

CLINICAL STUDY

Combined treatment for acromegaly with long-acting somatostatin analogs and pegvisomant: long-term safety for up to 4.5 years (median 2.2 years) of follow-up in 86 patients

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Abstract

Background: We previously reported on the efficacy, safety, and quality of life (QoL) of long-acting somatostatin analogs (SSA) and (twice) weekly pegvisomant (PEG-V) in acromegaly and improvement after the addition of PEG-V to long-acting SSA.

Objective: To assess the long-term safety in a larger group of acromegalic patients over a larger period of time: 29.2 (1.2–57.4) months (mean (range)).

Design: Pegvisomant was added to SSA monotherapy in 86 subjects (37 females), to normalize serum IGF1 concentrations ($n=63$) or to increase the QoL. The median dosage was 60.0 (20–200) mg weekly.

Results: After a mean treatment period of 29.2 months, 23 patients showed dose-independent PEG-V related transient liver enzyme elevations (TLEE). TLEE occurred only once during the continuation of combination therapy, but discontinuation and re-challenge induced a second episode of TLEE. Ten of these patients with TLEE also suffered from diabetes mellitus (DM). In our present series, DM had a 2.28 odds ratio (CI 1.16–9.22; $p=0.03$) higher risk for developing TLEE. During the combined therapy, a clinical significant decrease in tumor size by more than 20% was observed in 14 patients. Two of these patients were previously treated by pituitary surgery, 1 with additional radiotherapy and all other patients received primary medical treatment.

Conclusion: Long-term combined treatment with SSA and twice weekly PEG-V up to more than 4 years seems to be safe. Patients with both acromegaly and DM have a 2.28 higher risk of developing TLEE. Clinical significant tumor shrinkage was observed in 14 patients during combined treatment.

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Introduction

Recent studies of new medical treatment strategies with pegvisomant (PEG-V) for acromegaly have reported on high efficacy. PEG-V, alone or in combination with somatostatin analog (SSA), has an efficacy of >90% to control insulin-like growth factor (IGF1) (1–4). This is much higher than SSAs, with an efficacy of $\pm 66\%$ (5). However, PEG-V is at least unable to prevent tumor growth (4, 6) in contrast to SSAs. During SSA treatment as primary medical therapy, pituitary tumor shrinkage was observed in 52% of the patients versus 21% for adjuvant therapy (7). With combination therapy of SSA and PEG-V twice weekly, tumor shrinkage was observed in 14% of the patients (2).

Side effects of SSA therapy and PEG-V are elevated liver enzymes, but they have a different etiology. SSAs increase the risk for cholelithiasis, which can cause cholestatic liver enzyme disturbances. PEG-V induces mainly elevated transaminases. The mechanism

behind these PEG-V-induced elevated transaminases is unknown. A long-term report on daily PEG-V treatment reported elevated liver enzymes in 21 out of the 229 patients (6). When PEG-V is combined with SSA, there seems to be a better control of tumor size, but transient liver enzyme elevations (TLEE) seem to occur in about 34% of the patients and diabetic patients seem to be more prone (2). SSAs alone have the highest efficacy for tumor shrinkage but for the control of IGF1 they are less effective.

Recently, we have reported on the improved quality of life (QoL) after the addition of PEG-V to acromegaly patients with an IGF1 within the age-adjusted normal range during the long-acting SSA therapy (8). Therefore, combined therapy might be an attractive option for the treatment of acromegaly.

Despite these observations, the Canadian Health Authorities sent out a safety warning about the combination therapy on June 11, 2008, because of the development of TLEE. This warning was based on a

post-marketing study in 26 patients, conducted by Pfizer. We now report the safety of combined therapy assessed in 86 acromegalic patients over 29.2 (1.2–57.4) (mean (range)) months.

Patients and methods

Patients

Eighty-six acromegalic patients, 37 female, with a mean age of 54 (range 19–83) years were enrolled in our center, after their informed consent and approval by the local ethics committee. Their medical history revealed transsphenoidal surgery (TSS) in 44 subjects, TSS and radiotherapy in 20, while 42 subjects received primary medical treatment. Twenty-one subjects also suffered from diabetes mellitus (DM). All patients were on SSA treatment (octreotide LAR $n=31$, lanreotide Autogel $n=55$) for at least 6 months before PEG-V was added.

