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GH Receptor Antagonist: Mechanism of Action and Clinical Utility

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This review focuses on the development of GH receptor antagonist as a novel agent for treatment of acromegaly, its mechanism of action and potential areas of use. A brief overview of acromegaly, its diagnosis and existing medical, surgical and radiotherapy options of treatment is necessary to justify the addition of yet another therapeutic modality to the already vast therapeutic armamentarium.

Introduction

Acromegaly is a multisystem disease due to chronic hypersecretion of growth hormone (GH) from a pituitary adenoma [1]. The resultant increase in insulin like growth factor (IGF-1) causes somatic overgrowth whereas elevated GH on its own promotes certain metabolic derangements such as glucose intolerance or diabetes. Extension of the pituitary tumor outside the confines of the sella may cause ophthalmoplegia and chiasmal compression. The mortality and morbidity of acromegaly are determined by GH/IGF-1 induced end organ damage such as cardiomyopathy, arrthymias, sleep apnea, diabetes and osteoarthritis in addition to mass effects of tumor and accompanying hypopituitarism [2–5].

Diagnosis

The diagnosis of acromegaly essentially rests on a combination of physical findings, elevated GH and IGF-1 levels and inability of an oral glucose load to suppress plasma GH [6,7]. The biochemical criteria for the diagnosis and surveillance of acromegaly have changed over the years as a result of several epidemiological studies analyzing the mortality of acromegaly as a function of prevailing GH milieu [7,8].

Whereas many treated and even newly diagnosed patients may have random or mean daily GH levels within the "normal" range, the trough or interpulse GH concentrations are uniformly elevated in patients with active disease [9]. This feature of GH hypersecretion will be obviously missed unless a frequent (Q10–20 min) and prolonged (12–24 hr) blood sampling is performed. On the other hand, a single value of plasma IGF-1 faithfully reflects both the total daily GH output as well as the prevailing pattern of GH secretion [8,9]. Plasma IGF-1 needs to be interpreted according to strict age/ gender adjusted normative values. The criteria for glucose suppressed GH have also changed markedly. According to strict contemporary criteria, plasma GH needs to fall below 0.2–0.25ug/l to be defined as a manifestation of a normal physiological response [10–12]. Failure of GH to suppress normally (even in the presence of normal IGF-1) may potentially predict higher probability of recurrence. Thus, both GH (glucose suppressed) and IGF-1 are valuable parameters to be assessed in patients with acromegaly. Plasma GH is a more sensitive indicator of acute changes in tumor activity (i.e, after surgery, radiotherapy, dopamine and somatostatin analogues) whereas IGF-1 is an infinitely better parameter of overall normalcy of GH secretion and the clinical activity of acromegaly (arthropathy, soft tissue volume, perspiration, sleep apnea etc). Both GH ($<$1–2.5 ug/l) and IGF-1 (age/gender normal) have been shown to predict normalization of subsequent mortality rates [4,5]. The size and the invasiveness of the pituitary adenoma is best assessed by MRI.

Thus, the goals of therapy can be subdivided into 3 categories:

(1) Primary: normalization of plasma IGF-1 and abolition of the mass effects of the tumor.
(2) Secondary: therapy of associated morbidities (arthropathy, diabetes, arrhythmias etc.) and replacement of missing pituitary hormones in case of hypopituitarism.
(3) Ultimate: normalization of mortality rates and prevention of recurrence.

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Practical Aspects of Treatment of Acromegaly

Therapeutic choices for management of acromegaly are largely dictated by age and general health of the patient as well as efficacy, complications and risks of a particular therapeutic modality. General consensus [12] is that trans-sphenoidal adenomectomy is the first line therapy followed by medical therapy if the former is not curative. In some patients with unacceptable cardiovascular, surgical or anesthetic risks and adenomas not impinging on the optic chiasm, or those whose tumor is surgically inaccessible (e.g., largely confined to the cavernous sinus), primary medical therapy may be offered. If a maximum dose of medications fails to achieve remission and the tumor continues to grow, radiotherapy needs to be considered. Reoperation or treatment with GH receptor antagonist should be considered for patients resistant to surgical or medical approaches.

