Experience from the German Pegvisomant Observational Study

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Key Words

Acromegaly • Pegvisomant • Surveillance database •
Insulin-like growth factor-I • IGF-I • Normalization rate

Abstract

Background: The German Pegvisomant Observational Study (GPOS) was created immediately after marketing authorisation was received in Germany for Somavert® (pegvisomant) for the treatment of patients with acromegaly. In August 2006, the database underwent its fifth interim analysis of 263 patients, the vast majority of whom previously had insufficient disease control with other treatment modalities. The GPOS documents both safety and efficacy aspects of the treatment of patients with acromegaly by the first growth hormone-receptor antagonist, pegvisomant. This treatment led to normalization of disease activity in most patients, had favourable effects on glucose metabolism and improved signs and symptoms of the disorder. The safety profile indicates that pegvisomant treatment is well tolerated, and tumour growth is noted to occur at the same rate as for somatostatin analogue treatment. Transaminase elevations occurred in 16 of the 263 patients but spontaneously resolved in eight of them and promptly normalised in five patients who discontinued treatment. GPOS is presently the

largest database of pegvisomant-treated patients, and it comprises more than 87% of all patients treated with pegvisomant in Germany. **Conclusions:** The GPOS database provides important information about treatment modalities, safety and efficacy of pegvisomant in patients with acromegaly.

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Introduction

At the end of 2003, the first growth hormone (GH) receptor antagonist pegvisomant was approved in Europe for patients with acromegaly who are not adequately controlled by other treatment modalities or who do not tolerate other such treatments. Immediately after pegvisomant became available in Germany, the German Pegvisomant Observational Study (GPOS) was launched to monitor the safety and efficacy of the new drug in clinical practice. Initially, database analysis was performed every 6 months and the results were reported to the participating investigators. The results of the fourth interim analysis (data close was on 20 Dec. 2005) have recently been published [1]. The feedback on the safety and efficacy of pegvisomant in the treatment of acromegaly was

Fig. 1. Distribution of pegvisomant doses in patients with acromegaly treated for at least 1 year in whom IGF levels were available, stratified for normalisation or persistently elevated IGF levels related to age-related reference ranges.

considered important by the investigators and has led to an extraordinarily high enrollment rate: currently more than 87% of patients receiving this drug in Germany are in the database. The fifth interim analysis was performed by freezing the database at the beginning of August 2006. At that time, there were 263 patients at 83 different clinical sites throughout Germany.

Methods

This observational study was approved by the ethics committee at Charité Universitätsmedizin and the patients gave informed written consent. Patient history was collected and included date of diagnosis, previous therapies, concomitant diseases at baseline, concomitant medications, pegvisomant dose and biochemical analyses as well as any adverse events. All information was documented on paper-based case report forms, which were collected from the investigator sites, entered into a central database and analysed at an independent clinical research organization (Advanced Medical Services, Mannheim, Germany).

For those patients whose insulin-like growth factor (IGF)-I assays were available from the central laboratory, analyses were conducted by the Nichols Advantage® Specialty System technology as long as this method was available. Results were expressed in ng/ml and converted into age-related standard deviation scores (SDSs) according to the normative data of Brabant et al. [2]. Subsequently, the central laboratory assay was replaced by the DPC Immulite® method and results were converted into SDS for age by use of the normative data by Elmlinger et al. [3]. In those cases where IGF-I levels were not analysed in the central laboratory, the local IGF-I levels were recorded both in ng/ml and SDS for age or in relation to the upper limit of normal for age.

Results

The 263 patients in the database at data close in August 2006 showed an even gender distribution (136 males, 127 females); mean age ($\pm$ SD) was 49.7 ± 13.9 years and mean age at diagnosis was 40.7 ± 12.8 years. Therefore, the patients had a mean duration of disease activity of 9 years. Of the patients in the database, 89% had surgical removal of a somatotrope pituitary adenoma and 42% received radiation therapy. Previous medical treatment consisted of bromocriptine administration in 53 patients (20.2%) and cabergoline in 59 (22.4%), while 218 patients (82.9%) received octreotide and 24 patients (9%) were treated with lanreotide. Reasons for discontinuation of previous octreotide therapy were persistently elevated IGF-I levels in 71.3% of patients, side effects in 13.2% and both side effects and uncontrolled disease activity in 6.4%. At baseline, diabetes mellitus was reported as a concomitant condition in 29% of patients, gallstone disease in 24%, sleep apnoea syndrome in 21% and hypertension in 51%.

