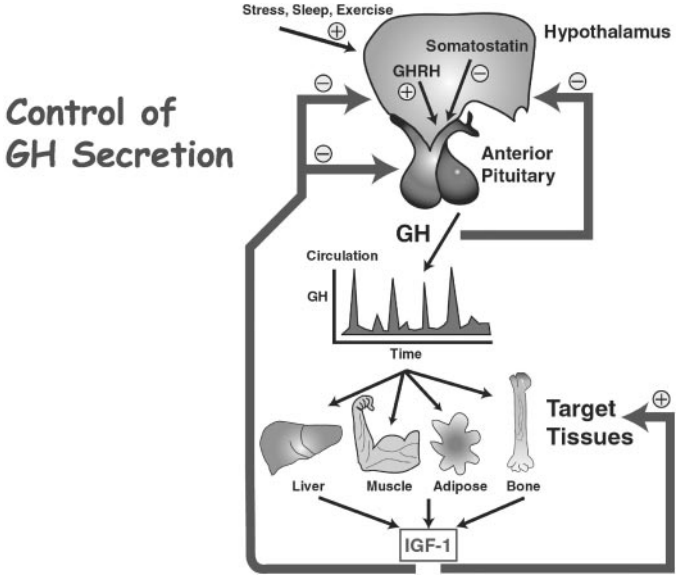

FIG. 2. Regulation of GH synthesis and secretion. The hypothalamic hormones GHRH and somatostatin elicit an increase and decrease in circulating GH levels, respectively. Circulating GH binds to the GHR on peripheral tissue such as muscle, liver, and bone to induce the secretion of IGF-I. IGF-I itself then has growth-promoting effects on target tissues. IGF-I can also decrease circulating GH levels via feedback inhibition at either the hypothalamic or pituitary level. [Adapted from J. J. Kopchick and J. M. Andry: *Mol Genet Metab* 71:293–314, 2000 (267).]

opposing effects on intracellular Ca^+ concentration (Fig. 2 and Ref. 24). The GHRH elicits an increase in intracellular Ca^+ via its G protein-coupled receptor by increasing the level of cellular cAMP (25). In somatotrophs, an increase in cAMP production leads to an increased transcriptional rate of the *trans*-acting pituitary-specific transcription factor, pit-1. Subsequently, pit-1 (also termed GHF-1) is responsible for enhancing the transcriptional rate of the GH gene (26). Conversely, SMS has an opposing effect on intracellular Ca^+ concentration compared with GHRH and, therefore, inhibits GH synthesis and secretion (25).

Recently, it has been demonstrated that GH release is also stimulated by a class of molecules known as GH-releasing peptides (27). The GH-releasing peptides are a group of short synthetic peptides that stimulate GH release via binding to a newly identified receptor, the GH secretagogue receptor (GHS-R) (28). The GHS-R cDNA encodes a seven-transmembrane G protein-coupled receptor of 364 amino acids and is highly conserved between rat, human, and pig (28). Kojima *et al.* (29) have identified and purified an endogenous GHS-R ligand termed ghrelin, a 28-amino-acid peptide found in both rat and human stomachs that, when n-octanoylated at serine-3, stimulates the release of GH both *in vitro* and *in vivo* (Fig. 2). The identification of ghrelin suggests that GH release can be regulated by peripheral signals, independent of those generated by the hypothalamus.

C. GH tertiary structure

The three-dimensional structures of porcine GH and hGH have been determined by x-ray crystallography (Fig. 1 and Refs. 6 and 30). As expected from their sequence similarities, these molecules share similar topographies. Both molecules contain two disulfide bridges and a four-helical bundle in which the helices are arranged in an "up-up-down-down" topology. Helices 1, 2, 3, and 4 are located between residues 9–34, 72–92, 106–128, and 155–184, respectively, in hGH. The disulfide linkages in hGH occur between residues Cys35-Cys165 and Cys182-Cys189. Three shorter connective helices also exist in hGH, two between helices 1 and 2 and one between helices 2 and 3. GH also contains a hydrophobic central core that is composed of approximately 20 hydrophobic amino acids. Residues in the lower half of helix 3 are hydrophobic and they are buried in this hydrophobic core (see Fig. 3).

III. GHR

A. Class I cytokine receptor superfamily

GH exerts its biological effects by binding to specific cell surface receptors. The GHR belongs to the class I cytokine receptor superfamily that includes receptors for PRL, erythropoietin, leptin, interferons, granulocyte colony stimulating factor, and the interleukins (31). These receptors are single-pass transmembrane proteins that contain an extracellular region, a single hydrophobic transmembrane domain of 24 amino acids, and an intracellular region. Although the overall sequence homology of these receptors is relatively low, they do contain highly conserved regions of amino acids. The family members contain two conserved pairs of cysteine residues involved in disulfide linkages and, with the exception of GHR, contain a conserved WSXWS (tryptophan, serine, any amino acid, tryptophan, serine) motif at the membrane proximal region of the extracellular domain (32, 33). The intracellular regions of these receptors also share two conserved motifs. Box I is a proline-rich membrane proximal region that consists of eight conserved amino acids (32, 33). Box 2 is a conserved region located approximately 30 amino acids C terminal of Box 1 that is characterized by a cluster of hydrophobic and charged amino acids (32, 33).

B. GHR gene and primary structure

The hGHR gene is localized on the short arm of chromosome 5 in the region p13.1-p12 (34). The 5′ untranslated region of this gene contains multiple exons that alternatively serve as exon 1 (35). A secretory signal peptide is encoded by exon 2, exons 3–7 encode the extracellular domain, exon 8 encodes the transmembrane domain, and exons 9 and 10 encode the intracellular domain of the receptor (36). The mouse GHR (mGHR) gene was cloned, characterized, and determined to be similar in size and sequence to the hGHR gene but contains two additional exons (37). These include an exon 4B, which is downstream of exon 4, and an exon 8A, which is upstream of exon 8. Exon 4B encodes an eight-

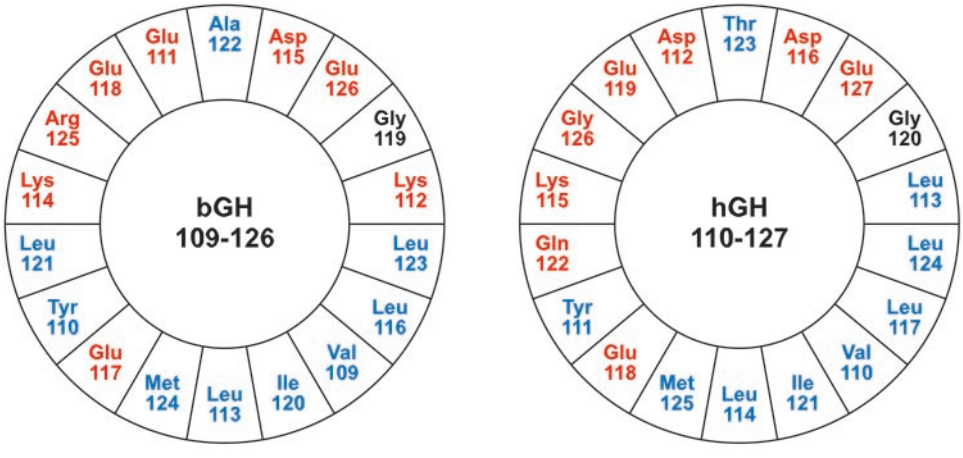

FIG. 3. Edmondson wheel projection of the third α-helix (amino acids 109–126) of bGH and hGH (amino acids 110–127). Each amino acid position is given. Amino acids in *red* are hydrophilic (*top half of wheel*) and those in *blue* (*bottom half of wheel*) are hydrophobic. Glycine-119 (bovine) and glycine-120 (human) are indicated in *black*.

amino-acid segment of the extracellular domain of the receptor and is present in all known mGHR transcripts. Exon 8A serves as an alternative splice site for the mGHR and rat GHR gene (37, 38). Alternative splicing via this exon gives rise to the mouse GH binding protein (mGHBP) transcript that contains the first seven exons of the mGHR gene as well as exon 8A but lacks the transmembrane and cytoplasmic domains. Thus, the transcript for the mGHR does not include exon 8A, as splicing occurs directly from exon 7 to exon 8. In humans, GHBP is produced via proteolytic cleavage of membrane-bound GHR; however, in mice, the mGHBP transcript gives rise to the soluble binding protein (35, 37, 38).

The GHRs are a single polypeptide chain that range from 614–626 amino acids in length with a predicted molecular mass of approximately 70 kDa. However, the observed experimental molecular mass of GHR ranges from 100 to 130 kDa due to posttranslational glycosylation and ubiquitination (33, 35, 39). The extracellular region of GHR contains seven cysteine residues and five potential N-linked glycosylation sites that are highly conserved between species. Also, the GHR contains a 24-amino-acid transmembrane domain and the intracellular Box 1 and Box 2 regions that are characteristic of the class I cytokine receptor family (32, 33). As stated above, members of the class I cytokine receptor superfamily contain an extracellular WSXWS motif (33, 40). In the GHR, this region contains the amino acid sequence YXXFS (tyrosine; X is glycine, serine, lysine, or glutamic acid; phenylalanine; and serine; Ref. 40). The importance of the GHR for the growth phenotype has been shown by disruption of the mGHR gene (41). These animals possess a dwarf phenotype and are a model for Laron syndrome (42). One particular and important characteristic of these animals is their extended lifespan (43). If removal of GH action results in lifespan extension, it would certainly be interesting to show a similar effect when using GH antagonists. However, no data exist in support of this notion.

C. GHR tissue distribution

GHRs are present in many biological tissues and cell types. Although first identified in hepatic tissue, GHRs are present in bone, kidney, adipose, muscle, eye, brain, and heart (44–48). GHRs have also been identified in various immune tissues including cultured human B cells (49), IM-9 lymphocytes (50), spleen, and thymus (51). The fact that GHRs are so ubiquitous suggests the pleotrophic nature of GH's effects.

D. GHR signal transduction

Although the mechanism(s) by which GH elicits biological responses are not fully understood, GH-induced GHR dimerization is thought to be the first step in the GHR signal transduction pathway (6, 33, 52). It has been shown that GH-induced GHR dimerization induces the activation of a 121-kDa GHR associated protein (53) that was later identified as Janus-kinase 2 (JAK2). Activation of JAK2s is thought to be the result of transphosphorylation after two JAK2s are brought together by hormone-induced dimerization. JAK2 is a member of the Janus-associated kinase family of cytoplasmic tyrosine kinases (54, 55), consists of 993 amino acid residues, and has a molecular mass of 130 kDa (55). JAK2 noncovalently associates with GHR via the Box-1 region, the area critical for JAK2 binding and phosphorylation (56). Furthermore, once activated, JAK2 is believed to promote self-tyrosine phosphorylation and tyrosine phosphorylation of the GHR at multiple tyrosine residues (57–59).