Surgery

Surgery is the cornerstone of therapy and procedure of choice for initial management. The success of surgery depends on the experience of the surgeon on the one hand and on the characteristics of the tumor (size, invasiveness, consistency) on the other hand. The former is exemplified by the wide variability of proportion of patients with post-operative GH <2.5 ug/l in different treatment centers [13,14]. The overall success rate even in the best neurosurgical centers is about 50% [13,14]. Some 85% of patients with microadenomas achieve normal IGF-1 levels post surgery, but the success rate plummets in patients with macroadenomas. Invasiveness of the tumor into the surrounding tissues (cavernous sinus especially) precludes curative outcome.

Complications of Surgery

Surgical damage of pituitary can lead to permanent hypopitutarism and result in need for lifelong hormone replacement. CSF rhinorrhea, visual impairment, sinusitis and hemorrhage are seen in a small number of patients. The likelihood of complications is directly related to the experience of the neurosurgeon, the size of the tumor and is more common after subfrontal rather than transsphenoidal surgery.

Radiotherapy

Radiation has been used as a therapeutic modality for acromegaly since 1909. Current modalities include conventional external radiotherapy (XRT) and stereotactic approaches (proton beam,gamma knife and LINAC). XRT is usually administered over four to six weeks in daily fractions to a total dose of 45–50 Gy. In most patients GH levels fall by about 50% in the first 1–2 years and continue to decrease slowly thereafter [15,16]. Medical therapy is often required to bridge the latency period until radiotherapy becomes effective. Multiple studies have reported declines in GH levels for up to 20–25 years, with ultimate GH values below 5 ug/l in 70–90% of cases [16]. Review of published data [17,18] however have shown that radiation therapy is much less effective than previously thought when its efficacy is judged by modern criteria. Radiation therapy was found to normalize IGF-1 levels in only 1/3 of patients after 10 years [18,19]. Understandably the patients with the highest initial GH levels fare the worst. Hypopituitarism develops in 50–70% of patients and in rare cases XRT may cause optic nerve damage and ophthalmoplegia. Radiation vasculopathy increases the risk of cerebrovascular accidents by 2–4 fold [20] and there is a 1–2% risk of developing radiation induced malignant tumors [21] incidence of neurocognitive deficits with significant memory loss and depression had never been quantified but many post radiation patients have these complaints.

Stereotactic radiosurgery (SRS)

Stereotactic radiosurgery modalities include use of a linear accelerator, gamma knife and proton beam [22]. Their advantage over XRT is largely limited to the need for only a single dose procedure. Rigid target fixation and computerized image acquisition optimize targeting and minimize radiation field scatter.

Although only limited data are available and the duration of follow-up was relatively short, summary of available data [19,23] does not demonstrate any superiority of stereotactic radiosurgery over conventional radiotherapy as judged by final IGF-1 values. It is also still uncertain whether SRS has a more rapid effect. Since only small tumor remnants are suitable for SRS, the low initial GH levels in this population of patients introduce a bias in favor of a seemingly more rapid normalization of plasma GH. The rate of side effects is comparable between the two modalities, but the risk of local neurotoxicity (chiasmal or temporal lobe damage) may be higher with SRS if the planning was faulty.

Dopamine Receptor Agonists

Dopamine stimulates GH release in normal individuals but paradoxically inhibits it in subjects with GH secreting adenoma. Review of meta- analysis of published studies [24] showed that daily doses of bromocriptine at 5–80 mg/day in 549 patients normalized IGF-1 in less than 10% of patients. Newer agents like quinagolide and cabergoline

have longer duration of action, higher specificity for the dopamine receptor and greater efficacy and have been shown to be better tolerated [25]. The largest study of patients with Cabergoline showed normalization of IGF-1 levels in 39% of patients [25] but other groups failed to confirm these results. Overall, dopamine agonists are only rarely effective, but their oral route of administration makes them attractive enough to attempt their use on at least a trial basis.