As of August 2006, follow-up data for treatment with pegvisomant were available for 6 months after the baseline visit in 218 patients, for at least 1 year in 160 patients, for 2 years in 99 patients and in 25 patients, this interim analysis comprises 3 years of treatment. Mean duration of treatment was 62.4 weeks.

In this cohort of patients with previously insufficiently controlled disease, a 6-month course of pegvisomant led to normalisation of IGF-I in 65.1%; after a year, the nor-

malisation rate reached 70.6%, after 24 months, 74.7% and after 3 years of treatment, 79.2% were normalised with respect to IGF-I levels. The dose range at data close for this interim analysis was between 10 mg given every other day in six patients and 50 mg/day in one patient. The median dose was 15 mg and the mean dose was 16.4 mg. Mean and median doses did not differ from previous interim analyses. Since the normalisation rate in clinical practice fell short of the normalisation rate previously reported in clinical studies [4, 5], dose distribution after at least 1 year of treatment was separately analysed for those patients with normalised IGF-I levels and those with still uncontrolled disease activity. The dose distribution for both subgroups is shown in figure 1. While the mean dose in the normalised patients was 17.3 mg/day, the patients who still had uncontrolled disease received 19.5 mg/day. Surprisingly, after 1 year of treatment, 40% of the uncontrolled patients were still receiving 10 or 15 mg of pegvisomant daily.

In the patients' self-assessed acromegaly symptom questionnaire, completed after 12 months of treatment, significant improvements were noted in total score and general physical condition as well as in the subscales of headache, fatigue, soft tissue swelling and numbness of limbs. In those 66 patients with diabetes, glycated haemoglobin (HbA_{1c}) fell significantly, from $7.0 \pm 1.4\%$ at baseline to $6.5 \pm 1.3\%$ after 6 months of treatment. This improvement persisted after 12 months of treatment. Fasting blood glucose levels declined from 137.7 ± 58.9 mg/dl to 117.4 ± 53.8 mg/dl after 12 months, but failed to reach statistical significance due to large variations.

Safety Analysis

Treatment with pegvisomant was discontinued in 29 patients due to adverse events (AEs) or serious adverse events (SAEs). In 19 cases the investigators considered these AEs or SAEs potentially related to pegvisomant treatment. A total of 32 patients experienced SAEs, 16 of which were elevated transaminases and hepatobiliary disorders. In seven of these patients gallstones were present; five patients discontinued pegvisomant treatment permanently and, in all cases, transaminases normalised. Surprisingly, in eight patients, normalisation of liver function tests (LFTs) spontaneously occurred without alterations in pegvisomant dosage, despite elevations of alanine amino transaminase as high as 10 times the upper limit of normal. Details of LFT abnormalities during pegvisomant treatment in this cohort have previously been published [6].

Pituitary tumour enlargement was suspected in 12 patients. In these cases, central reevaluation of serial magnetic resonance imaging (MRI) scans could not confirm any enlargement in five cases. Two patients did show a slight increase in tumour volume during pegvisomant treatment. However, since this was considered clinically irrelevant, treatment was continued in both patients. In three patients, tumour growth was documented at a constant rate, which did not change when the patients were switched from somatostatin analogue treatment to pegvisomant treatment. In two patients, a reexpansion of the somatotrope pituitary adenoma to its preexisting size was observed after the tumour volume had temporarily shrunk during somatostatin analogue treatment.