Upon GH-induced GHR dimerization and subsequent phosphorylation of JAK2 and GHR, a host of other intracellular proteins is phosphorylated. Among these are several approximately 95-kDa proteins termed the signal transducers and activators of transcription or STATs (60, 61). The STATs are a family of proteins that serve as intracellular signal mediators for cytokine-family members. GH induces the phosphorylation of STAT1, STAT3 (61, 62), and STAT5 (60, 61, 63, 64). Also, the GHR contains several intracellular tyrosine residues that become phosphorylated and provide docking/binding sites for the STAT proteins (57, 64). After binding to the GHR, STATs subsequently become phosphorylated (57, 64), form homo- or heterodimers, enter the nucleus, and regulate GH-specific gene transcription (65). Temporal patterns of GH secretion have been shown to differentially regulate liver STAT5 activation (66).

Recent studies have shed insight into the mechanism by which the GH-induced JAK/STAT signaling pathway is switched off. As well as rapidly activated tyrosine phosphatases [SHP1 and -2 (67)], a novel family of cytokine-inducible inhibitors of signaling, referred to as suppressors of cytokine signaling (SOCS), has been described to down-regulate JAK2 (68–70). The SOCS family currently consists of eight members [SOCS1–SOCS7 and cytokine inducible Src homology 2-containing protein (CIS)] that participate in a negative feedback loop to regulate cytokine signaling (70). The SOCS genes are highly conserved among species but have limited homology to other family members, suggesting that each member may have a specific role in the feedback signaling (69). The primary target of SOCS activity in the JAK/STAT pathway appears to be at the level of the JAKs and STATs themselves. SOCS-1 has been shown to associate with and reduce the activity of JAK2 (67). SOCS-3 and CIS also have been shown to inhibit the JAK/STAT pathway via competitive binding to STAT5 docking sites on cytokine receptors. Additionally, CIS has been shown to increase proteosome-mediated destruction of the GHR complex (69, 70). Therefore, the method by which SOCS disrupt the JAK/STAT pathway seems to be variable.

IV. Biological Activities of GH

In the early part of the last century, it was demonstrated that a pituitary factor, now known to be GH, regulated growth (71, 72). Although a significant physiological effect of GH is the promotion of postnatal longitudinal growth (73), GH also has been associated with alterations in lipid, carbohydrate, nitrogen, and mineral metabolism (74–81). Other activities of GH include its ability to regulate differentiation of preadipocytes to adipocytes (82), to aid in the maintenance and development of the immune system (83), and to have various effects on the brain and cardiac function (84–86).

In 1957, Salmon and Daughaday (87) proposed the so-

matomedin hypothesis, which stated that the observed effects of GH are mediated by the activation of IGF-I. Green *et al.* (88), in 1985, proposed the dual effector theory of GH action, which states that GH induces differentiation of target cells directly and also induces the secretion of IGF-I. IGF-I was then postulated to promote clonal expansion of the differentiated cells. More recently, IGF-I has been shown to be produced and secreted in response to GH stimulation in many tissue types including liver and bone (Fig. 2 and Refs. 89 and 90). Although all actions of GH are mediated through the GHR, it still is not certain which effects are IGF-I directed and which effects are directly caused by GH.

The IGF-I gene has recently been disrupted conditionally in mouse liver (91, 92), resulting in significantly depressed serum levels of IGF-I, but no corresponding diminution of growth was seen. These data suggest that circulating IGF-I may not be the important agent in growth promotion, but paracrine- and/or autocrine-derived IGF-I may be the salient molecule.

We must point out that the molecular mechanisms resulting in autocrine, paracrine, and endocrine actions of IGF-I are still to be determined. However, independent of the mechanism of IGF-I action, GH stimulation of IGF-I synthesis and secretion is presumed to occur via interaction of GH with the GHR. Therefore, a GH antagonist would be expected to inhibit endocrine, autocrine, and paracrine actions of IGF-I. The correction by pegvisomant of the major metabolic complications of acromegaly, such as insulin resistance, cortisol metabolism, and lipoprotein abnormalities (see *Section IX.E.5*), indicates that this therapy does more than just lower circulating IGF-I.

Abnormal secretion of GH is observed in multiple disease processes. In children, hyposecretion of GH results in short stature, whereas hypersecretion before epiphyseal fusion yields gigantism. Although GH is clearly not important for longitudinal bone growth in adults, deficiency is associated with reduced well-being, central obesity, increased fat mass, dyslipidemia, and increased mortality. Hypersecretion in adults is usually caused by a pituitary somatotroph tumor and results in acromegaly. In animals, transgenic mice that express bovine (b)GH are significantly larger than nontransgenic controls and develop severe kidney disease (93). A link between GH and the occurrence and progression of malignancies has been shown (94, 95). Elevated levels of GH have also been correlated with diabetic complications (96–100). In addition, overexpression of GH has been associated with increased renal and glomerular growth (101). Thus, scenarios in which GH levels are elevated have been implicated in several physiological disorders.

V. Development of a GH Antagonist

A. Early GH structure-function studies

Early structure-function studies attempted to determine specific regions of the GH molecule that were important for the binding of GH to GHR. Via homolog-scanning mutagenesis, three such epitopes on the hGH molecule were identified (102). These GHR binding determinants include the loop between amino acids 54 and 74, the amino-terminal region of helix 1, and the central portion of helix 4 to the carboxyl terminus. Subsequently, alanine-scanning mutagenesis was performed on these GH determinants to identify specific side chains required for the hGH-hGHR interaction (103). These studies identified a total of 12 amino acids, located in helix 1, the loop connecting helix 1 and 2, and helix 4, that are involved in the ligand-receptor interaction. Alanine-scanning mutagenesis of hGHR revealed that tryptophan-104 and -169 were key amino acids that made contact between GH and the GHR (6, 33, 33, 102, 103).

B. The importance of GH's helix 3

Independently, after the elucidation of the three-dimensional structure of GH (30), Chen *et al.* (1) observed that the amino acids composing the third α-helix, residues 109–126 in bGH and 110–127 in hGH, are arranged in an amphiphilic orientation (Fig. 3). Furthermore, it was noted that three amino acids, 117, 119, and 122 of bGH, are positioned so that this helix 3 does not form an idealized amphiphilic helix. Because it was previously shown that peptides containing the third α-helix of GH possessed low but significant growth-promoting activity (104), it was hypothesized that the generation of a perfect amphiphilic helix 3 would result in a GH analog with enhanced biological activity. Thus, a mutant bGH gene was engineered, bGH-M8, which encoded the following amino acid substitutions: glutamate-117 to leucine (E117L), glycine-119 to arginine (G119R), and alanine-122 to aspartate (A122D) (1). Surprisingly, transgenic mice expressing this bGH analog had decreased circulating IGF-I concentrations and exhibited a dwarf phenotype (1, 3). The growth ratio between the transgenic mice and nontransgenic littermates ranges from 0.58 to 1.00 and was directly proportional to the circulating concentration of bGH-M8 (1). The observed dwarf mouse phenotype, and the fact that bGH-M8 inhibited the binding of ^{125}I-bGH to liver membranes, revealed that bGH-M8 was the first reported example of a GHR antagonist (1). *In vitro*, this GH antagonist was also shown to antagonize other actions of GH including adipocyte differentiation and the insulin-like effect of stimulating glucose oxidation and lipolysis by adipose tissue (2, 105). Similar studies with the hGH analog, hGH G120K, were performed and yielded similar results (106).

Additional bGH analogs, with single amino acid substitutions at positions 117, 119, and 122 were generated to investigate further which residues are critical for the growth-promoting activity of GH. These studies revealed that the glycine at position 119 of bGH and glycine-120 of hGH are critical for the growth-promoting activity of the respective molecule. Expression of these mutated GH genes in *vivo* resulted in dwarf mice (Fig. 4 and Ref. 4). Thus, alteration of one residue (*i.e.*, glycine-119 of bGH or glycine-120 of hGH) changed the molecule from a growth enhancer to a growth suppressor or GH antagonist. It was further demonstrated that substituting the glycine residue in the third helix with any amino acid other than alanine converted the GH molecule from an agonist to an antagonist (4). Subsequently, these results were confirmed by a second group (6) who demonstrated that substitution of glycine-120 of hGH with arginine resulted in a GH antagonist.

C. The GH-GHR interaction

The aforementioned data prompted Chen *et al.* (4) to hypothesize that the antagonistic properties of bGH-M8 and bGH-G119R were due to the inability of these GH analogs to interact with a secondary target protein. It was predicted that a cleft was located near the center of the third α-helix, primarily due to glycine (Fig. 5). Thus, it was also hypothesized that this secondary target protein fit into the cleft to generate a GH-GHR-X trimeric complex that is critical for the growth-promoting activity of GH (4). This secondary target protein was later identified by De Vos *et al.* (6) to be a second GHR. These crystallography studies of the GH-GHR complex demonstrated that two molecules of GHR interact with one molecule of GH to form a GHR-GH-GHR heterotrimeric complex (Fig. 6 and Ref. 6). The crystal structure revealed that glycine-120 of hGH, which is equivalent to glycine-119 of bGH, is closely apposed to tryptophan-104 of GHR 2 (6, 33). The binding of GH to two GHRs was determined to be a sequential process that involves the trapping of GH by the first receptor via a high-affinity binding site 1, consisting of amino acid residues in the large loop and fourth helices of GH, followed by the binding of a second GHR to the same GH molecule at a low-affinity binding site 2, consisting of amino acids primarily in the first and third helices of GH (6, 33). These data confirmed the previous findings of Chen *et al.* (1) relating to the "second target hypothesis of GH action" and demonstrated the mechanism by which the GH antagonist acts, *i.e.*, it fails to induce proper or functional GHR dimerization.

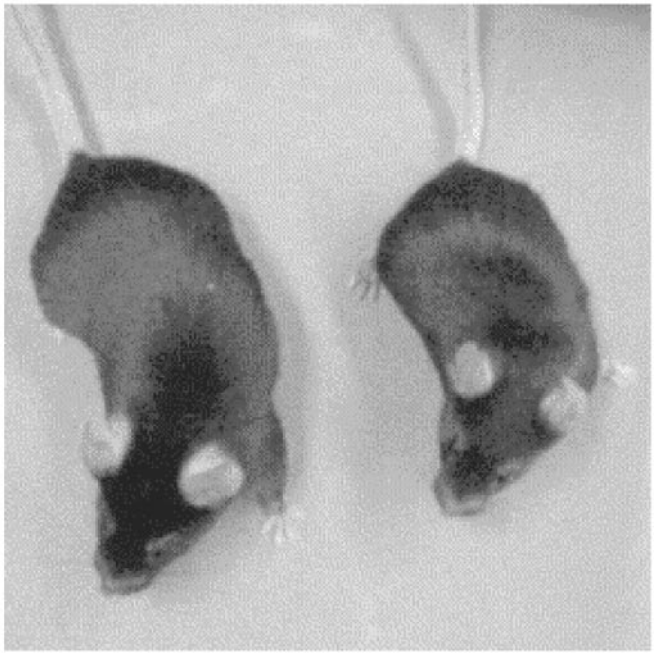

FIG. 4. Transgenic mouse expressing bGH G119K. The mouse with a dwarf phenotype (*right*) expresses bGH G119K and is pictured *beside* a sex-matched nontransgenetic littermate (*left*).