Methods

All patients continued long-acting SSA therapy and on top of that, PEG-V was added twice weekly. Results were derived from two data sets. The first data set contains data from acromegalic patients ($n=63$) with elevated IGF1 levels at baseline. This group is described in this article as the ‘uncontrolled group’. The second data set of patients ($n=23$), who were titrated up with PEG-V to improve the QoL, are described as ‘QoL group’.

Of the uncontrolled group, 19 acromegalics started with a 25 mg, another 13 with 40 mg, and the last 26 patients started with a variable dose of PEG-V weekly guided by their baseline IGF1. This variable start dose was based on our previous observation that baseline IGF1 predicted the PEG-V dose that is necessary to control IGF1 (2). Intervals of dose adjustments were 6 weeks until a controlled IGF1 was achieved twice. The subjects then visited our outpatient clinic every 16 weeks. The QoL group started with 20 mg PEG-V weekly and the dosage was adjusted on the basis of their QoL. The intervals of dose increments were 8 weeks until either serum IGF1 decreased below 2 s.d. or a worsening in QoL was observed after the initial improvement. Subjects visited our outpatient clinic at least every 16 weeks. The QoL was assessed by the acromegaly QoL questionnaire (9) and the patient-assessed acromegaly symptom questionnaire (3, 4). The dose of PEG-V was administered by the patients themselves. If the once weekly dose exceeded 80 mg, patients divided the dosage into two equal parts and injected twice weekly. At every visit to our outpatient clinic, safety parameters were assessed.

Safety assessment included: EKG, serum concentrations of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ -glutamyl-transpeptidase, total bilirubin, and lactate dehydrogenase. Yearly, change in pituitary tumor volume was assessed by MRI and by the same neuroradiologist.

Statistical analysis

The non-paired data were assessed with the Mann–Whitney test, and cross-tables and odds ratio with the Fischer’s exact test. Statistical analysis of the data was performed by GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego, CA, USA. Statistical significance was accepted at $P<0.05$. Data are expressed as mean \pm s.d. unless otherwise specified.

Results

Safety analyses were performed in all 86 patients with a follow-up of 29.2 ± 20.2 months (Fig. 1) and a median dose of 60 mg (range; 20–200) mg weekly. The dose of PEG-V in the uncontrolled group was median 60 mg (mean, 77; range, 20–200) weekly. The dose in the QoL group was also 60 mg (53; 20–80) (median (mean; range) weekly.

TLEE were observed in 23 patients (23/86, 27%; Table 1). Relevant TLEE of more than three times the upper limit of normal (ULN) were observed in 13 patients (13/86, 15%). In 2 out of these 13 patients, the TLEE could be explained by gallstones and 1 patient developed a transient drug-induced hepatitis, which have been reported elsewhere (2, 10). Ten out of 23 subjects with TLEE also suffered from DM. The odds ratio for developing TLEE was 2.28 (CI 1.16–9.22; $p=0.03$) for diabetic subjects. Six patients with TLEE $\geq 3 \times$ ULN were also diabetic. The risk for developing relevant TLEE for diabetics subjects was 3.31 (odds ratio, CI 1.00–11.37; $p=0.07$). TLEE occurred after 33 ± 25 (range 8.0–92.0) weeks after the start of PEG-V. In diabetic acromegalic patients, TLEE were observed after 29.6 ± 7.4 weeks versus 34.6 ± 30.2 weeks in non-diabetic subjects, which was not significantly different. The TLEE of $\geq 3 \times$ ULN in diabetics were observed after 25.3 ± 18.0 weeks versus 29.4 ± 25.8 weeks in non-diabetic subjects, neither significantly different. The duration of the TLEE was 12.1 ± 6.1 weeks, without a significant difference

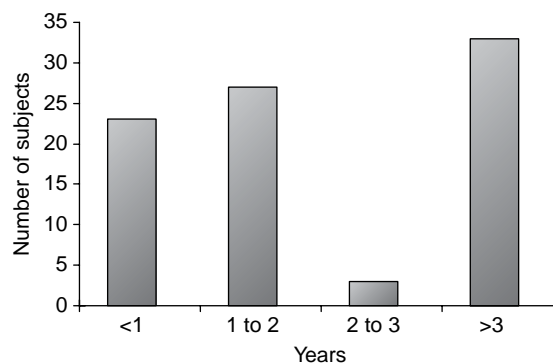


Figure 1 Number of subjects treated with twice weekly PEG-V and SSA, divided over treatment periods of one, two, three, or more than 3 years.