Discussion

The GPOS is currently the largest database of patients with acromegaly treated with pegvisomant worldwide. More than 87% of all patients receiving pegvisomant in Germany are documented in this database, thus reflecting clinical practice in a reliable manner. Initially, investigators were informed about the results of database analysis every 6 months, then on an annual basis. The present interim analysis shows a lower normalisation rate under the conditions of clinical practice than in previous controlled studies [5]. The normalisation rate rises from 65% after 6 months of pegvisomant treatment to almost 80% after 3 years of treatment. We observed a reluctance to titrate to adequate doses in a timely manner. This may be caused by previous experience with the use of somatostatin analogues. With the somatostatin analogues, patients were maintained on a fixed dose for prolonged periods of time to monitor eventual declines in IGF-I levels after periods of a year or more. The pharmacodynamics of the GH receptor antagonist, however, differ substantially from those of the somatostatin analogues. For a given fixed dose of pegvisomant, no further decline of IGF-I can be expected beyond 4 to 6 weeks of treatment [4].

In those patients with diabetes mellitus as a concomitant disease, the introduction of pegvisomant treatment led to a significant improvement of HbA_{1c}. In contrast to somatostatin analogues, the GH receptor antagonist does not inhibit pancreatic insulin secretion; it reduces insulin resistance by inhibiting the effects of excess GH.

Transaminase elevations and hepatobiliary disorders considered potentially related to pegvisomant treatment by the investigators were observed in 16 of the 263 patients (6.1%). In half of these patients, LFT elevations dis-

appeared spontaneously without pegvisomant dose modification. LFT elevations normalised after discontinuation of the drug in all five patients in whom pegvisomant treatment was discontinued because of this AE.

Suspected pituitary tumour enlargement could not be confirmed objectively in five patients. Pituitary tumours previously stable in size showed enlargement in two of 263 patients after initiation of pegvisomant therapy. Two other patients showed reexpansion of pituitary tumours previously reduced in size by somatostatin analogue treatment. This rate of confirmed tumour enlargement is in keeping with and comparable to that observed during somatostatin analogue treatment [7].

Conclusions

In Germany, data from the GPOS database demonstrated that pegvisomant leads to normalisation of IGF-I levels in 80% of those patients previously not sufficiently treated in clinical practice. The database provides important information about treatment modalities, safety and efficacy of pegvisomant in patients with acromegaly. A future merging of this GPOS with the global ACROSTUDY surveillance project is highly desirable. Ultimately, all investigators and their patients will benefit from a broader database and, once established on a global scale, this will also facilitate interesting comparisons between countries.

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Acknowledgments

The authors wish to express their gratitude to all colleagues who contributed patient data to the German Pegvisomant Study for making this study so successful for the benefit of our patients. Furthermore, we thank Dr. Isabell Schreiber and Dr. Katja Brübach, Pfizer Germany, for the dedicated maintenance of the database and Ms Gabriele Schillinger for expert secretarial assistance in preparation of the manuscript.

Disclosure Statement

C.J.S. is a consultant for Serono and Novo Nordisk, and has been a teacher and speaker at Pfizer, Lilly, Novartis and Novo Nordisk. He is a member of the Advisory Committees/Review Panels of Pfizer, Lilly and Biopartners, and an Advisory Board member of Pfizer and Lilly. Consulting fees have been received from Biopartners and Novo Nordisk, and honoraria from Novartis, Novo Nordisk, Lilly and Pfizer. M.B. declares a relevant financial relationship with a commercial interest. The author is a speaker/teacher at Pfizer KIMS and Acro Study, Novartis, and Novo Nordisk and an advisory committee and board member of Pfizer KIMS and Acro Study. Honoraria from Pfizer have been received. M.D. has a relevant financial relationship with a commercial interest. He is a teacher/speaker at Pfizer, Inc. and a Board member of Pfizer Inc. He has received honoraria from Pfizer, Novo Nordisk, Ipsen, Jenapharm and Bayer Health. K.M. declares no conflict of interest. G.K.S. has a relevant financial relationship with a commercial interest. He is a consultant for Novo Nordisk and Pfizer, has been teaching/speaking at Pfizer and Novartis, and is an Advisory Board member of Pfizer. He has received consulting fees from Novo Nordisk and honoraria from Pfizer and Novartis. B.S. has a relevant financial relationship with a commercial interest. He is employed at Pfizer and has received salaries from Pfizer Ltd.