CASE REPORT

Pegvisomant-induced cholestatic hepatitis with jaundice in a patient with Gilbert's syndrome

Ignacio Bernabeu¹, Jose Cameselle-Teijeiro², Felipe F Casanueva^{1,3} and Monica Marazuela⁴

¹Endocrine Division, Departamento of Medicina, Complejo Hospitalario Universitario de Santiago, Hospital Clínico Universitario de Santiago, Universidad de Santiago de Compostela, Travesía Choupana s/n, 15706 Santiago de Compostela, La Coruña, Spain, ²Pathology Department, Complejo Hospitalario Universitario de Santiago, Universidad de Santiago de Compostela, Santiago de Compostela, Spain, ³Instituto Salud Carlos III, Centro de Investigación Biomédica en Red (CIBER), Area Fisiopatología Obesidad y Nutrición (CiberObn), Santiago de Compostela, Spain and ⁴Endocrine Division, Hospital Universitario de La Princesa, Universidad Autónoma de Madrid, Madrid, Spain

(Correspondence should be addressed to I Bernabeu; Email: ignacio.bernabeu.moron@sergas.es)

Abstract

We report on a patient with active acromegaly and Gilbert's syndrome who developed severe hepatic dysfunction during pegvisomant (PEGv) monotherapy. She was partially resistant to all previous therapies, including long-acting somatostatin analogs and cabergoline. Five months after starting PEGv therapy, with an already normalized IGF1, she developed cholestatic liver dysfunction with jaundice. Liver or biliary diseases including biliary sludge, cholelithiasis or liver steatosis were excluded. A liver biopsy was in keeping with drug-induced liver injury. The discontinuation of PEGv was followed by full clinical and biochemical recovery in 6 weeks. PEGv therapy was not resumed. Apart from a minimal increase of bilirubin levels, no liver function test abnormalities were found during the 4-year follow-up period after the PEGv was discontinued. Drug-induced liver injury is the most serious systemic adverse event resulting from PEGv therapy. Since patients with mild and asymptomatic liver disease could be at a higher risk of PEGv-induced hepatotoxicity, frequent monitoring of hepatic enzymes should be required in these cases.

European Journal of Endocrinology 160 869–872

Introduction

Pegvisomant (PEGv) monotherapy is the most effective therapy for acromegaly (1, 2). Although it is generally well tolerated, there is concern about certain adverse events, primarily drug-induced liver injury, which is considered the most serious (3, 4). Drug-induced liver injury can be a consequence of immune-mediated hypersensitivity or an idiosyncratic reaction and is unpredictable in most cases. Its predominant clinical presentation can resemble acute hepatitis or cholestatic liver disease, although it is sometimes characterized by a mixed pattern (5).

Gilbert's syndrome is the most common inherited disorder of bilirubin glucuronidation and is produced by a mutation in the gene *UGT1A1*, encoding bilirubin uridinediphosphoglucuronate glucuronosyltransferase, which conjugates bilirubin to glucuronic acid. Approximately, 9% of the general population is homozygous for the genetic defect, but not all develop hyperbilirubinaemia. Patients with Gilbert's syndrome usually have mild and predominantly unconjugated hyperbilirubinaemia of no clinical significance (6).

We report here in detail clinical, biochemical, and histological findings in a patient with active acromegaly and Gilbert's syndrome (homozygous A[TA]7TAA) who

developed severe hepatic cholestatic dysfunction with jaundice related to PEGv therapy.

Case report

A 27-year-old woman was diagnosed with acromegaly on July 2001. This patient was included in a previous report regarding PEGv efficacy (7). She had elevated insulin-like growth factor-1 (IGF1; 593 ng/ml; normal range 109–358) and non-suppressible GH (GH nadir 16.4 ng/ml post-oral glucose tolerance test (OGTT)). Magnetic resonance imaging (MRI) showed an invasive pituitary macroadenoma of 73 cc. In August 2001, she underwent surgery twice by transsphenoidal and transcranial approaches for subtotal resection of a sparsely granulated somatotroph adenoma.

After surgery and despite substantial tumor reduction, a large residual intrasellar and parasellar adenoma and GH hypersecretion persisted (basal GH: 18.6 ng/ml and IGF1: 783 ng/ml). In November 2001, she underwent radiation (50 Gy). Since then, she has been treated with maximum doses of lanreotide SR and subsequently octreotide LAR (Oct LAR) in combination with cabergoline (Cab) 1.5 mg/week, with partial biochemical and no tumor response to the treatment.