VI. Engineering of a Long-Acting GH Antagonist

The potential of a GHR antagonist for the treatment of clinical conditions resulting from elevated GH, such as acromegaly, or those in which GH or IGF-I may play a pathophysiological role was immediately recognized. However, for this novel class of antagonists to be developed as a useful therapy, the issue of the molecules' short half-life needed to be addressed. Due to its relatively small size (approximately 22 kDa), GH is normally cleared via the kidneys and/or GHR internalization and has a serum half-life of approximately 30 min. Clark *et al.* (107) have shown that addition of polyethylene glycol (PEG)-5000, a 5-kDa reagent that selectively conjugates to primary amino groups, to GH significantly

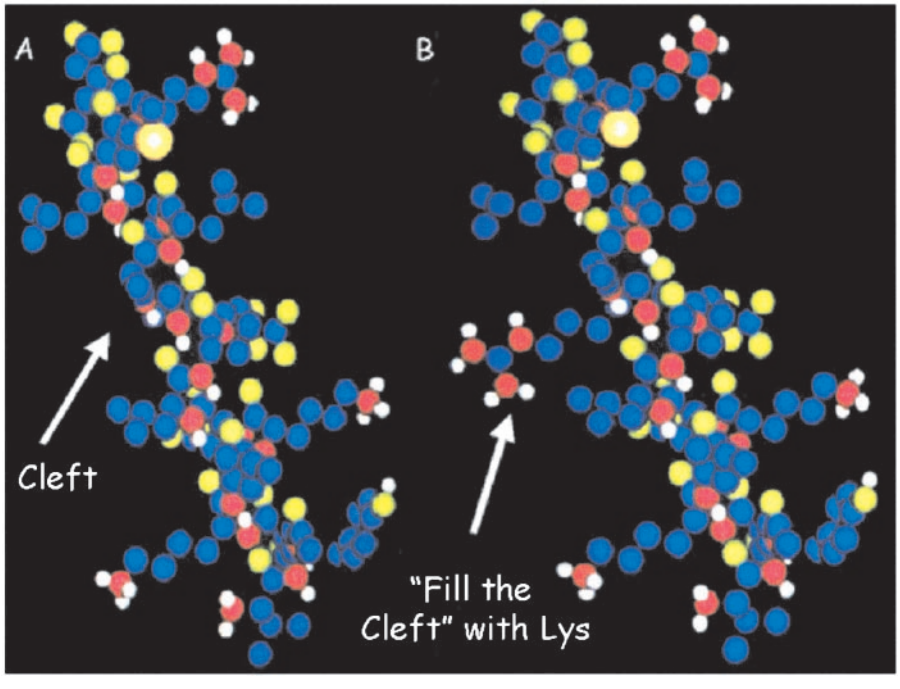

FIG. 5. Partial space-filling model of the third α-helix of bGH. A, The "cleft" due to the glycine residue in the third α-helix of GH is indicated. B, Partial space-filling model of GH. When GH is altered such that the glycine residue is substituted, in this case with arginine, the cleft is filled preventing proper interaction of the GH molecule with a second GHR.

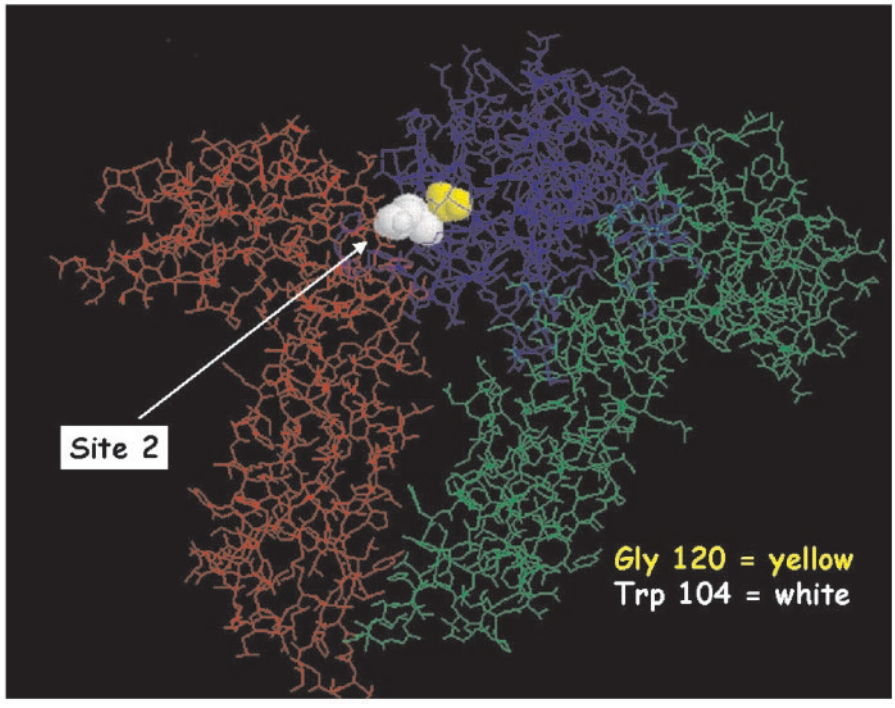

FIG. 6. "Stick model" of the co-crystal structure of one molecule of hGH (*blue*) and two molecules of the extracellular domain of the GHR (*red* and *green*). The two GHR molecules utilize almost identical binding determinants to interact with different determinants on hGH. Glycine-120 hGH is indicated in *yellow* interacting with tryptophan-104 of hGHR, in *white*.

expanded the effective molecular mass, resulting in a long-acting GH analog with a half-life of over 2 d. The same strategy was employed for the hGH antagonist. For these studies, the hGH antagonist with lysine substitute for glycine at position 120 was used. Although the addition of PEG-5000 increased the half-life of hGH G120K, it resulted in a molecule with a decreased site 1 binding affinity. To circumvent this problem, it was reasoned that one could restore the antagonistic potency of PEG-5000 G120R by engineering a molecule that retained the G120K mutation while at the same time introducing additional mutations that increased site 1 binding affinity.

Independently, and at the time the GH antagonist was reported by Chen *et al.* (1–4), Cunningham and Wells (108) were attempting to engineer more potent GH analogs via identifying critical binding determinants in site 1 of the GH molecule. Eight separate amino acids were identified that, when altered, increased the binding affinity for site 1. Furthermore, it was noted that these mutations had an additive effect and, when combined, greatly increased the affinity of GH analog for binding site 1 (7, 108). Thus, a GH analog was produced that contained these eight amino acid substitutions (which increased the binding affinity of GH to the GHR) plus the original G120K substitution (the amino acid substitution that generates a GH antagonist) and would be expected to yield a GH antagonist with high potency. Furthermore, when these nine mutations were combined with the aforementioned addition of PEG-5000, the resulting molecule, known as PEG-hGH G120K (B2036 peg), was shown to maintain both its binding and antagonistic properties. PEG-hGH G120K (pegvisomant) is now in the final stages of clinical trials, under the trade name Somavert (Pharmacia, Peapack, NJ) for sc injection in the treatment of acromegaly.

After GH binding to the GHR, the complex is internalized. The precise mechanisms responsible for the GH/GHR internalization is outside the scope of this review; however, Refs. 109–115 describe these events. In this context, the nonpegylated GH antagonist binds to the GHR with approximately the same affinity as GH, forms dimers, and is internalized (52) but cannot transduce an intracellular GH-specific signal. Recently, pegvisomant, like the nonpegylated form of the GH antagonists, has been shown to form dimers with the GHR and to be internalized (52, 116, 117). Thus, the antagonists do not inhibit dimer formation, but presumably prevent "proper" or functional dimerization of the GHR.

As stated above, it was believed that the GH antagonist with eight amino acid residue changes in site 1 would bind to the GHR with increased affinity and that the G120K substitution would prevent GHR dimerization. Although the site 1 amino acid substitutions increase affinity for antagonist binding to GHBP, recent evidence has suggested that the eight amino acid substitutions within site 1 do not increase binding of the nonpegylated GH antagonist for the cell-surface GHR (116). However, of the eight amino acid changes made within binding site 1, two (namely lysine to alanine and lysine to arginine at positions 168 and 172, respectively) are nevertheless critical with regard to site 1 binding of the pegylated antagonist. Pegylation at these lysine residues would block or sterically hinder binding of the antagonist to the first GHR. Substitution of these residues removes potential pegylation sites within binding site 1 and, thus, ensures that site 1 of pegvisomant remains accessible to the GHR (116). Nevertheless, pegylation of the antagonist does reduce site 1 binding affinity and, thus, large doses of pegvisomant are required to effectively antagonize GH action in patients with acromegaly.

Although not specifically pertinent to the efficacy of the GHR antagonist, recent evidence has altered our concept of

GHR dimerization, as data suggest that rather than inducing sequential binding of two GHRs, ligand binding may produce a conformational change within preformed GHR dimers. Therefore, GH antagonists containing the G120K mutation may not inhibit the recruitment of a second GHR after site 1 binding, but instead prevent functional dimerization by sterically inhibiting conformational changes within these GHR dimers (116).

VII. *In Vivo* Experience with Pegvisomant

A. Rodent

As discussed previously, glycine at positions 119 and 120 of bGH and hGH, respectively, is critical for their respective growth-promoting activity. Unlike bGHG119R, the G120R molecule is relatively ineffective in rodents (118) and, as a result, pharmacological studies of pegvisomant have concentrated on primates and humans. The treatment of hypophysectomized and GH-deficient dwarf rats with G120R during GH infusion failed to antagonize GH action (118). In these animals, G120R paradoxically stimulated skeletal growth, and co-infusion of G120R with hGH produced an additive effect. In normal mice, pegvisomant lowers serum IGF-I to 70% of baseline values when doses of 4 mg/kg (over 10 times the standard daily dose used for the treatment of acromegaly in humans) are administered. Lower efficacy of pegvisomant in rodents is presumed to be due to the amino acid substitutions within the antagonist having been designed to increase binding to the hGHR. This is supported by *in vitro* studies in which pegvisomant binds to mouse hepatocyte microsomal membrane preparations with 20- to 50-fold less affinity than similar preparations of human liver. Rat hepatocytes have a 10-fold reduced affinity for hGH than mouse cells. Rodents are therefore not an ideal model of GHR blockade by pegvisomant, but at high doses some suppression of IGF-I is observed.

Thus, mice and rats are not good models in which to determine the efficacy and activity of pegvisomant. However, nonpegylated molecules with a single amino acid change, namely glycine to lysine at position 119 within the third α-helix, are potent GH antagonists in mice. Several studies have shown that these GH antagonists inhibit the progression of diabetes-induced glomerulosclerosis (96, 98–101), inhibit hypoxia-induced retinal neovascularization (119), and inhibit the size and progression of dimethyl butyric acid-induced breast tumors in rodents (120).

B. Primate

Two separate studies in which a 1-mg/kg sc injection of pegvisomant was administered to ovariectomized female rhesus monkeys (*Macaca mulatta*) demonstrated significant reductions in serum IGF-I and other GH-dependent factors. In the first study (121), serum IGF-I fell by 61% within 3 d of administration after a single dose, was maximally suppressed by d 10, and returned to normal levels within 14 d of drug withdrawal. The reduction in serum IGF-I was accompanied by a significant increase in serum GH. Mean serum GH was 86 ± 11 μg/liter in pegvisomant-treated monkeys compared with 15 ± 6 μg/liter in controls.