Table 1 Clinical and biochemical parameters of 23 patients with elevated liver enzymes during combination therapy.

| Sex | Age (years) | Time between start of PEG-V and LFT (weeks) | PEG-V dose at onset of LFT elevations | Peak LFT (\times ULN) | | | DM | Follow-up In all patients PEG-V was continued |
|-----|-------------|---|---------------------------------------|--------------------------|------|-------------|----|--|
| | | | | ALT | AST | γ GT | | |
| M | 53 | 17 | 60 | 31.6 | 14.2 | 18.4 | + | MRCP showed gallstones, LFT declined rapidly and normalized <8 weeks |
| M | 30 | 86 | 60 | 8.8 | 4.7 | 5.7 | - | Galway obstruction. LFT normalized after cholecystectomy <1 week |
| M | 62 | 18 | 40 | 2.8 | 2.0 | 10.4 | + | LFT normalized <12 weeks |
| M | 38 | 20 | 60 | 1.8 | 1.3 | 1.1 | - | LFT normalized <18 weeks |
| M | 48 | 46 | 160 | 2.4 | 1.1 | 1.2 | + | LFT normalized <18 weeks |
| M | 61 | 24 | 60 | 3.0 | 1.8 | 1.5 | + | LFT normalized <12 weeks |
| M | 44 | 48 | 60 | 4.8 | 2.9 | 5.1 | - | LFT normalized <18 weeks |
| M | 30 | 50 | 200 | 1.5 | 0.4 | 0.8 | + | LFT normalized <6 weeks |
| M | 46 | 8 | 80 | 4.3 | 3.3 | 2.2 | - | LFT normalized <12 weeks |
| M | 47 | 25 | 60 | 31.9 | 7.1 | 7.6 | + | LFT normalized after PEG-V was withdrawn |
| M | 47 | 16 | 80 | 14.5 | 5.9 | 5.4 | - | LFT normalized <12 weeks |
| M | 61 | 21 | 60 | 4.0 | 2.2 | 2.0 | - | LFT normalized <6 weeks |
| M | 44 | 60 | 60 | 2.9 | 1.3 | 2.9 | + | LFT normalized <10 weeks |
| M | 54 | 16 | 40 | 4.3 | 2.4 | 1.8 | - | LFT normalized <8 weeks |
| F | 27 | 14 | 60 | 5.3 | 3.8 | 1.7 | - | LFT normalized <12 weeks |
| F | 68 | 8 | 40 | 5.5 | 3.6 | 2.2 | + | LFT normalized <18 weeks |
| F | 66 | 12 | 40 | 2.0 | 1.2 | 2.0 | + | LFT normalized <18 weeks |
| F | 57 | 24 | 60 | 5.1 | 2.6 | 3.0 | - | LFT normalized <12 weeks |
| F | 72 | 40 | 40 | 2.1 | 1.6 | 0.4 | - | LFT normalized <12 weeks |
| F | 45 | 92 | 40 | 2.3 | 1.2 | 1.0 | - | LFT normalized <3 weeks |
| F | 45 | 16 | 40 | 14.6 | 8.5 | 1.4 | - | LFT normalized <26 weeks |
| F | 74 | 68 | 40 | 1.8 | 1.4 | 2.5 | - | LFT normalized <8 weeks |
| F | 47 | 33 | 80 | 1.7 | 1.3 | 0.7 | + | LFT normalized <8 weeks |

Yrs, years; \times ULN, times upper limit of normal; LFT, liver function tests; DM, diabetes mellitus.

between diabetic 13.0 ± 5.1 weeks versus non-diabetic acromegalics 11.3 ± 7.0 weeks. No correlation was observed between TLEE and PEG-V dose. In the QoL group, we observed TLEE in five subjects. Four of these patients were also reported to have TLEE in our prior study (8). After re-exposure with PEG-V during dose finding for an optimal QoL, TLEE reoccurred in all subjects. In Fig. 2, TLEE of two of these patients are presented, while the two other subjects had similar results.

Another known side effect of PEG-V treatment, at the injection site, which did not occur during our previous follow-up is lipohypertrophy (11). Reversible lipohypertrophy was observed in three patients at the abdominal injection sites, after at least 3 months of treatment. By changing the site of injection more frequently, the lipohypertrophy disappeared after 8 months. The PEG-V dose injected by these patients ranged from 60 mg once weekly to 60 mg twice weekly. None of these patients injected insulin or discontinued treatment.