Somatostatin Analogues

Five somatostatin receptor subtypes, SSTR1-5, each encoded on a separate chromosome are responsible for a variety of heterogenous effects of somatostatin (SRIF) in different organs and tissues. SSTR2 and 5 are predominant subtypes expressed in the normal pituitary and inhibit GH and TSH release. *In vitro*, somatostatin retains its inhibitory effect on GH secreting tumors and this has led to the development of somatostatin analogs for clinical use in the treatment of acromegaly [26]. Octreotide is an octapeptide that is almost selectively SSTR2 specific. It has *in vivo* half life of 2 h, and inhibits GH secretion with 45 fold greater potency than native SRIF [27]. A single sc injection suppresses GH secretion for up to 8 h.

Octreotide LAR is a formulation prepared as slowly bio-degrading polymer which allows prolonged release of the drug. Steady state conditions are achieved after 2–3 monthly I.M injections at which time the maximal suppression of GH and IGF-1 can be observed. Although recommended by the manufacturer to be given as monthly doses, the long half life often enables once every 6–8 week dosing.

Lanreotide is available in Europe and is another long acting somatostatin analog administered as intramuscular injections once every 7–14 days. Lanreotide autogel, a new galenic form is a pure aqueous solution of lanreotide and can be administered by deep sc injections every 28 days [28].

All SRIF analogs inhibit GH secretion and IGF-1 levels in patients with acromegaly. Their efficacy is dose dependant and inversely proportional to baseline GH concentrations [28,29] Overall they normalize IGF-1 concentrations in up to 60% of patients. Additionally they are capable of shrinking pituitary somatotropinomas in the majority of cases, although the degree of shrinkage is highly variable, between 20–80% [30]. Most importantly, they effectively prevent future tumor growth. Some patients however are either insensitive to the drug or have unacceptable degree of side effects.

A new analog, SOM 230 binds to all the SSTR's except subtype 4 and has 40 higher fold affinity for SSRT5 than octreotide. SOM 230 is more potent in inhibiting GH secretion compared to octreotide in cultured rat pituitary cells and *in vivo* in animals [31]. This novel peptide is currently in Phase 2 trials.

The main side effects of all somatostatin analogs are diarrhea, nausea, abdominal pain and pain at the injection site. Gallstones which are usually asymptomatic are seen in 3–12% of patients [29]. Their formation is thought to be due to inhibition of gall bladder emptying and CCK secretion. Long acting somatostatin analogs were equally effective as primary or secondary therapy. Symptoms such as soft tissue swelling, increased perspiration, fatigue and arthritis improved in 50–100% of patients when the drug was used as primary therapy in acromegaly [28,29]. Headache appears to improve better with short acting than long acting analogs. Manifestation of cardiovascular disease, primarily LVH and ejection fraction improve with normalization of IGF-1. There is also reduction of joint thickening and sleep apnea.

In summary, surgery and radiation are potentially curative modalities and carry a one time price tag. However they are either very operator dependant (surgery) or slow acting and neurotoxic (radiation). Dopamine agonists are very ineffective and may be used in occasional patients only. SRLs accomplish both biochemical and tumor restraining goals of therapy but are not always effective and quite expensive in the long run.

Importantly, all of the above modalities work at the level of the tumor and their efficacy is determined by the peculiarities of the neoplastic tissue: rate of growth, fibrosis, radioresistance, presence of dopamine or somatostatin receptors.

Alternative approaches to treatment of acromegaly would be aimed at preventing GH action rather than suppressing its secretion. Two experimental models—fasting [32,33] and estrogen therapy [34,35] provided initial clues to that approach.

Early studies have shown that high doses of estrogen seem to offer clinical benefits to patients with acromegaly [34,35]. Subsequently it was shown that estrogen antagonizes GH signal transduction by suppressing JAK-2 phosphorylation [36]. Raloxifene, a SERM, suppressed plasma IGF-1 in acromegalic women [37] and men [38], but IGF-1 normalization was only seldom seen.

Fasting was shown to decrease the abundance of GHR mRNA in the liver and other tissues in rats and Ho et al. have shown that fasting lowers circulating IGF-1 in patients with acromegaly at the same rate as in normal controls [33]. Both after fasting and after estrogen plasma GH increases as a result of disruption of the negative feedback loop.Thus fasting and estrogen can lower plasma IGF-1 in patients with acromegaly by lowering GHR number or by interfering with the GH signal transduction. Unfortunately neither of these modalities can be used practically.