In a second study (122), five monkeys were treated with the same 1.0-mg/kg sc dose of pegvisomant at weekly intervals. Serum IGF-I was observed to fall within 24 h of administration and continued to decline until d 5, with a fall of 78 ± 4% from baseline. Serum IGF binding protein (IGFBP)-3 and acid labile subunit (ALS) were also significantly suppressed by d 5 to 30 ± 5% and 36 ± 10% below baseline, respectively. Administration of recombinant IGF-I during GHR antagonism restored serum IGF-I and IGFBP-3 values to normal, but the ALS response was inconsistent (122).

C. Human

A phase I, double-blind, randomized, placebo-controlled, single rising-dose study of pegvisomant in healthy male volunteers has recently been reported (123). Thirty-six subjects (mean age of 25 yr) were randomized into four groups (n = 6) and received either placebo or pegvisomant at a dose of 0.03, 0.1, 0.3, or 1 mg/kg as a single sc injection. Serum pegvisomant concentrations showed a dose-dependent increase with peak concentrations occurring approximately 36 h after administration and values greater than 5000 μg/liter from 24–144 h after administration in the 1.0-mg/kg-dose group. Mean serum IGF-I fell in a dose-dependent manner and reached statistical significance on d 3 with doses of 0.3 mg/kg or more. In the 0.3-mg/kg group, there was 28% suppression of serum IGF-I compared with baseline at 72 h, and 49% on d 5 in the 1.0-mg/kg group. There was no effect of pegvisomant on other hormone systems studied.

VIII. Acromegaly

A. Mortality and acromegaly

Acromegaly is the result of GH hypersecretion, in the vast majority of cases, from a pituitary somatotroph tumor. GH-secreting pituitary adenomas may occur as part of the multiple-endocrine neoplasia syndrome type I, and, when GH hypersecretion develops before epiphyseal fusion, pituitary gigantism results.

The first clinical description of acromegaly is generally attributed to Marie and de Souza-Leite (1886; Ref. 124), who noted hypertrophy of the extremities including the face, hands, and feet. In 1887, Minkowski (125) noted that such hypertrophy was accompanied by enlargement of the pituitary gland, and later, in 1894, Tamburini (126) documented the presence of a pituitary adenoma. In 1909, Cushing (127) postulated that the production of a growth-promoting hormone by the hyperfunctioning pituitary resulted in the clinical condition of acromegaly.

Acromegaly occurs with equal frequency in both sexes with a prevalence of between 55 and 59 patients per million and an incidence of 3–4 per million (128, 129). The diagnosis is often made incidentally, as less than 20% of patients actively seek medical attention for a change in appearance or enlargement of the extremities (130). The condition develops insidiously over many years and, in most cases, the diagnosis

is established after 4–10 yr of active disease. Clinical features reflect excess secretion of GH, local effects of an expanding pituitary mass, and hypopituitarism and include bony proliferation, coarsening of the facial features, soft tissue swelling, hyperhidrosis, macroglossia, headache, visual disturbance, amenorrhea, impotence, diabetes mellitus, or, more commonly, impaired glucose tolerance, hypertension, carpal tunnel syndrome, and sleep apnea (130). Increased serum IGF-I and the failure of GH suppression to below 1 μg/liter after oral glucose (75 g) administration are diagnostic.

Acromegaly is associated with considerable morbidity and mortality, primarily from cardiovascular causes (128, 129, 131–135). In one case-note review of 79 individuals with acromegaly treated between 1964 and 1989 in Stoke-on-Trent, United Kingdom, the ratio of observed to expected deaths was 2.68 (132). This review also documented that normalization of serum GH was the best determinant of therapeutic outcome, as the mortality rate for subjects in whom serum GH was suppressed below 2.5 ng/ml (5 mU/liter) was not statistically different than that of the normal population (132). The importance of tight control of the GH/IGF-I axis has also been demonstrated in two long-term outcome studies after surgery, where mortality rates achieved by patients with a biochemically defined postsurgical "cure" were equivalent to those of matched normal controls (136, 137). In contrast a 2.4- to 4.8-fold increased rate of death was observed in those patients with persistent disease activity after treatment (136, 137). Rajasoorya *et al.* (134), in 1994, reported a series of 145 individuals with acromegaly over the period of 1964 to 1989 in which the last known serum GH value was significantly higher in patients who had died compared with those alive (33 $\pm$ 17.5 *vs.* 4 $\pm$ 0.5 ng/ml respectively; $P < 0.0002$). Other determinants predicting outcome were age and serum GH level at the time of diagnosis and the presence of hypertension or cardiac disease. In the cohort described by Rajasoorya *et al.* (134), survival, irrespective of treatment, was reduced by an average of 10 yr. Although the most common cause of death is cardiovascular disease, there are significant increases in death rates due to lung infections and possibly malignancies (131, 138, 139). Up to 46% of patients with acromegaly harbor colonic polyps, which are frequently precursors of colonic carcinoma, and a 2.45-fold increased incidence of malignant tumors was reported in one study (139, 140). In a further multicenter retrospective cohort study of 1362 subjects with acromegaly (133), overall cancer incidence was not elevated, but mortality from colonic malignancy was increased. This study also confirmed that serum GH values below 2.5 ng/ml after treatment were associated with a reduction in mortality, and, along with earlier studies, clearly demonstrated the crucial importance of achieving biochemical control in acromegaly and, to that end, the need for aggressive management. Subsequently, a retrospective analysis has alluded to a reduction in mortality after normalization of serum IGF-I by transsphenoidal surgery (137).

B. Criteria for "remission"

Therapeutic goals in acromegaly include protection of the optic chiasm, amelioration of symptoms, preservation of pituitary function, and treatment of the pituitary tumor, but the primary goal of treatment is the restoration of normal serum GH and IGF-I levels, as this is associated with normalization of life expectancy (132–134). An epidemiologically safe mean serum GH value after treatment (2.5 ng/ml) should, ideally, be accompanied by serum IGF-I reduction into the normal range for age and sex (137). Thus, the recent consensus statement defined acceptable biochemical "cure" as the achievement of an age- and sex-matched serum IGF-I value, in addition to a serum GH level of less than 1 μg/liter after 75 g of oral glucose (141).

C. Current treatment of acromegaly

1. Surgery. Existing treatment modalities for acromegaly modify disease activity by reducing pituitary GH release (Table 1). Consequently, their efficacy is defined by tumor-dependent characteristics. Surgery is the first-line treatment for acromegaly, as it offers the prospect of cure in a proportion of subjects with rapid reduction of serum GH and

TABLE 1. Summary of the efficacy of surgery, radiotherapy, conventional drug therapy, and pegvisomant in the treatment of acromegaly

Treatment	Safe GH (%)	Normal IGF-I (%)	Tumor size reduction	Efficacy dependent on tumor characteristics	Comments
Transsphenoidal surgery	23–65 (Macro) 60–90 (Micro)	—	Yes	Yes	Outcome dependent on expertise of surgeon, pretreatment GH, tumor position
Conventional radiotherapy	90	60–80	Yes	Yes	Efficacious but slow reduction of GH and IGF-I
Dopamine agonists	10–20	10–43	May be seen in PRL cosecreting tumors	Yes	More efficacious in PRL cosecreting tumors
SMS analog	22–55 (sc) 60–70 (LA)	45 (sc) 50–60 (LA)	Uncertain	Yes	Tumor shrinkage in selected patients, no randomized studies
Pegvisomant	NA	97	No	No	Top of IGF-I dose response cure not reached

Appropriate references quoted in text. LA, Long acting; macro, macroadenoma; micro, microadenoma; NA, not appropriate.

improved well-being in the remainder. Ideally, pituitary surgery should completely remove the GH-secreting adenoma while preserving or restoring normal anterior pituitary function and protecting the optic apparatus where appropriate. Numerous factors determine surgical outcome with respect to biochemical cure, but of paramount importance is the choice of pituitary surgeon. In a study conducted in Manchester, United Kingdom, 73 patients with acromegaly were operated on by any one of nine surgeons between 1974 and 1997, and in fewer than 20% of subjects did serum GH levels fall below 2.5 ng/ml (142). In a similar study conducted in Birmingham, United Kingdom, 8 surgeons operated on 89 patients with acromegaly between 1963 and 1993, 33% of whom achieved a serum GH value less than 2.5 ng/ml. However, remission rates (<2.5 ng/ml) increased to 64% when practice was altered, and all transsphenoidal surgery undertaken by a single dedicated pituitary surgeon (143). Other centers have reported similar findings (137, 144–146). Factors influencing postsurgical GH concentration include pituitary tumor size, degree of extrasellar extension (particularly into the cavernous sinus), and high presurgery serum GH levels (136, 137, 142, 144–147). Sheaves *et al.* (145), in 1996, observed a 65% remission rate when the preoperative serum GH level was below 20 mU/liter (50 ng/ml) but only 18% in subjects with values above 100 mU/liter (200 ng/ml). When strict criteria for surgical remission are adopted (*i.e.*, serum GH < 2.5 ng/ml, or normalization of serum IGF-I), surgical remission is possible in 61–91% of subjects with microadenomas, but for macroadenomas, remission rates may be as low as 23% (137, 145, 146, 148). Such variable surgical results have led some to question the role of pituitary surgery in acromegaly for all patients (149, 150).

Although retrospective studies have suggested that SMS analogs before surgical decompression may improve postsurgical hormonal parameters and remission rates, randomized studies are lacking (151–156).

2. Radiotherapy. Conventional, three-field, pituitary radiotherapy (CRT) has a well-established role in the treatment of acromegaly, either to effect remission after the failure of surgery or when surgery is contra-indicated or refused. Standard treatment schedules involve the administration of 4000–5000 cGy delivered in 160- to 180-cGy fractions over 5–6 wk. Such regimes do not damage the optic chiasm but do cause hypopituitarism (157, 158). The possibility of second brain tumors after CRT has been the subject of debate, and this question has yet to be satisfactorily answered, but, if anything, the possibility appears to be low (159, 160). Serum GH falls slowly after CRT with, in general, a 50% decline within 2 yr, improving to 75% within 5 yr (161–165). However, it may take 20 yr before 90% of patients achieve serum GH values below 5 ng/ml (163, 165). Barkan *et al.* (166), in 1997, reported the failure of CRT to normalize serum IGF-I values despite the achievement of epidemiologically safe serum GH concentrations, but more recent data suggest that serum IGF-I is often normalized after pituitary radiotherapy (165–167).

Although randomized trials of stereotactic and conventional radiotherapy are lacking, stereotactic radiotherapy is attractive, because, by restricting the treatment field to encompass only tumor, it is possible to deliver a larger dose of highly focused radiation exclusively to the pathological lesion. This may lead to more rapid inhibition of tumor growth and GH secretion, with a lower incidence of hypopituitarism and less damage to surrounding tissues. It may also allow the treatment of tumors beyond the reach of the surgeon, particularly in the cavernous sinus.