In 12 out of the 86 patients, no tumor size decrease could be assessed due to empty sella prior to the start of combined treatment. In 14 (19%) patients out of the remaining 74 (86-12) patients with an assessable tumor size, the size of the tumor decrease by more than 20%, which is considered to be clinically significant. Two patients with tumor shrinkage underwent TSS in the

past and one also received radiotherapy. The other 12 patients were on primary medical therapy. In none of the 86 patients was a tumor size increase observed.

Discussion

We report that long-term combined treatment of long-acting SSA and (twice) weekly PEG-V appears to be safe up to more than 57 months. TLEE do occur during combined therapy, but they appear to be completely reversible without decreasing the dose of PEG-V. When PEG-V is withdrawn and reintroduced after a complete wash-out of more than 2 months, TLEE reoccur in all our patients. The frequency of TLEE in our series, with twice weekly PEG-V, is 27% (23/86) versus a report on daily PEG-V 9% (21/229) (6). The frequency is lower when only TLEE of $\geq 3 \times$ ULN are taken into account (in our series in 15.0% (13/86) of the subjects versus 5.2% (12/229) in daily PEG-V (6)). The elevated transaminases of $\geq 3 \times$ ULN all occur within the first year of combined treatment. Therefore, assessment of the liver enzymes, as indicated by the package insert of PEG-V, is mandatory. Our advice is, close monitoring of the liver enzymes especially in the first year, because within this time period the TLEE seem to occur.

Previously, we reported that diabetic acromegalics have a 5.1 (odds ratio) higher risk to developing TLEE

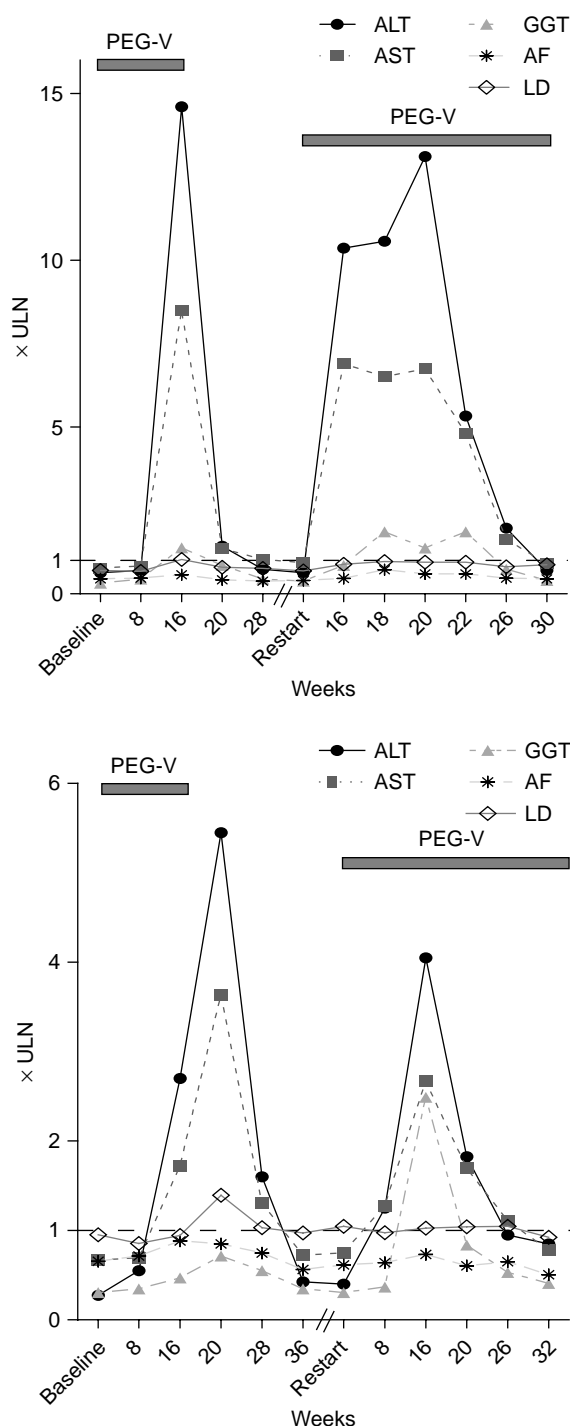


Figure 2 Elevated liver enzymes during combination therapy in two patients. Both patients were treated with combination treatment for two consecutive periods divided by a wash-out period of more than 4 months.

