Drug-induced hepatitis in an acromegalic patient during combined treatment with pegvisomant and octreotide long-acting repeatable attributed to the use of pegvisomant

J Feenstra, M O van Aken, W W de Herder, R A Feelders and A J van der Lely
Department of Internal Medicine, Endocrinology Unit, Erasmus Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands
(Correspondence should be addressed to J Feenstra; Email: j.feenstra.1@erasmusmc.nl)

Abstract
We report on a patient with acromegaly who developed severe drug-induced hepatitis during combined treatment with the long-acting somatostatin-analog octreotide and the GH receptor antagonist pegvisomant. The hepatic enzyme disturbances normalized after discontinuation of pegvisomant. After rechallenge with monotherapy pegvisomant, however, the hepatic enzyme disturbances reappeared within a few weeks, indicating that most likely pegvisomant alone and not the long-acting somatostatin analog or the combination of these two drugs was responsible for this case of drug-induced hepatitis. Clinicians should be aware of this potential severe adverse drug reaction and therefore frequent control of hepatic enzymes is mandatory during treatment with pegvisomant.

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Introduction
Pharmacotherapy is increasingly gaining ground in the treatment of acromegaly. Pegvisomant, a pegylated analog of human growth hormone (GH), and somatostatin analogs such as octreotide and lanreotide are the mainstays of the medical treatment. Pegvisomant monotherapy as well as combined treatment with pegvisomant and somatostatin analogs will normalize insulin-like growth factor-I (IGF-I) serum concentrations in nearly all acromegalic patients (1–3). Although pharmacotherapy of acromegaly is generally well tolerated, safety data from long-term studies on the use of pegvisomant are scarce (4).

We report on a 45-year-old male with active acromegaly who developed severe hepatic liver enzyme disturbances during combined treatment with long-acting octreotide and weekly pegvisomant injections.

Case report
A 45-year-old male was diagnosed with acromegaly (IGF-I 106.2 nmol/l, maximal reference value <35 nmol/l). On magnetic resonance imaging (MRI) scanning a pituitary macro-adenoma with suprasellar and bilateral parasellar extension combined with compression of the optic chiasm was diagnosed. Patient underwent transphenoidal adenomectomy for a somatotropit pituitary tumor. However, serum IGF-I concentrations remained elevated after surgery (IGF-I 63.3 nmol/l), and pituitary MRI scanning 3 months postoperatively demonstrated residual intrasellar and right parasellar adenoma despite substantial tumor volume reduction. Therapy with a long-acting somatostatin analog was initiated (monthly i.m. injections of octreotide long-acting repeatable (LAR) 30 mg), but the patient remained symptomatic after 6 months of treatment due to active acromegaly (IGF-I 90.3 nmol/l). Subsequently, weekly s.c. pegvisomant 60 mg injections were added to the regimen of monthly long-acting somatostatin injections. Hepatic enzymes were normal at baseline, when combined treatment with the long-acting somatostatin analog and pegvisomant was initiated. After 5 months of combined treatment, biochemical evaluation revealed a gradual increase in serum levels of hepatic enzymes. Alkaline phosphatase increased to 149 U/l (N <119), γ-glutamyl transpeptidase to 372 U/l (N <34), aspartate aminotransferase to 467 U/l (N <30) and alanine aminotransferase to 1148 U/l (N <30). After discontinuation of pegvisomant, the elevated hepatic enzymes normalized within 2 months while treatment with Sandostatin LAR-30 was continued. Additional laboratory analysis showed no arguments for a viral hepatitis. Ultrasonography revealed bile stones without any sign of biliary obstruction or hepatic steatosis. Evaluation of a histological specimen of the liver was compatible with medication-induced hepatitis.

As we hypothesized that the combined treatment of long-acting somatostatin analog and pegvisomant might have been responsible for the increased hepatic
enzymes, and monotherapy with long-acting somatostatin analog failed to normalize IGF-I, we discontinued long-acting somatostatin therapy and started treatment with monotherapy daily pegvisomant 20 mg 2 months after the last injection of long-acting somatostatin analog. Unfortunately, elevation of aspartate transaminase to 60 U/l and alanine aminotransferase to 91 U/l reappeared within 6 weeks (Fig. 1). Therefore, we decided to discontinue pegvisomant monotherapy permanently, after which the increased hepatic enzymes rapidly normalized within a few weeks.

Treatment of acromegaly with the combination of pegvisomant and a long-acting somatostatin analog has proven to be an effective therapy for patients who still have active acromegaly despite 6 months of monotherapy with long-acting somatostatin analog (1). However, data on the safety aspects of this combined treatment are scarce. Pegvisomant therapy is generally well tolerated, and substantial hepatic enzyme disturbances have been rarely encountered in previous clinical studies (2,3). Our patient developed severe hepatic enzyme disturbances several months after initiating combined treatment. Hepatic enzymes normalized rapidly after discontinuation of pegvisomant while long-acting somatostatin therapy was continued. It might be suggested that the hepatic enzyme disturbances observed in our patient could be attributed to the simultaneous treatment with both a somatostatin analog and pegvisomant. It could be hypothesized that this combination of drugs might have induced hepatic steatosis, as the combined effects of these drugs on hepatic glucose metabolism are not well understood.

Histological examination of a liver specimen, however, indicated medication-induced hepatitis without signs of hepatic steatosis. To exclude the possibility that the combination of pegvisomant and long-acting somatostatin analog was causally related we performed a rechallenge with monotherapy pegvisomant, after which hepatic enzyme disturbances reappeared within a few weeks. These findings suggest strongly that most likely pegvisomant alone, and not the long-acting somatostatin analog or the combination of these two drugs, was responsible for this case of drug-induced hepatitis. The mechanism of pegvisomant-induced hepatic enzyme disturbances remains the subject of conjecture. Because of the low frequency and dose independency, idiosyncratic drug toxicity has to be assumed (5). Although substantial hepatic enzyme disturbances are encountered only infrequently during treatment with pegvisomant, clinicians should stick to the advice as mentioned in the product information of pegvisomant that regular hepatic enzyme control is mandatory.

References


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