There are three forms of stereotactic radiotherapy: proton beam therapy, the Gamma Knife (Electa Instruments AB, Stockholm, Sweden), and the linear accelerator (LINAC). Facilities for proton beam therapy are very restricted such that most experience has been gained with photon therapy (Gamma knife and LINAC; Refs. 168–170).

3. Medical therapy. The first effective medical treatment of acromegaly was dopamine agonists that stimulate GH secretion in normal individuals but paradoxically suppress GH secretion in a proportion of patients with acromegaly (171). In 549 cases reported in 31 series in which the dose of bromocriptine ranged from 7.5–60 mg/d, GH levels were reduced below the suboptimal value of 5 ng/ml in just 20% of patients. Seven of the 31 reports measured serum IGF-I, which normalized in only 10% of those treated (172–179). Newman (180) recently reviewed the efficacy of two dopamine agonists, cabergoline and quinagolide, in acromegaly. Two reports including 28 subjects with acromegaly treated with quinagolide (a dose of 0.15–0.6 mg/d) reported serum IGF-I normalization in 43% of patients, and 5 reports including a total of 96 subjects treated with cabergoline (0.3–7.0 mg/wk) suggest IGF-I normalization is achieved in 34% of patients (181–186). In the largest of the cabergoline series, 64 patients treated with between 1 and 3.5 g/wk (1 patient received 7 g/wk), 39% were observed to have serum IGF-I concentrations below 300 μg/liter (183). A random measurement of serum GH was less than 2 ng/ml in 46% of patients. However, in the 16 PRL-cosecreting tumors, a random serum GH of less than 2 ng/ml was observed in 50% of cases (183). As these data demonstrate, dopamine agonists are more effective in the 33% of GH-secreting tumors that also secrete PRL (185). Overall, dopamine agonist therapy is of limited efficacy in acromegaly and is less effective than the SMS analog octreotide (174, 175).

Analogs of SMS are the most widely used form of medical therapy for acromegaly. Native SMS inhibits GH release and exists in two forms, SMS-14 and an amino-terminal extended SMS-28, with both peptides being encoded by a common preprosomatostatin gene located on chromosome 3q28 (187, 188). The various actions of SMS are mediated through specific cell-surface receptors expressed in the central nervous system, leptomeninges, anterior pituitary, mucosa of the gastrointestinal tract, and both the endocrine and exocrine pancreas (189). Five human subtypes of the SMS receptor have been cloned, all of which possess seven membrane-spanning domains (190–193) and are functionally linked to adenylate cyclase through coupling mechanisms involving guanine nucleotide-binding (G) protein (194–196). Octreotide (Sandostatin, Novartis Pharma, Basel, Switzerland), a synthetic octapeptide, was the first analog introduced into clinical practice and is 45 times more effective than SMS-14 at inhibiting GH secretion (Fig. 7 and Ref. 197). Unlike native

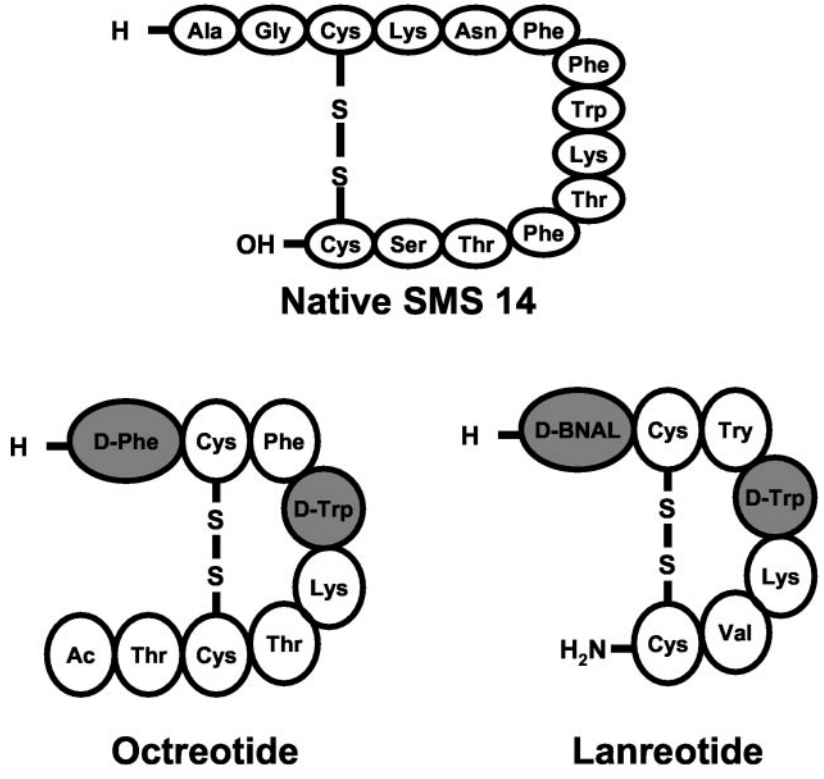

FIG. 7. Peptide structure of native SMS 14 and the SMS analogs octreotide and lanreotide. The presence of D-tryptophan, a nonphysiological amino acid, within the ring structure of these analogs stabilizes the molecule and reduces enzymatic degredation. Half-life is thereby prolonged in comparison to native SMS.

SMS, which binds with equal affinity to all five SMS-receptor (SSTR) subtypes, octreotide binds with high affinity to SSTR-2 and -5, with moderate affinity for SSTR-3, but does not bind to SSTR-1 and -4 (196, 198, 199). The acute suppression of GH secretion in response to octreotide administration in patients with acromegaly is dependent on SSTR availability (200), which in turn predicts the long-term effect of octreotide therapy on serum GH and IGF-I concentrations in most patients (201–203). Maximal suppression of serum GH and IGF-I is seen with sc doses of 300–600 μg/d with little additional benefit from further increments (204, 205). Most long-term studies of octreotide therapy in acromegaly report statistically significant suppression of serum GH, with serum IGF-I normalization in approximately 50–60% of patients (204–207), although the ability of octreotide to normalize serum IGF-I is dependent on preoctreotide serum GH levels and SSTR number (206). In the largest series analyzing the efficacy of octreotide over 6 months, GH levels fell below 2.5 μg/liter (5 mU/liter) in 22–45% of cases, with normalization of serum IGF-I in 45% (206, 207). The combination of octreotide and bromocriptine may prove more effective than either drug alone, although this finding has been questioned (208, 209). In nonrandomized clinical trials, octreotide is reported to reduce somatotroph tumor size in up to 50% of patients (201, 204, 206). In one study, a reduction in tumor size of more than 20% was observed in 15 of 34 (44%) patients receiving octreotide (207).

The observation that, for a given dose of octreotide, continuous infusions are more effective than sc bolus regimes (210), along with the inconvenience of three-times-daily administration, has led to the development of long-acting im preparations administered fortnightly (lanreotide) or every 4 wk [Sandostatin-LAR (Novartis Pharma) and Lanreotide Autogel (Ipsen Biotech Lab, Paris, France)]. These preparations have improved patient acceptability and compliance and produce similar control of serum GH and IGF-I to that observed with short-acting octreotide (211–214). Sandostatin-LAR is octreotide incorporated into microspheres of poly(D-L-*lactide-co*-glycolide). In a prospective, open-label, multicenter study of Sandostatin-LAR every 4 wk (10–30 mg) involving 151 selected patients in whom mean serum GH was below 10 μg/liter on sc octreotide, a serum GH concentration below 2.5 μg/liter was recorded in 69.8% of patients and a normal serum IGF-I in 65.8% (212). In 128 subjects continuing therapy for 48 wk, 94% demonstrated serum GH values below 5 μg/liter and 56.1% below 2 μg/liter (212). The most frequent adverse events reported in this study were diarrhea (11.3%), abdominal pain (6%), flatulence (4.6%), and injection site pain (212). There are few studies reporting the efficacy of Sandostatin-LAR beyond 12 months. Flogstad *et al.* (211) reported stable and consistent suppression of serum GH below 2 μg/liter in 9 of 14 octreotide-sensitive patients receiving 20, 30, or 40 mg of Sandostatin-LAR for 18 consecutive injections.

Slow-release lanreotide (Somatuline, Ipsen Biotech Lab; Fig. 7) has a fixed injection dose of 30 mg given at variable intervals of 14, 10, or 7 d. During a six-month, open-label, prospective study involving 14 patients with acromegaly that was not controlled after transsphenoidal surgery and (in 10 cases) pituitary radiotherapy, mean serum GH levels fell from 21.4 μg/liter to 7.3 μg/liter and mean serum IGF-I fell to 272 μg/liter (215). In a further open-label study involving 57 patients of whom 50 received 6 months of lanreotide therapy, serum GH suppressed below 2 μg/liter in 66% and

IGF-I normalized in 38% of patients (216), with similar results having been observed other groups (214, 217).

Two studies have suggested that Sandostatin-LAR produces improved suppression of serum GH and IGF-I, compared with lanreotide, using established dosing schedules (218, 219). Together, these studies involved a total of 22 patients who initially received lanreotide and subsequently switched to Sandostatin-LAR. Of the 22 patients involved in both studies, GH was suppressed below 2.5 μg/liter (5 mU/liter) in 10 individuals during lanreotide therapy and in 12 patients during Sandostatin-LAR treatment. Serum IGF-I was suppressed into an age-related normal reference range in 9 patients with lanreotide therapy and 12 patients with Sandostatin-LAR therapy. In both studies, Sandostatin-LAR produced a significant further suppression of mean serum GH compared with lanreotide (218, 219). More recently Chanson *et al.* (220) have described similar findings in group of 125 patients with acromegaly.

The use of a new formulation of lanreotide (Autogel), four weekly deep sc injections, has been reported to be as effective as conventional lanreotide for use in acromegaly (221). There are, however, no comparative studies of Lanreotide Autogel and Sandostatin-LAR.

Both SMS analogs and dopamine agonists have side effects that may limit their clinical usefulness. In particular, SMS analogs are known to inhibit the release of glucagon, insulin, and serotonin, as well as other gut hormones, and are associated with cholesterol gallstone formation (222).

IX. Pegvisomant in Acromegaly

With appreciation of the importance of vigorous control of the GH/IGF-I axis, and even more stringent outcome criteria against which to judge the efficacy of therapy, has come the recognition that despite the use of all current modes of treatment, a significant cohort of patients with acromegaly remain inadequately controlled. Pegvisomant is an analog of hGH and represents an exciting new prospect in the medical management of acromegaly. As previously stated, the ability of current treatment modalities to achieve biochemical remission is inextricably linked to pituitary tumor characteristics. Tumor size and position, pretreatment serum GH, and the expression of SSTRs all influence treatment outcome. Whereas SMS analogs bind centrally to specific tumor receptors to mimic physiological inhibition of GH release, pegvisomant acts on peripheral GHRs, blocking "proper" GHR dimerization to prevent GH-induced signal transduction. This approach offers the prospect of higher normalization rates and greater specificity of effect in comparison to current therapies for acromegaly.