Pegvisomant

The scientific discovery of GH receptor antagonist Pegvisomant began 15 years ago with the elucidation of the structure- function relationship of GH and its receptor. GH is a 22 Kda polypeptide with 191 amino acids, 2 disulphide bonds and four alpha helices. It is synthesized in the somatotrophic cells of the anterior pituitary and is central to the regulation of growth and differentiation primarily modulating gene expression and metabolism in target tissues. It has numerous other biological effects including enhancement of milk production, nitrogen retention, lipolysis and diabetogenic effects. Although GH may have direct metabolic effects on peripheral tissues most of its growth promoting effects are mediated by IGF-1 (insulin like growth factor), a member of the insulin like peptide family. GH binding to the extracellular portion of the receptor is followed by the dimerization of GHR and initiation of the GH signaling [39,40]. The GH molecule has 2 separate receptor binding domains: site 1 and site 2. The secondary structure of GH consists of four α helix core with 2 disulphide bonds, such that noncontiguous regions of the aminoacid chain contribute to the two binding regions. Site 1 is made up of the loop between aminoacid residues 54 and 74 at the C terminal half of helix four and *N* terminal region of helix one. The *N* terminal residues of the first and third helices contribute to binding site 2. Once GH binds to the initial GH receptor via site 1, a second identical receptor is recruited by site 2, leading to receptor dimerization and subsequent cellular activation (Fig. 1). Glycine in the third α helix of GH is particularly important for GH's biological activity. If it is replaced with variety of other amino acids, GH is converted from growth enhancer to a growth suppressor or GH antagonist (Fig. 2). Kopchick et al. [39–41] demonstrated that the GH antagonist could inhibit the cell differentiation promoting activities of GH on mouse pre-adipocytes at equimolar concentrations. The lipolytic and insulin like activities of GH were completely inhibited by 10 fold excess of GH antagonist using rat adipose tissues. Transgenic mice that express a GH mutant with the so called perfect amphiphilic helix 3 have decreased circulating insulin like growth factor (IGF-1) concentrations and exhibit a dwarf phenotype. By combining site specific mutagenesis of the GH gene with an *in vivo* assay of the ability of GH analogs to regulate growth of transgenic mice, a GH antagonist was discovered. Thus, GH antagonists acted to inhibit GH action both *in vivo* and *in vitro*.

Creation of pegvisomant

Pegvisomant is a GH analog that includes single amino acid substitution at position 120 within binding site 2 which prevents its binding to GH receptor [41] (Fig. 2).

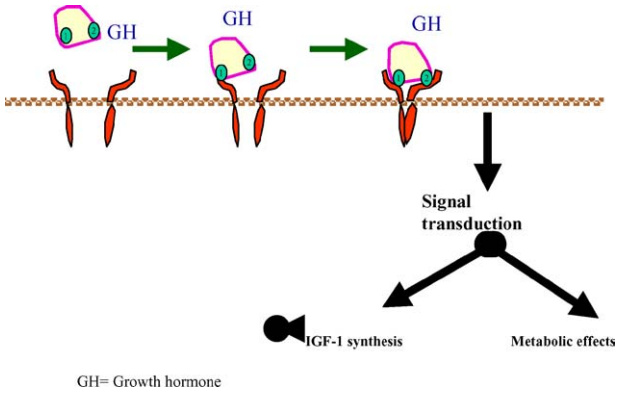

Fig. 1. *Schematic representation of GH-GHR interaction and biological effects.*

The additional changes included 8 amino acid substitutions within binding site 1 that actually increase its binding properties and PEG moieties that increase half life and reduce immunogenecity of the molecule. When the resulting GHR antagonist molecule- the original substitution of Gly 120 at site 2 as well as eight mutations in site 1- was combined with PEG 5000, the final molecule was shown to maintain GHR binding and antagonistic properties with extended half life of 100 hours. The generic name is pegvisomant and trade name is Somavert.