She developed FSH, LH, and TSH deficiencies and was adequately treated with levothyroxine and an estradiol/norethisterone transdermal patch. She was also receiving therapy with atorvastatin (20 mg/d) for hypercholesterolaemia and paracetamol (on demand, to a maximum dose of 1.5–2 g/d) for persistent headache. She remained on these treatments without any related adverse events and with a persistently elevated IGF1 for the next 27 months.

In February 2004, on availability of PEGv and as the patient maintained persistently elevated IGF1 levels (509 ng/ml), she started with PEGv 10 mg/day, 30 and 15 days after discontinuation of the Oct LAR and Cab respectively. IGF1 levels at 1, 3, and 5 months after starting treatment were within the normal range (Table 1). An MRI performed 3 months after starting the PEGv therapy did not show any changes in tumor volume. Liver function tests showed normal transaminases and mild hyperbilirubinaemia (Table 1).

At month 5 (July 2004) after starting PEGv therapy and 6 months after the discontinuation of Oct LAR, she experienced an increase in transaminases and bilirubin. Four days before her next scheduled endocrine visit, she was admitted to hospital with right upper quadrant abdominal pain that had persisted for 6–8 h, fatigue, nausea, and conjunctival jaundice. Liver function test results were raised (Table 1), with a characteristic cholestatic profile (5). All potentially hepatotoxic drugs, including oestrogens, atorvastatin, paracetamol, and PEGv therapy were discontinued. Additional studies ruled out viral or autoimmune hepatitis, haemochromatosis, fatty liver, primary biliary cirrhosis, Wilson’s disease and α -1-antitrypsin deficiency. An abdominal ultrasound (US) on admission revealed no sign of biliary sludge, cholelithiasis or hepatic steatosis. A liver biopsy was performed, showing non-specific changes with mild intrahepatic cholestasis, mild portal inflammation, and minimal hepatocellular degeneration in keeping with drug-induced liver injury (Fig. 1).

Recovery started 11 days after discontinuing the PEGv. Liver function test results returned to previous baseline levels, and IGF1 levels increased to 709 ng/ml in 6 weeks (Table 1). She then began treatment with high doses of lanreotide autogel and Cab. Atorvastatin, transdermal oestrogens, and paracetamol were also

resumed at this time. Since then, no liver function test abnormalities, excluding a minimal increase of bilirubin levels (less than twice the upper limit of normal (ULN), have been found during the 4-year follow-up period.

Discussion

To date, 41 cases of hepatic dysfunction have been described during PEGv therapy in the 509 patients reported (1, 2, 4, 8–12). The total incidence of 8% was higher with the combined treatment of PEGv plus somatostatin analogs (SSA; 38%) (4, 10, 12), than with PEGv monotherapy (4.2%) (1, 2, 4, 8, 9). The time between the initiation of PEGv therapy and hepatotoxic effects was variable, ranging from 2.3 (4) to 92 (12) weeks.

Two types of hepatic dysfunction have been reported during PEGv therapy: hepatocellular and cholestatic (3). Hepatocellular liver injury is the most common type of dysfunction. Its pathogenesis is unclear, as it does not appear to be dose related or associated with any identifiable predictor (4). Cholestatic liver dysfunction was present in 9 out of 41 reported cases, all of them previously treated or under SSA. Biliary sludge or cholelithiasis was found on the US (4, 10–12) and both were associated with SSA therapy or its withdrawal (3, 13). However, it is difficult to determine the exact incidence of PEGv-induced cholestatic liver injury, since alkaline phosphatase (APh) and bilirubin levels were not always available in the reported cases (4). It is likely that most of these patients had associated hepatocellular damage, as aspartate aminotransferase ranged between 3.1 and 25.7 times the ULN (4, 10–12). A liver biopsy was performed in only two cases of hepatocellular dysfunction, both receiving combined treatment with PEGv and SSA (4, 11). Liver biopsies showed chronic mild hepatitis with mixed portal inflammation in one patient, previously presenting with Gilbert’s syndrome (4), and medication-induced hepatitis in the other (11).

Although our patient was receiving other therapies such as transdermal oestrogen, atorvastatin, and paracetamol, which have been associated with hepatotoxicity, the doses were small, and after the acute

Table 1 Chronological development and values of alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyl transpeptidase (GGT), total bilirubin (T. BIL), alkaline phosphatase (APh) and IGF1 levels during octreotide LAR (Oct LAR) and cabergoline (Cab) treatment and pegvisomant (PEGv) monotherapy, on the first day of admission (D1) and thereafter (D3, D11, D36).