A. Monitoring disease activity during pegvisomant therapy

Clearly, serum GH cannot be used as a marker of disease activity in patients with acromegaly who receive pegvisomant, as pegvisomant makes no attempt to lower circulating GH levels. Furthermore, the structural homology between native GH and the GH antagonist, which differ by only 9 amino acids, means pegvisomant is detected in conventional GH assays, resulting in spuriously high serum GH estimation. In the presence of pegvisomant, the direct measurement of serum GH is possible using a customized two-site GH immunoassay (123). An indirect measurement of serum GH using a modified chemiluminescence assay (empirically corrected for pegvisomant cross-reactivity) has been devised and is reported to correlate well with the results of direct measurement (123).

In the absence of serum GH as a marker of disease activity, reduction of serum IGF-I into the age-related reference range has been the primary goal of pegvisomant therapy in acromegaly.

B. Phase II studies

A phase II, randomized, placebo-controlled, multicenter study of pegvisomant provided proof of concept that pegvisomant lowers serum IGF-I in patients with active acromegaly (223). Forty-six patients with a serum IGF-I value at least 50% above the age-related upper limit of normal received placebo, 30-, or 80-mg of pegvisomant once weekly for 6 wk. Mean serum IGF-I levels were unchanged in the placebo group but fell by 16 $\pm$ 4.8% and 31 $\pm$ 6.7% in the 30-mg ($P = 0.04$) and 80-mg ($P = 0.001$) groups, respectively. Free IGF-I fell by 47% in the 80-mg group (226). Although a dose-related decline in serum IGF-I and other markers of the GH/IGF-I axis was seen, serum IGF-I was normalized in only a minority ($n = 3$) of patients.

The pharmacokinetics of the drug provided a probable explanation for the low serum IGF-I normalization rate. Phase I studies in healthy volunteers had demonstrated peak serum concentration levels at 36 h and maximal suppression of serum IGF-I on d 5 after a single sc dose of pegvisomant (123). As a reversible, competitive receptor antagonist, sustained concentrations of pegvisomant are crucial to efficacy. With a half-life of approximately 70 h in humans and a weekly dosing schedule, it was suspected that adequate serum concentrations of pegvisomant were not maintained throughout the dosing interval. Pharmacokinetic modeling suggested that the trough concentration of pegvisomant would be increased by 20% by delivering the same weekly dose but divided into a daily dose.

C. Phase III studies

A 12-wk, phase III, multicenter, double-blind, randomized, placebo-controlled study of 112 patients provided convincing evidence of the effectiveness of daily pegvisomant (10, 15, or 20 mg) in patients with a serum IGF-I level at least 30% above the upper limit of an age-related reference range. Short-acting SMS analogs and dopamine agonist therapy were discontinued 2 and 5 wk before study entry, respectively. Clinical/laboratory assessments (including completion of a questionnaire designed to evaluate five symptoms and signs of active disease—soft tissue swelling, arthralgia, headache, perspiration, and fatigue) and ring size measurement using standardized European Jewelers' rings on the left fourth digit were undertaken at baseline, 2, 4, 8, and 12 wk after commencement of therapy or placebo. Pituitary anatomy was assessed at baseline and after 3 months using magnetic resonance imaging.

Dose-dependent reductions in serum IGF-I, free IGF-I, IGFBP-3, and ALS were observed in the three pegvisomant-treated groups. Mean serum IGF-I levels fell significantly in a dose-dependent manner in the 10-, 15-, and 20-mg treatment groups (Fig. 8). The percentage of patients achieving a serum IGF-I value within the age-adjusted reference range was 54%, 81%, and 89%, respectively (Fig. 9 and Ref. 224).

The serum IGF-I reduction was accompanied by a rise in serum GH (Fig. 10 and Ref. 224). After 12 wk of pegvisomant therapy, mean serum GH increased in a dose-dependent manner in the 10-, 15-, and 20-mg/d groups and reached statistical significance in the 15- and 20-mg dose groups, with a mean rise of 2.7, 9.2, and 14.4 ng/ml over baseline, respectively (224). Pituitary tumor volume was calculated from magnetic resonance images by a blinded single evaluator, and no change in tumor volume was observed in any patient (224). The rise in serum GH, and the fall in serum IGF-I (and other markers of the GH/IGF-I axis), occurred within 2 wk and remained constant thereafter (Figs. 8 and 10).

Importantly, the fall in serum IGF-I was accompanied by significant improvements in the signs and symptoms of active acromegaly. The mean scores for individual symptoms and signs, and the total score, decreased in all the pegvisomant-treated groups. Significant decreases were seen in the total score and those for soft-tissue swelling, excessive perspiration, and fatigue. The improvement in soft-tissue swelling was confirmed by a dose-dependent, and statistically significant, decline in ring size in the groups receiving 15 and 20 mg of pegvisomant per day; a mean decrease of 2.5 ring sizes was observed for the latter group (224).

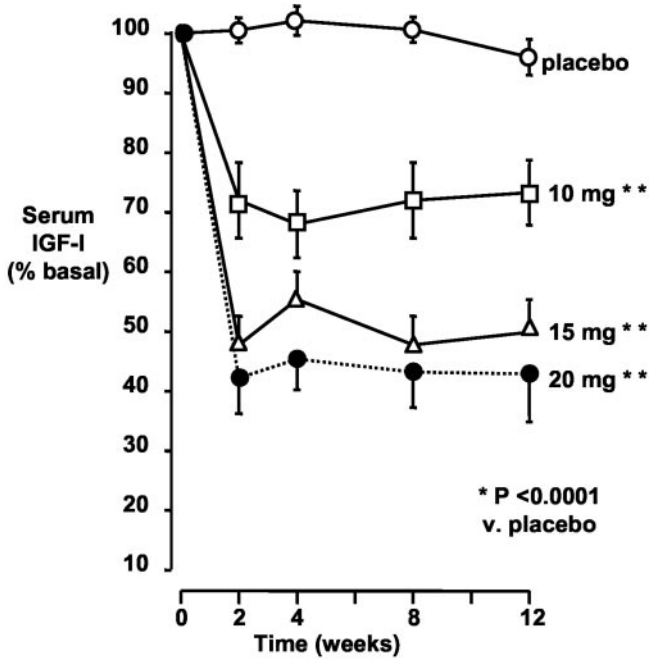

FIG. 8. Percentage reduction in serum IGF-I in 111 patients with acromegaly receiving pegvisomant for 12 wk. The data show a dose-dependent decline in serum IGF-I. All patients had active disease before starting pegvisomant, based upon a serum IGF-I level at least 30% greater than the upper limit of an age-related reference range. [Adapted from P. J. Trainer *et al.: N Engl J Med* 342:1171–1177, 2000 (224).]

Pegvisomant was well tolerated, and the incidence of reported adverse events was similar in the placebo and three treatment groups. Injection site reactions were reported in six patients receiving pegvisomant. Two patients from the placebo group withdrew from the study, one due to persistent headache and a second after only 5 d of therapy when optic chiasmal compression was observed on the prestudy magnetic resonance scan. One patient assigned to 15 mg/d withdrew due to persistent headaches, and a second patient in this group withdrew after 8 wk of therapy because of elevated serum aminotransferase levels. In this patient serum alanine aminotransferase and aspartate aminotransferase rose to 904 U/liter (normal range, 0–47 U/liter) and 389 U/liter (normal range, 0–37 U/liter), respectively. No change in serum bilirubin or alkaline phosphatase was documented. The abnormal liver function tests (LFTs) returned to normal on withdrawal of pegvisomant but rose again during a 4-wk rechallenge with 10 mg/d. Thereafter, pegvisomant was stopped and the abnormal LFTs normalized. No change in mean serum aminotransferase levels was seen in the cohort of patients (n = 80) receiving pegvisomant. The relatively high doses of pegvisomant required to achieve serum IGF-I normalization in these clinical studies have not proved to be a problem. As discussed below, the use of such doses (in some cases over 3 yr) has not been associated with a major incidence of side effects, significant antibody formation, or tachyphylaxis (225).

D. Long-term experience with pegvisomant in acromegaly

Recently, an analysis of the long-term safety and efficacy of pegvisomant in 186 patients (mean duration of treatment was 425 d) receiving pegvisomant in an open-label manner after completion of the phase II and III studies described above has been reported (228). Normalization of serum IGF-I was observed in 97% of those patients receiving pegvisomant for over 12 months (Fig. 11).

These studies have demonstrated impressive rates of serum IGF-I normalization in patients with active acromegaly receiving pegvisomant. In comparison to existing medical therapies for acromegaly, pegvisomant represents a significant improvement: serum IGF-I normalization rates of greater than 90% are observed in patients with active disease when receiving daily pegvisomant at doses up to 40 mg/d. Pegvisomant therefore represents the most effective medical therapy for acromegaly, and further improved rates of serum IGF-I normalization are expected when higher doses of the competitive antagonist are employed. The long-term effectiveness of pegvisomant has been demonstrated over 1 yr, but many questions regarding this therapy are still to be answered, particularly the reliance on serum IGF-I as a marker of disease activity and long-term safety data regarding changes in pituitary tumor volume.

E. Outstanding questions for pegvisomant in the treatment of acromegaly

1. Monitoring of GHR antagonist therapy and the potential for overtreatment. The consensus statement defining the desired

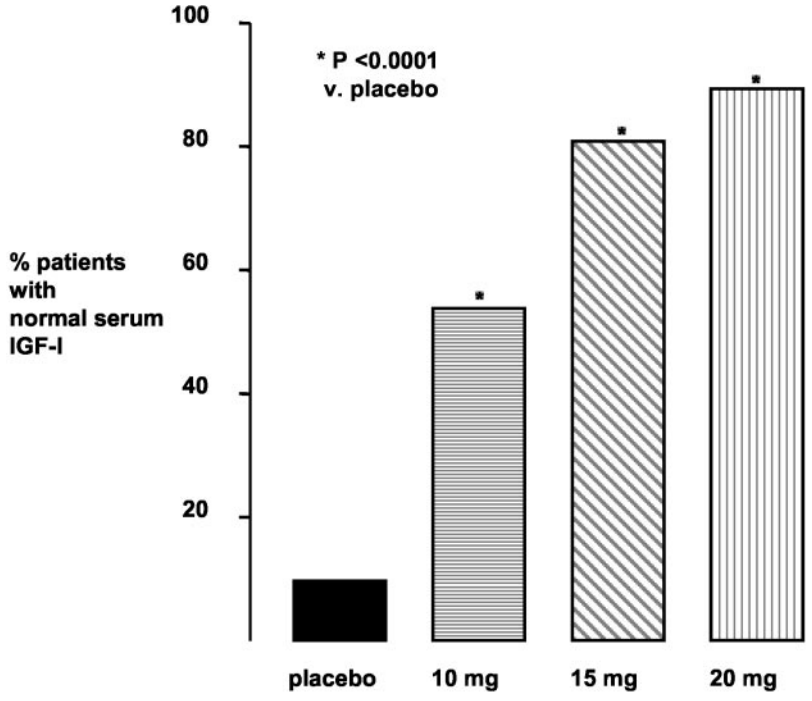

FIG. 9. Percentage of patients with acromegaly achieving a normal age-related serum IGF-I value during 12 wk of pegvisomant therapy. The data demonstrate normalization in 54%, 81%, and 89% of patients in the 10-, 15-, and 20-mg/d groups, respectively. [Adapted from P. J. Trainer *et al.: N Engl J Med* 342:1171–1177, 2000 (224).]

