LETTER TO THE EDITOR

Subcutaneous lipoatrophy induced by long-term pegvisomant administration

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The growth hormone (GH) receptor antagonist pegvisomant, the most recent drug released for
treatment of acromegaly, is well tolerated and causes adverse effects in only a minority of patients.
Side-effects include self limited local reactions at the injection site and mild liver toxicity (1).
However, they do not modify the effectiveness of pegvisomant. We report the first case of
injection-site lipoatrophy induced by pegvisomant, which was associated with transiently impaired
drug bioactivity.

A 33-year-old caucasian acromegalic woman started treatment with pegvisomant (15 mg s.c., daily)
in March 2004. The treatment was followed by a clear decrease in serum IGF-1 levels from 910.5 ±
70.4 to 260.7 ± 11.3 µg/l (mean of 5 determinations performed during 2 years, reference range 115–
307) and was well tolerated until December 2007, when the skin of both arms, where the patient
had been injecting the drug, became irregularly excavated (Figure, top). Ultrasonography showed
atrophy of subcutaneous fat tissue, causing close contact between dermis and the underlying
muscle. Ultrastructural analysis of the skin showed that subcutaneous fat tissue was extensively
substituted by abundant collagen fibres and fibroblasts, and infiltrated by mast cells, lymphocytes
and histiocytes (Figure, bottom), and that the endothelial basement membranes of capillaries and
venules were consistently thickened and reduplicated. Moreover, serum IGF-1 levels rose
significantly (394 µg/l). This increase was confirmed by the biochemical re-evaluation performed
ten days later (IGF-1: 412 µg/l). Furthermore, the soft tissues thickened and arthralgia and
hyperhidrosis worsened markedly. However, one month after changing the injection-site of
pegvisomant from the arms to the abdomen and the thighs, serum IGF-1 levels normalized again
(197 µg/l).

Pegvisomant is obtained by amino acid substitutions in the GH molecule (which lead to non
functioning GH receptor dimerization) and by the addition of several polyethylene glycol molecules
(which enhance its half-life) (2). Recently other pegylated molecules, such as integrin, interferon-α,
interleukin-2, rhG-CSF mutant and hirudin, were proposed for treatment of autoimmune diseases,
hepatitis, AIDS and cancer (3). We speculate that subcutaneous lipoatrophy could be due to a local
inflammatory reaction to polyethylene glycol molecules of pegvisomant, injected for a prolonged period in a limited skin area. However, this adverse effect has not been reported until now in patients treated with other pegylated drugs. An alternative explanation may be that lipoatrophy is a consequence of GH resistance induced by prolonged and deeply penetrating pegvisomant administration. The increase in serum IGF-1 levels following the occurrence of lipoatrophy suggested the reduction of pegvisomant effectiveness, probably due to altered absorption. Indeed, serum IGF-1 levels normalized again when the patient changed the site of injection. Although plasma pegvisomant levels were not evaluated, the daily and correct injection of the drug was confirmed by the relatives of the patient, thus excluding non-compliance. Previously, the necessity of paying close attention to the rotation of injections was stressed by other authors, who reported the occurrence of abdominal lipohypertrophy in patients treated with pegvisomant (1, 4 and 5). It is noteworthy that the effectiveness of this drug was also reduced in one of these cases (5). In conclusion, acromegalic patients should rotate pegvisomant injection-sites to avoid local reactions and to maintain also an appropriate drug bioactivity.
REFERENCES


Figure legend:
Subcutaneous fat atrophy in deltoid area of the left arm (top), and ultrastructural analysis of an adipocyte showing that subcutaneous fat was partially substituted by fibroblasts (F), densely packed collagen (C) and endothelial cells (E) (original magnification, 3900 X) (bottom).

Fig.1(top)
Fig. 1 (bottom)