Pegvisomant Efficacy

The relatively long half life of Pegvisomant allows once daily subcutaneous administration. Pegvisomant, if given in sufficient quantities, has been shown to normalize IGF-1 levels in almost all patients with acromegaly in a dose dependant fashion. In a randomized trial [43] of 112 patients for 12 weeks with increasing doses of pegvisomant 10, 15 and 20 mg per day, it was found that serum IGF-1 levels normalized in 90% of patients with acromegaly with significant improvement in signs and symptoms such as soft tissue swelling, excessive perspiration and fatigue [43–45]. In longer term studies, pegvisomant decreased IGF-1 levels in 97% of 90 patients treated for more than 12 months using up to 40 mg/day [47]. Also corrected were the metabolic defects of acromegaly such as insulin resistance and changes in cortisol and lipid metabolism [48,49] GH induces gluconeogenesis and lipolysis, resulting in increased blood glucose and FFA and this is reversible in patients with acromegaly during pegvisomant therapy [43,47]. A single injection of pegvisomant rapidly suppressed IGF-1 levels by 31% and enhanced GH secretion. An increase in plasma GH within days of initiating chronic Pegvisomant therapy was also observed [47]; within 2 weeks, plasma GH concentrations plateaued at 2–3 times basal levels. The decrease in IGF-1 levels correlated with the increase in GH burst amplitude [50].

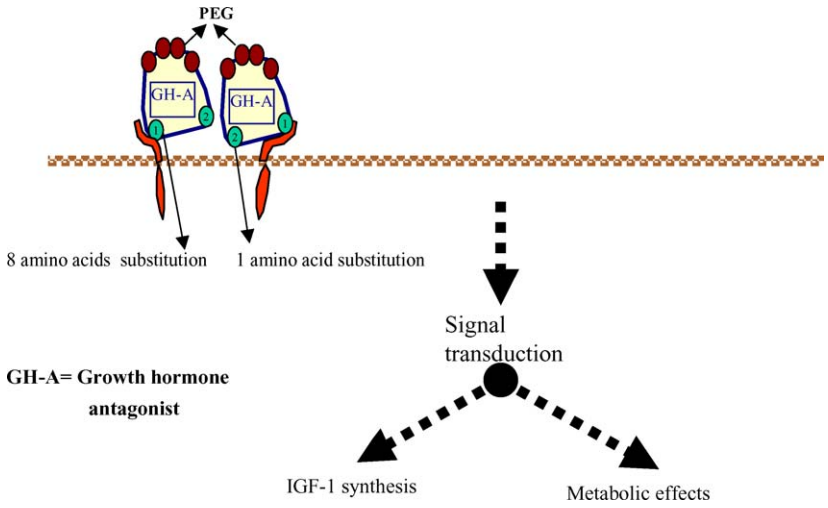

Fig. 2. *Schematic representation of GH- GH-A- GHR interaction and inhibition of biological effects.*

Long term clinical efficacy

A second study [47] was done after the initial 12 week trial and pegvisomant injections were given to 160 patients for 6 months ($n = 131$), 12 months ($n = 90$) and for 18 months ($n = 39$) to evaluate the long term efficacy. Development of GH antibodies was evaluated periodically and MRI of the pituitary was done every 6 months to evaluate potential changes in tumor size. No change in mean tumor size was observed, however GH levels increased in the first 2 weeks of therapy. There was no additional increase in GH levels thereafter and no evidence of tachyphylaxis. Of note, the serum IGF-1 levels normalized in 97% of patients with a dose of up to 80 mg/day for 12 months.

Long term therapy with pegvisomant caused improvement in metabolic parameters of acromegaly such as reduction of fasting insulin levels and corresponding fall in serum glucose concentrations [51,52]. Van der Lely et al. [47] reported a significant decrease in fasting serum insulin and glucose levels in patients treated with pegvisomant for 18 months. Rose and Clemmons [52] observed that in 4 out of five patients normalization of IGF levels was accompanied by improvement in insulin sensitivity. This was associated with a fall in fasting insulin levels enabling one of the patients to discontinue oral hypoglycemic agent, another one to switch from insulin to oral anti- diabetic agent and the third one to decrease insulin dose by 50%. In another study, conversion of patients from LAR to pegvisomant resulted in significant fall in HbA1C and glucose levels [51]. Thus GH antagonist therapy lowered insulin levels and glucose and improved insulin sensitivity.