(2). In the present study, we observed that diabetic acromegalics have a 2.3 times higher risk for developing TLEE. Significance was just lost when TLEE of $\geq 3 \times$ ULN were used for the analysis, probably due to the

small number of subjects. Apparently, diabetic acromegalic patients should be monitored even more closely, but in our series TLEE in diabetic acromegalic subjects appear to be also transient and completely reversible without discontinuation or dose adjustment of PEG-V. The moment of occurrence in diabetic subjects tends to be earlier; however, this was not significant. The mechanism behind these PEG-V-induced elevated transaminases is still unknown; however, since diabetic acromegalics are more prone to develop the TLEE, it might be hypothesized that insulin resistance and lipid accumulation in the liver may predispose for these transient elevated transaminases. During the TLEE, no deterioration of the glycemic control occurred. It seems to be the other way around. The glycemic control is improving, and when there is no further improvement of the glycemic control the TLEE rarely occur. Most of these diabetics were on oral drug therapy and no correlation between any medication and the occurrence of TLEE could be found.

In this present series, there is no relationship between cumulative dose of PEG-V and the TLEE. Patients treated longer than 2 years had no TLEE even though many of them have had much higher cumulative dose than patients with TLEE. Patients with higher weekly dose of PEG-V did not have higher change for developing TLEE than patients with a lower dose.

In our previous QoL study, five subjects developed TLEE (8). Four of these patients participated in our present dose-finding series. All developed TLEE again after the re-exposure to PEG-V and TLEE disappeared during continuation. In our hands, the combined therapy appears to be safe with regard to TLEE. TLEE are reversible in all our patients and seem not to re-occur during continuous PEG-V treatment. Therefore, we do not support the drug-warning by the Canadian health authorities that states that combination therapy might not be safe due to elevated transaminases.

Our recommendation for the work-up of a patient with TLEE is to closely monitor patients in which TLEE of more than 3 times ULN is observed. We advise to exclude cholelithiasis in all of these patients. However, in patients with more than 10 times ULN, we advise to perform not only an ultrasound of the liver and bile ducts but also a liver biopsy and discontinue PEG-V treatment in the case of drug-induced hepatitis.

Another side effect that was observed was a painless lipohypertrophy in three patients. In all patients, it resolved within 8 months after changing the injection sites more frequently. None of these patients were dissatisfied with their treatment and insisted continuation with PEG-V. This is in contrast with another report, in which PEG-V was discontinued (11).

An important observation is that in 19% of our patients, we observed a clinically significant tumor shrinkage of $>20\%$. The patients with the highest percentage of tumor shrinkage are the ones that receive

primary medical treatment. This is most likely the effect of the continuous treatment with long-acting SSA. Primary medical-treated acromegaly patients might show more tumor shrinkage than patients treated with adjuvant SSA (7). Therefore, we can conclude that long-acting SSA are still able to induce tumor shrinkage, even in the presence of PEG-V. The most important aspect of our present analyses was safety; however, efficacy is also available. In the uncontrolled group of 63 acromegaly patients, 60 (95%) had an IGF1 within the age-adjusted normal limits. All three patients with elevated IGF1 started recently with combination therapy (range 1.2–4.0) months.

An argument for combined therapy might be the improved QoL that we observed when PEG-V was added to long-acting SSA treatment (8). In addition, the improved insulin sensitivity compared with SSA alone (2, 12), the advantage of tumor size control over PEG-V monotherapy (2, 6, 13), and lower necessary dose of PEG-V, which can lead to a cost reduction in at least some patients (1), favor the combined use of SSA and PEG-V. Therefore, we believe that combination therapy deserves a prominent place in the medical treatment of acromegaly.

In conclusion, although further research is necessary, our series indicate that combination therapy with long-acting SSA and twice weekly PEG-V is safe. Mild and transient elevated liver enzyme levels were observed in 15% of the patients. During continuation of PEG-V therapy, these liver enzyme abnormalities do not re-occur. However, re-exposure to PEG-V treatment after a wash-out period for whatever reason will again induce another episode with elevated liver enzymes in those subjects who are sensitive for this side effect. Finally, diabetic patients seem to be more prone to develop these episodes of transient elevated liver enzyme tests.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the scientific work reported.

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