	Normal range	February-04	March-04	May-04	July-04	D1	D3	D11	D36
AST	0–25 UI/l	13	13	11	40	60	68	23	10
ALT	0–28 UI/l	13	13	12	137	126	147	86	12
GGT	5–38 UI/l	4	7	14	131	104	81	49	16
T. BIL	0.2–1.2 mg/dl	1.44	2.07	0.9	5.8	6.9	4.6	2.7	2.04
APh	65–195 UI/l	157	103	103	274	294	217	158	105
IGF1	109–358 mg/dl	509	180	173	126				709
Acromegaly therapy		Oct LAR 30 CAB	PEGV 10 mg/d	PEGV 10 mg/d	PEGV 10 mg/d	None	None	None	None

Figure 1 (A) Liver biopsy showing preserved architecture, feathery degeneration, glycogenated nuclei, and mild-portal inflammation with mononuclear cells. (B) At higher magnification lymphocytes and rare eosinophils (arrows) are observed. Hematoxylin–eosin stain; original magnification: A, $\times 200$; B, $\times 400$. Full colour version of this figure is available via <http://dx.doi.org/10.1530/EJE-09-0040>.

episode, she resumed all these therapies in similar doses with no recurrence of liver abnormalities during a four-year follow-up. No data are available regarding concomitant drugs in previously reported cases (1, 2, 4, 8–12).

An increased risk of symptomatic gallstones (with acute cholecystitis or biliary colic requiring cholecystectomy) has been described between 2 and 4 months following SSA withdrawal, particularly in men (13, 14). This mechanism does not seem to have played a role in the patient's hepatic dysfunction because she was female; the acute episode occurred 6 months after SSA discontinuation and the US was normal.

Although we cannot rule out the possibility of a stone that had already passed by the time the US was performed, we consider this very unlikely. Bile duct stones able to cause biliary colic and jaundice are usually large and less likely to pass through the bile ducts spontaneously (15). US has a very high sensitivity and specificity for the detection of bile duct stones (16) and biliary dilatation (17). In addition, the US was performed during the acute abdominal pain episode coinciding with jaundice and peak levels of bilirubin and APh.

This is the second case of liver injury during PEGv therapy in Gilbert's syndrome, and to our knowledge, the first one with hyperbilirubinaemia (5.7 times the ULN) and clinical jaundice. The Gilbert's syndrome patient reported initially (4) developed an isolated transaminase increase with normalization of his mild hyperbilirubinaemia, which reappeared after the transaminase values had returned to normal. Gilbert's syndrome was considered as unrelated to the development of hepatitis in this first case.

Gilbert's syndrome has a high prevalence in western populations and is sometimes under-diagnosed (6). The *UGT1A1* gene has an important role in hepatic glucuronidation of several drugs prior to excretion. Diminished excretion of these non-metabolized drugs could potentially cause their accumulation and increase their toxicity (6), as has been previously described (18). It is possible that diminished hepatic glucuronidation of PEGv in individuals with Gilbert's syndrome could increase the risk of liver damage. The incidence of hepatic dysfunction during PEGv treatment (8%) is similar to the incidence of the homozygous mutation in the *UGT1A1* gene (9%). The hypothetical relationship between under-diagnosed Gilbert's syndrome and liver dysfunction during PEGv therapy warrants additional studies.

PEGv hepatotoxicity has been also described in two patients positive for hepatitis C virus and without any sign of overt hepatic disease (8). Hepatic function must therefore be evaluated carefully prior to PEGv therapy, as patients with mild hepatic abnormalities could be at a higher risk of PEGv hepatotoxicity. In these cases, liver function should be monitored more strictly and should not only include transaminases but also APh and bilirubin levels to assist in the diagnosis of different patterns of PEGv hepatotoxicity (4).

Declaration of interest

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

Funding

This work was supported by grants to MM from FISS 07/1119 and Mutua Madrileña.

Acknowledgements

CiberObn is an initiative of the Instituto de Salud Carlos III (ISCIII).