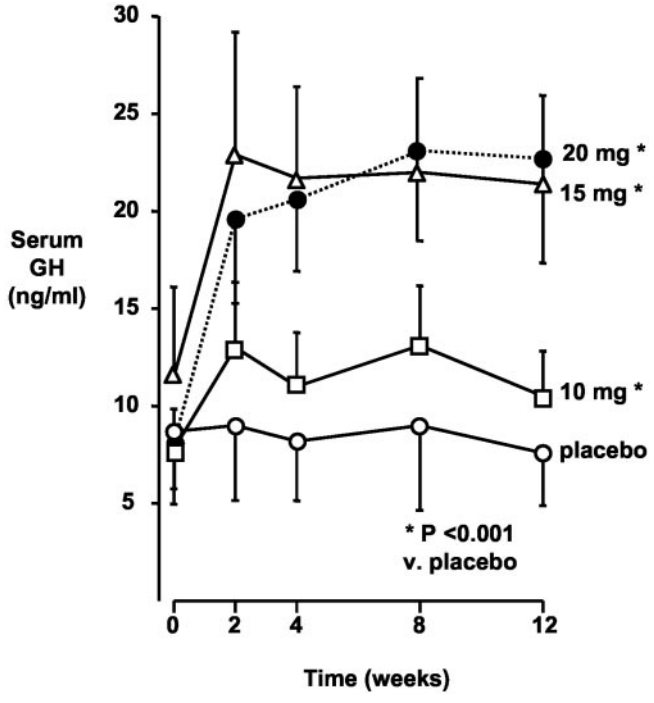

FIG. 10. Dose-dependent rise in serum GH during 12 wk of pegvisomant therapy in 111 patients with active acromegaly. Serum GH increased during the initial 2 wk of therapy but thereafter remained stable. This was not associated with reduced efficacy (see Fig. 8). [Adapted from P. J. Trainer *et al.: N Engl J Med* 342:1171–1177, 2000 (224).]

outcome of treatment for acromegaly includes criteria for both GH and IGF-I (141). As discussed, the longer established and well-validated GH criteria are not applicable to patients on pegvisomant. The sole reliance on serum IGF-I as a marker of disease activity emphasizes the need for improvement in the quality of serum IGF-I assays and a better understanding of the relationship between serum IGF-I and disease activity and morbidity/mortality. Melmed (226) has highlighted the problems with many commercial serum IGF-I assays and the need for standardization and development of age- and gender-specific reference ranges.

In acromegaly, although a tight correlation is seen between serum IGF-I and GH (134, 227, 228), results are discrepant in approximately one quarter of patients who have either elevated GH and normal serum IGF-I or more frequently acceptable serum GH and elevated serum IGF-I (229). Previous CRT (230) and gender (231) modulate the relationship between serum GH and IGF-I and, in part, may explain these discrepancies. However, much more prospective information is needed concerning the relationship between serum IGF-I and mortality/morbidity in acromegaly.

Whether IGF-I acts principally in an autocrine, paracrine, or endocrine manner, and the extent to which circulating IGF-I values are a true measure of IGF-I activity, is the subject of much debate. In support of a role for circulating IGF-I mediating many of the growth-promoting effects of GH are studies involving patients with mutations of the GHR gene resulting in a condition termed GH insensitivity or Laron's syndrome. This condition manifests as profound IGF-I deficiency despite normal or high circulating GH (232–234) and represents a unique biological model allowing the measurement of the effects of injected, and therefore circulating, IGF-I without the confounding effects of GH. Treatment of patients with GHR mutations using recombinant human IGF-I (rhIGF-I) is associated with a fall in serum GH and normalization of serum IGF-I levels, in the absence of any obvious change in IGFBP-3 concentration (235, 236). rhIGF-I promotes linear growth in children with Laron's syndrome (235, 237) and causes a reduction in fat mass, an increase in lean mass, increased protein turnover, a fall in serum insulin, and

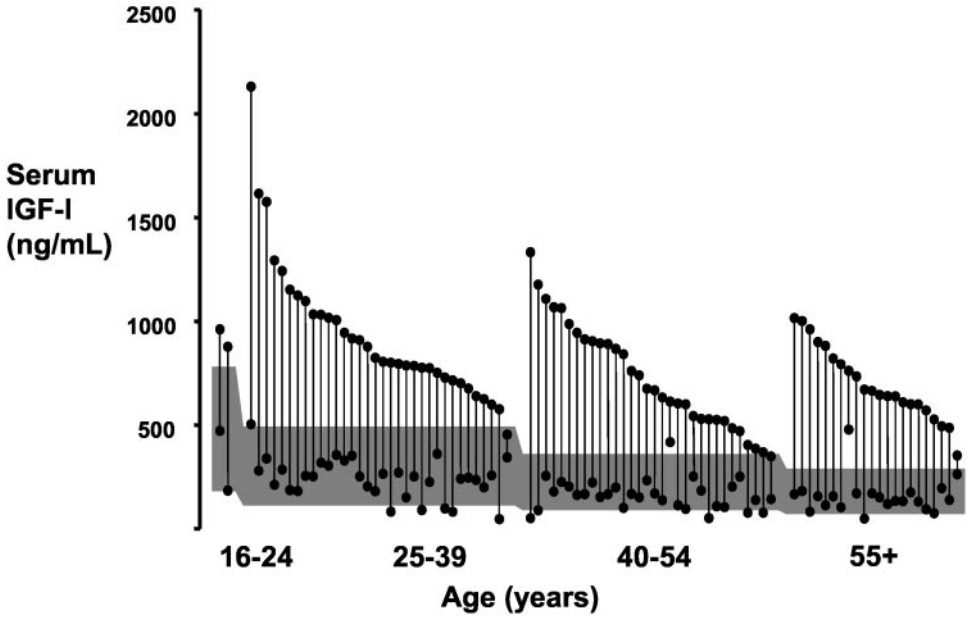

FIG. 11. Baseline and lowest serum IGF-I concentration in 90 patients receiving daily pegvisomant (5–40 mg/d) for over 12 months. *Shaded area* represents age-adjusted normal range for serum IGF-I. Ninety-seven percent of patients normalized serum IGF-I. [Adapted with permission from Elsevier Science from A. J. van der Lely *et al.: Lancet* 358:1754–1759, 2001 (225).]

increased glucose production (238). Excessive rhIGF-I has been reported to induce features of acromegaly in a girl with Laron's syndrome (239). These findings are similar to those observed after GH replacement in adult GH deficiency (GHD) (240) and suggest circulating IGF-I, as opposed to auto- or paracrine, is important in mediating many of the actions of GH. This supports the appropriateness of serum IGF-I as a marker of disease activity in pegvisomant-treated patients with acromegaly.

In our experience, with sufficiently high doses of pegvisomant, it is possible to reduce serum IGF-I below the age-related lower limit of normal in patients with acromegaly, raising the question of overtreatment and its diagnosis. Even when serum IGF-I is reduced to the normal age-related reference range, the potential for overtreatment remains, as many patients with adult GHD, diagnosed using provocative tests of GH secretion, have normal serum IGF-I values. Serum IGF-I is of diagnostic value in patients with childhood onset GHD, but in patients with GHD of adult onset, the value of serum IGF-I in predicting the response to provocative tests of GH secretion declines with increasing age (241, 242). In elderly patients with GHD, although serum IGF-I is significantly lower than that observed in normal age-matched subjects, values below the lower limit of the normal reference range are observed in only 17% of patients (243). GHD may account for the increased mortality observed in patients with hypopituitarism on full replacement therapy except GH (244–247). Thus, although a reduction in mortality is anticipated after serum IGF-I normalization in acromegaly when pegvisomant is used, the reliance on serum IGF-I data in the absence of meaningful serum GH data represents a formidable task. The diagnosis of overtreatment represents a further challenge, as standard provocative tests cannot be employed due to high circulating GH levels. Long-term prospective studies are thus required to define the optimal treatment target for serum IGF-I in patients receiving this therapy, as morbidity and mortality may increase with overtreatment. In the absence of evidence, it would seem reasonable to titrate serum IGF-I down to the middle of the age-related reference range.

2. Elevated GH and tumor growth. The fall in serum IGF-I with administration of pegvisomant to patients with acromegaly is accompanied by a rise in serum GH (224). When pegvisomant was administered to normal subjects as a single sc injection, no acute rise in serum GH was observed, prompting speculation that pegylation of the antagonistic protein prevents its passage across the blood-brain-barrier, although the dose of pegvisomant used and the sampling interval are alternative explanations of the failure to document an increase in plasma GH levels (123). Administration of pegvisomant (either weekly or daily) over several weeks is associated with increased serum GH (measured using a customized assay that does not cross-react with pegvisomant) in primates and humans. This rise occurs within 2 wk and is constant thereafter (224). Wilson (121) observed a 6-fold increase in serum GH in rhesus monkeys receiving 1.0 mg/kg of pegvisomant weekly, and Trainer *et al.* (224) reported dose-dependent increases in serum GH in patients with active acromegaly. The mechanism by which pegvisomant induces a marked increase in serum GH has not been elucidated and could be the result of increased GH secretion, delayed clearance, or both. In normal volunteers, recent evidence suggests the mechanism is exclusively due to increased GH secretion as pulse amplitude increased during pegvisomant treatment, but the half-life of circulating GH and clearance rate were unaltered (117). However, further studies are required in patients with acromegaly. GHRH and SMS are the two principal regulators of GH secretion and are secreted from the median eminence of the hypothalamus, which lies outside the blood-brain-barrier but is also modified through negative feedback loops involving both GH and IGF-I (248–252). Pegvisomant could stimulate increased GH secretion by a direct action on the pituitary adenoma or

the median eminence or, more probably, by an indirect effect secondary to the lowering of circulating IGF-I acting through feedback mechanisms within the central nervous system, at the median eminence, or directly at the somatotroph tumor.

Available data suggest that the increase in serum GH in patients with acromegaly receiving pegvisomant is not associated with a loss of efficacy. A concern at the initiation of the first clinical studies was that GH would continue to rise and potentially overcome the receptor-blocking action of pegvisomant (*i.e.*, induce tachyphylaxis). As previously discussed, the rise in serum GH after the introduction of pegvisomant in patients with acromegaly mirrored the fall in serum IGF-I and appeared to plateau after 2 wk of therapy, with no further rise thereafter in patients receiving therapy for over 12 months (224, 225).