There was development of anti pegvisomant antibodies in 17% of patients, but titres were low and not accompanied by tachyphylaxis. Elevation of hepatic enzymes had been observed in less than 1% of patients and returned to normal with the cessation of pegvisomant. Also the tumor size increased only in 2 of the patients requiring further therapy with irradiation but these tumors appeared to be invasive at the outset.

Since then additional 8 patients out of a total cohort of about 600 patients were shown to increase the tumor size during pegvisomant therapy. It is still unknown whether the decline in IGF-1 was the causative factor (analogous to the development of Nelson's syndrome) or just a propensity of some tumors to grow irrespective of any external influence.

Thus, overall, pegvisomant is remarkably effective in normalizing plasma IGF-1 and abrogating the metabolic effects of elevated GH. The more widespread use of this drug is limited by its cost, the relative inconvenience of daily injections (as opposed to monthly administration of somatostatin analogues), lack of efficacy against the headache and the uncertainity about its effects on tumor progression.

Safety and Tolerability

In summary, Pegvisomant lowered IGF-1 levels and improved insulin sensitivity in patients with acromegaly. There is no evidence of tachyphylaxis [47] although there is some development of antibodies. The general guidelines for follow-up include monitoring tumor size with MRIs semiannually and then yearly for the first few years unless the tumor is known to be actively growing in which case earlier exams may be required. Also visual perimetry is recommended for patients with visual problems before surgery and in patients with macroadenomas and residual extrasellar tumors after surgery.

The main side effects of Pegvisomant therapy are injection site reactions (10%), deranged liver function tests (elevated AST and ALT) and increase in pituitary tumor size [46,47]. The latter two side effects occur in less than 1% of patients.

Future Directions

Indirect and early experimental data suggest that GH receptor antagonists can be potentially used not only in the treatment of acromegaly but also in cancer and diabetes.

Diabetic retinopathy

Modulation of IGF-1/GH axis in diabetic patients have implications in microvascular complications of diabetes as was first noted in patients with pituitary ablation that arrested the progression of diabetic retinopathy. GH has been shown to stimulate proliferation of human retinal microvascular endothelial cells *in vitro*. There has been a positive correlation between GH concentration and progression of diabetic retinopathy [53]. Over expression of IGF-1 in retinal tissue promotes retinopathy and GH receptor antagonists protect from ischemia induced retinal neovascularization. The role of GH in diabetic retinopathy was studied by Smith et al. using dwarf transgenic mice expressing GH receptor antagonist gene and normal mice given inhibitor of GH secretion, MK 678 [53]. In both groups retinal neovascularization was inhibited. This was inversely proportional to the decline in serum IGF-1 levels and was reversed by addition of exogenous IGF-1. This suggests that systemic inhibition of GH or IGF-1 or both may have a therapeutic role in preventing retinopathy.

However direct human study in patients with established diabetic retinopathy failed to substantiate the beneficial effects of pegvisomant on disease progression. Beck et al. [54] studied effects of GH receptor antagonist in 25 patients with diabetes mellitus and proliferative retinopathy and found no evidence of regression of diabetic retinopathy. The extent of neovascularization was unchanged in 16 patients and there was some progression in 9 patients treated with daily injections of 20 mg of Pegvisomant. The authors concluded that the lack of effect could be due to the improvement in overall diabetes control seen in their patients as part of pegvisomant induced improvement of insulin sensitivity and the known association of worsening of retinopathy initially with better glycemic control.