References

- 1 Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, van der Lely AJ, Dimaraki EV, Stewart PM, Friend KE, Vance ML, Besser GM, Scarlett JA, Thorner MO, Parkinson C, Klibanski A, Powell JS, Barkan AL, Sheppard MC, Malsonado M, Rose DR, Clemmons DR, Johannsson G, Bengtsson BA, Stavrou S, Kleinberg DL, Cook DM, Phillips LS, Bidlingmaier M, Strasburger CJ, Hackett S, Zib K, Bennett WF & Davis RJ. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. *New England Journal of Medicine* 2000 **342** 1171–1177.
- 2 van der Lely AJ, Hutson RK, Trainer PJ, Besser GM, Barkan AL, Katznelson L, Klibanski A, Herman-Bonert V, Melmed S, Vance ML, Freda PU, Stewart PM, Friend KE, Clemmons DR, Johannsson G, Stavrou S, Cook DM, Phillips LS, Strasburger CJ, Hackett S, Zib KA, Davis RJ, Scarlett JA & Thorner MO. Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. *Lancet* 2001 **358** 1754–1759.
- 3 Hodish I & Barkan A. Long-term effects of pegvisomant in patients with acromegaly. *Nature Clinical Practice. Endocrinology and Metabolism* 2008 **4** 324–332.
- 4 Biering H, Saller B, Bauditz J, Pirlich M, Rudolph B, John A, Buchfelder M, Mann K, Droste M, Schreiber I, Lochs H & Strasburger CJ. Elevated transaminases during medical treatment of acromegaly: a review of the German pegvisomant surveillance experience and a report of a patient with histologically proven chronic mild active hepatitis. *European Journal of Endocrinology* 2006 **154** 213–220.
- 5 Kaplowitz N. Drug-induced liver injury. *Clinical Infectious Diseases* 2004 **38** S44–S48.
- 6 Chowdhury N, Wang X, Chowdhury JR, Kaplan MM & Bonis P. Gilbert's syndrome and unconjugated hyperbilirubinemia due to bilirubin overproduction. In *UpToDate*, Ed. DS Basow, Waltham, MA: UpToDate, 2008.
- 7 Marazuela M, Lucas T, Alvarez-Escola C, Puig-Domingo M, Miguel-Nova P, Duran-Hervada A, Manzanares R, Luque-Ramirez M, Halperin I, Casanueva FF & Bernabeu I. Long-term treatment of acromegalic patients resistant to somatostatin analogs with the GH receptor antagonist pegvisomant: its efficacy in relation to gender and previous radiotherapy. *European Journal of Endocrinology* 2009 **160** 535–542.
- 8 Colao A, Pivonello R, Auriemma RS, De Martino MC, Bidlingmaier M, Briganti F, Tortora F, Burman P, Kourides IA, Strasburger CJ & Lombardi G. Efficacy of 12-month treatment with the GH receptor antagonist pegvisomant in patients with acromegaly resistant to long-term, high-dose somatostatin analog treatment: effect on IGF1 levels, tumor mass, hypertension and glucose tolerance. *European Journal of Endocrinology* 2006 **154** 467–477.
- 9 Barkan AL, Burman P, Clemmons DR, Drake WM, Gagel RF, Harris PE, Trainer PJ, van der Lely AJ & Vance ML. Glucose homeostasis and safety in patients with acromegaly converted from long-acting octreotide to pegvisomant. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 5684–5691.
- 10 Feenstra J, de Herder WW, ten Have SM, van den Beld AW, Feelders RA, Janssen JA & van der Lely AJ. Combined therapy with somatostatin analogues and weekly pegvisomant in active acromegaly. *Lancet* 2005 **365** 1644–1646.
- 11 Feenstra J, van Aken MO, de Herder WW, Feelders RA & van der Lely AJ. Drug-induced hepatitis in an acromegalic patient during combined treatment with pegvisomant and octreotide long-acting repeatable attributed to the use of pegvisomant. *European Journal of Endocrinology* 2006 **154** 805–806.
- 12 Neggers SJ, van Aken MO, Janssen JA, Feelders RA, de Herder WW & van der Lely AJ. Long-term efficacy and safety of combined treatment of somatostatin analogs and pegvisomant in acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 4598–4601.
- 13 Paisley AN, Roberts ME & Trainer PJ. Withdrawal of somatostatin analogue therapy in patients with acromegaly is associated with an increased risk of acute biliary problems. *Clinical Endocrinology* 2007 **66** 723–726.
- 14 Paisley A & Trainer P. Is withdrawal of somatostatin analogue therapy in patients with acromegaly associated with an increased risk of acute biliary problems? *Clinical Endocrinology* 2008 **68** 153–154.
- 15 Tranter SE & Thompson MH. Spontaneous passage of bile duct stones: frequency of occurrence and relation to clinical presentation. *Annals of the Royal College of Surgeons of England* 2003 **85** 174–177.
- 16 Portincasa P, Moschetta A, Petruzzelli M, Palasciano G, Di Ciaula A & Pezzolla A. Gallstone disease: symptoms and diagnosis of gallbladder stones. *Best Practice & Research. Clinical Gastroenterology* 2006 **20** 1017–1029.
- 17 Freitas ML, Bell RL & Duffy AJ. Choledocholithiasis: evolving standards for diagnosis and management. *World Journal of Gastroenterology* 2006 **12** 3162–3167.
- 18 Burchell B, Soars M, Monaghan G, Cassidy A, Smith D & Ethell B. Drug-mediated toxicity caused by genetic deficiency of UDP-glucuronosyltransferases. *Toxicology Letters* 2000 **112–113** 333–340.

Received 17 February 2009

Accepted 24 February 2009