GH is a tumor marker in acromegaly and, by implication, elevated serum GH as a result of increased GH secretion may be a harbinger of future tumor growth. No significant change in mean tumor volume was observed during the 12-wk placebo-controlled study reported by Trainer *et al.* (224), but 57 of the 112 subjects had previously received conventional pituitary radiotherapy a minimum of 12 months before enrollment. Prior radiotherapy is likely to decrease the potential for tumor growth during pegvisomant therapy. To date, there are limited long-term data on the risks of tumor growth in patients with acromegaly receiving pegvisomant therapy. In the 131 patients reported by van der Lely *et al.* (225), for the group as a whole, no significant alteration in mean tumor volume was observed after a mean duration of treatment of 1 yr. (Fig. 12). Changes in tumor volume were not related to patients' previous history of pituitary irradiation and duration of therapy (225). Two patients have required treatment for tumor progression while receiving pegvisomant, but in both of these cases there is no obvious association between tumor growth and treatment duration (225). Before pegvisomant, both had large globular tumors with impingement on the optic chiasm despite recent transsphenoidal surgery. In the first case, baseline tumor volume was 5.53 cm^3 and was subsequently estimated at 5.66 cm^3 after three months of 15 mg/d. Pegvisomant was then discontinued, and six months elapsed before its reinstitution, at which point accurate assessment of tumor size was not possible. Six months later, at the next routine pituitary magnetic resonance imaging examination, tumor size had increased to 8.71 cm^3 and the patient received pituitary irradiation (225). The second patient had a baseline tumor volume of 2.93 cm^3 and initially received weekly pegvisomant (80 mg) for 3 months, during which time the tumor volume decreased to 2.75 cm^3. This patient then received octreotide for 5 months before restarting pegvisomant. A repeat pituitary magnetic resonance imaging scan was not undertaken until 2 months after recommencement of pegvisomant, whereupon a tumor volume of 4.28 cm^3 was observed, which had increased to 4.92 cm^3 11 months after the restart of pegvisomant. Subsequently, this patient discontinued pegvisomant but continued tumor growth on SMS analogs. Insufficient suppression of serum IGF-I by SMS analogs alone, and a return of symptoms, prompted referral for a second transsphenoidal procedure to debulk the pituitary mass (225, 253). We do not believe that in either of these cases a causal relationship between pegvisomant and tumor growth has been established. However, the total number of patient years remains small, such that caution is required and regular assessment of pituitary anatomy is necessary in all patients receiving this therapy, as the risk of tumor expansion has not been fully elucidated. Particular attention will need to be paid to pituitary tumor size in those patients receiving pegvisomant as primary therapy as pegvisomant will not protect from tumor growth.

3. Antibody formation and possible tachyphylaxis. Pegvisomant has nine amino acid substitutions that distinguish it from hGH as a foreign protein, potentially leading to the formation of antibodies that could reduce efficacy. Pegylation of the GHR antagonist protein, in addition to increasing half-life, has the benefit of reducing immunogenicity by modification of immune system recognition. In the double-blind study reported by Trainer *et al.* (224), anti-GH antibodies were detected in only eight patients who received pegvisomant, in titers ranging from 1:4 to 1:64. Pegvisomant antibodies were detected in 27 patients (16.9%) in the long-term study re-

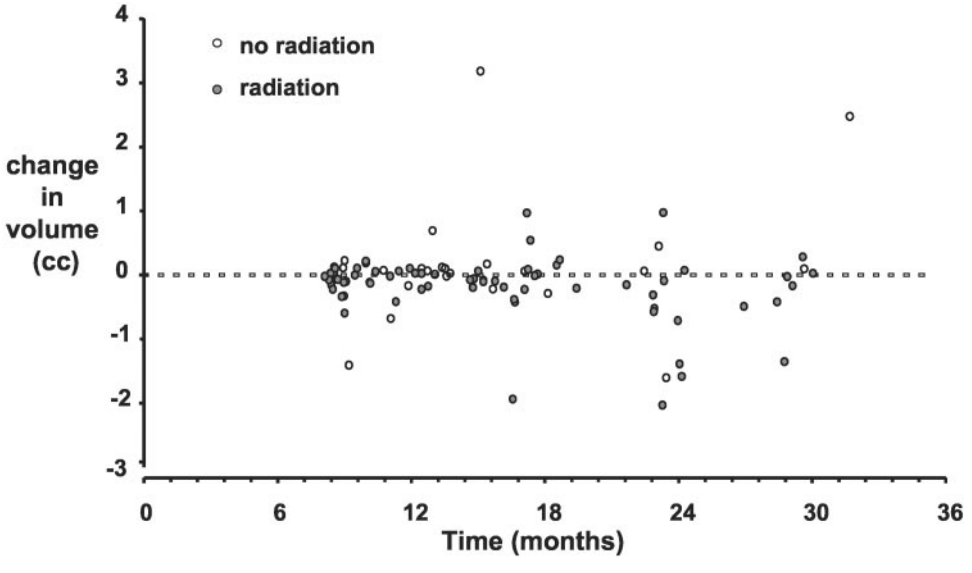

FIG. 12. Lack of association between duration of pegvisomant and change in tumor volume in 131 patients. [Adapted with permission from Elsevier Science from A. J. van der Lely *et al.*: *Lancet* 358: 1754–1759, 2001 (225).]

ported by van der Lely *et al.* (225), in 11 patients on only one occasion (in titers ranging from 1:4 to 1:16). Three patients had sustained low titers of anti-GH antibodies, but in all cases serum IGF-I was normalized and the appearance of either antibody was not associated with reduced efficacy (225). Even if the proportion of patients developing antibodies increases with time, we know from patients receiving GH in GHD that antibody formation is not associated with loss of efficacy (254, 255).

4. Altered LFTs. The development of altered LFTs in two patients receiving pegvisomant (15 mg/d) during the phase III double-blind and open-label studies has already been discussed (224, 225). Although, to date, only 2 of 160 patients have shown changes in LFTs, and the true incidence and mechanism of pegvisomant-induced deranged LFTs remains unclear. At present, such changes appear to be entirely reversible on withdrawal of pegvisomant therapy. Nevertheless, monitoring of LFTs is essential in any patient receiving pegvisomant.

5. The effect of pegvisomant therapy for acromegaly on other hormonal parameters and intermediary metabolism. Little data exist on the effects of pegvisomant on intermediary metabolism and hormonal parameters other than those directly affected by GH. Trainer *et al.* (256) have recently reported the effect of serum IGF-I reduction using pegvisomant on 11β-hydroxysteroid dehydrogenase (11β-HSD) activity. 11β-HSD type I is a bidirectional enzyme responsible for the interconversion of cortisol to its inactive metabolite cortisone. Patients with active acromegaly are known to have accelerated cortisol clearance, whereas in adults with GHD the opposite is seen. Using the urinary ratio of cortisol and cortisone metabolites as a marker of net 11β-HSD activity, a significant decrease in cortisol clearance was seen during the administration of pegvisomant to seven patients with acromegaly (256).

Although no change in mean HBA1c values has been observed in patients with acromegaly receiving pegvisomant, normalization of serum IGF-I in these individuals is associated with significant reductions in fasting plasma glucose and insulin (225). In a separate study (257), insulin sensitivity, as measured using the Homeostatic Model Assessment equation, is also improved.

Adult GHD is associated with elevated total cholesterol (TC), low-density lipoprotein (LDL), and apo-lipoprotein B levels. These decrease after GH therapy (258–260), which has also been associated with a significant increase in lipoprotein a (261), an independent risk factor for cardiovascular disease. Parkinson *et al.* (262) have recently demonstrated, compared with established normal age-matched control data, lowered serum TC and LDL levels in patients with active acromegaly, in whom pegvisomant induced normalization of serum IGF-I, was associated with a significant increase in serum TC, LDL, and apo-lipoprotein B, as well as a significant decline in lipoprotein a. After normalization of serum IGF-I, the distribution of serum TC and LDL levels in this cohort were not significantly different than those of the general population (262). Given that LDL receptor number and activity are in part mediated by GH (263, 264), these findings are consistent with the theory that normalization of serum IGF-I using pegvisomant is associated with normalization of lipoprotein metabolism.

The clinical significance of these changes in intermediary metabolism remains to be established, but the ability of pegvisomant to not only control circulating IGF-I but also to correct metabolic abnormalities associated with active acromegaly suggests that GH receptor blockade is an effective treatment strategy for patients with acromegaly.

6. Comparison with SMS analog therapy. Two recent reports (265, 266) have confirmed the efficacy of pegvisomant in patients refractory to all conventional modes of therapy including SMS analogs. All 13 patients reported in these studies had persistently elevated serum GH and IGF-I despite receiving large doses of SMS analogs. Subsequently, normal serum IGF-I values were achieved with pegvisomant alone in all patients studied. It is also apparent that, even at a pegvisomant dose of 40 mg/d, the top of the serum IGF-I dose-response curve has not been reached, prompting speculation that normalization of serum IGF-I can be achieved in all patients with active acromegaly, when adequate serum concentrations of pegvisomant are obtained.

7. Combination therapy. An attractive notion is combination medical therapy, using an agent that reduces pituitary GH release together with pegvisomant to block GH action. However, with serum IGF-I normalization in over 90% of patients with acromegaly receiving pegvisomant, the indications for combined therapy will be limited. The routine use of SMS analogs and pegvisomant in combination may also be prohibitively expensive. We have experience of combined octreotide and pegvisomant therapy in one patient. This patient described dramatic improvement in headache within minutes of sc octreotide injection, but despite transsphenoidal surgery, CRT, and Sandostatin LAR (30 mg every 4 wk) plus bromocriptine (20 mg daily), persistent disease activity was observed. Treatment with 40 mg of pegvisomant alone resulted in normalization of serum IGF-I, and all reported symptoms improved except for headache, which remained unresponsive to conventional pain relief and prevented the patient from sleeping or working. Pituitary magnetic resonance scans showed no evidence of pituitary tumor growth. To control headache, 50 μg of octreotide three times per day, and subsequently, Sandostatin LAR (30 mg every 4 wk) was combined with pegvisomant (40 mg/d) and the headache resolved. An additive effect of pegvisomant and Sandostatin LAR on serum IGF-I was observed. This case highlights that although biochemical remission can be achieved using pegvisomant in patients with octreotide-resistant acromegaly (266), a small subset with octreotide-sensitive headache may require combined pegvisomant and SMS analog therapy. To date, however, there is limited experience comparing the efficacy of pegvisomant as a single agent with its use in combination with other medical therapies. Dopamine agonists, in particular cabergoline, which has the advantage of being relatively inexpensive, orally active, and with a similar half-life, could potentially be combined with pegvisomant for twice-weekly administration, possibly reducing the overall dose of pegvisomant required and, therefore, cost.

X. Summary

An understanding of the molecular events involved in the interactions between GH and its receptor has led to the rapid development of a "designer" GH antagonist for use in conditions characterized by excess GH action and elevated serum IGF-I. The efficacy of pegvisomant in lowering serum IGF-I in acromegaly is no longer in dispute. Attention must now focus on long-term safety of pegvisomant with regard to tumor volume changes, alteration of LFTs, effects on the metabolic consequences of acromegaly, and the potential differences between pegvisomant and existing medical therapies.

On a larger scale, pegvisomant has the potential to significantly improve treatment of diabetic microvascular complications and human malignancy. We excitedly await the potential applications of GH antagonists to these other clinically important areas. Also, as studies continue on the interaction between GH and its receptor, hopefully, orally active, nonpeptidyl GH agonists and antagonists will be discovered, developed, and used.

Acknowledgments

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J.J.K. is supported in part by the State of Ohio's Eminent Scholars Program, which includes a gift from Milton and Lawrence Goll and by Sensus Corporation. C.P. and P.J.T. have received research grants and travel support from Novartis Pharmaceuticals UK Ltd., Ipsen Biotech, Pharmacia Corporation, and Sensus Drug Development Corporation.

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