Diabetic nephropathy

In both humans and animals, GH and insulin like growth factors (IGF-I & II) have been implicated in the development of diabetic microangiopathy which includes nephropathy and glomerulosclerosis [55]. The role of IGF system in the development of kidney disease was shown in insulinopenic diabetes model produced by Streptozotocin in rats [56]. In early experimental diabetes a transient increase in kidney IGF-1 mRNA is a consistent finding followed by renal and glomerular growth. Chen et al. [56] showed that transgenic mice expressing GH antagonist were protected from diabetes induced glomerulosclerosis and GH induced nephropathy. This suggested a causative relationship between elevated IGF-1 and morphological and hemodynamic changes seen with nephropathy. Studies by Landau et al. confirm that GH/IGF-1 axis plays an important role in early diabetic renal changes and specific GH antagonists could be a novel therapy to prevent diabetic nephropathy. They [55,56] showed that STZ induced diabetic rats had prominent changes in IGF-1 and IGFBP gene expression with pronounced increase in IGFBP-1 mRNA in renal cortex. This increased IGFBP-1 mRNA expression causes IGFBP's to act as carriers of IGF-1 which may operate as local modulators of IGF action in various physiological and pathological conditions. The authors demonstrated an early accumulation of IGF-1 in kidneys before the onset of renal enlargement and elevated GFR and renal plasma flow and suggested that there was a causal relationship between elevated IGF-1 and the morphological and hemodynamic changes. The rats then had sustained elevated levels of IGF-1 for 6 months after induction of diabetes during the development of thickening of basal membrane and elevation of urinary albumin excretion. This suggested that IGF-1 played a strong role in the patho-physiological process associated with long term diabetic renal disease It is not yet known whether Pegvisomant may have a preventative effect in development of renal lesions and end organ damage in diabetic patients or may even reverse the already existing damage.

Interestingly, Pegvisomant had no effect on renal expression of GH/IGF-1 axis proteins like IGFBP-3 and GHR in STZ induced diabetic rats. These rats when injected with daily G-120 PEG every day for 3 weeks compared to their age matched hyperglycemic counterparts, were found to have reduction in glomerular hypertrophy, GHR mRNA levels in kidney and normalization of urinary albumin excretion. Thus the GH receptor antagonist appears to have protective effects over the kidney in diabetes, preventing the development of nephropathy [56,57]. Human studies will be needed to test this hypothesis clinically.

Cancer

Two potential targets for pegvisomant therapy can be contemplated: prevention of cancer development and modification of growth of the already existing tumors. The role of IGF-1 in inducing prostate, breast and colon cancers

has been suggested from some epidemiological studies [58,59]. IGF-1 is shown in experimental studies to induce the proliferation and anti-apoptotic effects of colon cancer cell lines [59]. Colon cancers constitute 18% of all cancers in acromegaly and the mechanism is thought to be the increased epithelial cell proliferation rate induced by IGF-1/ GH excess [60]. This then reduces apoptotic rate and may induce the accumulation of genetic defects leading to cancer of the colon [61,62]. *In vivo* progression and metastatic potential of human colon cancer explants were significantly inhibited in LID mice (liver specific IGF-1deficient) and both markedly increased by administration of recombinant IGF-1 [64].

IGF-1 is found to have a mitogenic and anti-apoptotic effect and is thought to have a role in inducing breast cancer particularly in premenopausal women [64]. GH receptor antagonists may be useful in this case as they can significantly reduce IGF-1 levels. Raloxifene has been shown to reduce IGF-1 levels and attenuate the development of breast cancer in women [65]. Pollack et al. [66] have also shown that GH antagonist transgenic mice have resistance to progression of breast tumors induced by 9, 10 Dimethyl-1,2-benzanthracene (DMBA). After a 39 week treatment with DMBA, 68% of GH antagonist treated mice were without tumors as opposed to 31% of control mice. The protective effect of GH receptor antagonist was reversed with the administration of recombinant IGF-1.

IGF-1 is a mitogen which can increase the H3 thymidine incorporation in primary cultures of human meningioma cells and Pegvisomant not only inhibited the incorporation but also the growth of the human meningioma cells [67].

This clearly suggests that GH receptor antagonists may have a beneficial role in GH/IGF-1 dependant cancers and may reduce risk of developing these cancers.

Summary

Pegvisomant, a GHR antagonist that was introduced into the armamentarium of therapy for acromegaly is a significant therapeutic advance based on its unique mechanism of action as a peripheral GH antagonist. Unlike somatostatin analogs and dopamine agonists which bind to specific pituitary tumor receptors and act by inhibiting GH secretion, Pegvisomant acts by blocking GH action at the site of GH receptor peripherally. As a consequence, GH levels may rise and cannot be used as a marker of disease activity but IGF-1 levels are the primary measure of efficacy of therapy. The long term studies with doses up to 40 mg/day for up to 18 months have shown normalization of IGF-1 in 97% of patients with acromegaly without development of tachyphylaxis. However the still lingering uncertainty about the potential increase in pituitary tumor size clearly requires some resolution in subsequent studies.

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