

COMMENTS AND RESPONSES

Pulmonary Embolism in Patients with Unexplained Exacerbations of Chronic Obstructive Pulmonary Disease

TO THE EDITOR: We read with great interest the article by Tillie-Leblond and colleagues (1) on the prevalence of pulmonary embolism in patients with chronic obstructive pulmonary disease (COPD) who are hospitalized for severe exacerbation of unknown origin. This paper deserves 2 comments.

First, the authors reported that a low clinical probability as assessed by the Geneva score (2) could not rule out pulmonary embolism. This is hardly a surprise, because that clinical prediction rule was never intended to be used alone to rule in or rule out pulmonary embolism. Rather, it allows a more rational interpretation of test results, with the predictive value depending not only on test characteristics but also on pretest probability. The 9.2% prevalence of pulmonary embolism among patients classified as having a low clinical probability in Tillie-Leblond and colleagues' study is similar to that observed in previous studies using the Geneva rule and suggests that this rule has good performance in patients with COPD.

Second, the authors proposed a "modified" Geneva score in which they replaced malignant disease with recent surgery. That modification was arbitrary and should be validated in another patient population before it can be generalized. Indeed, the proportion of patients with malignant disease was particularly high in Tillie-Leblond and colleagues' study. We would like to point out that this modified Geneva score has nothing to do with and should not be confused with the recently published revised Geneva score (3), which was derived from a large multicenter database using recommended methods for clinical prediction rules and was externally validated.

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Potential Financial Conflicts of Interest: None disclosed.

References

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2. Wicki J, Perneger TV, Junod AF, Bounameaux H, Perrier A. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. *Arch Intern Med.* 2001;161:92-7. [PMID: 11146703]
3. Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. *Ann Intern Med.* 2006;144:165-71. [PMID: 16461960]

IN RESPONSE: The aim of our study was to evaluate the prevalence of pulmonary embolism in a selected population of patients with COPD who were admitted for severe exacerbations of unknown origin. Statistical analysis to select predictive variables for pulmonary

embolism identified 3 criteria: cancer, previous thromboembolic disease, and a decrease in PaCO₂ from baseline. It was not possible to define a specific score in patients with COPD who had a severe exacerbation of unknown origin according to a multivariate logistic regression model, as was done in the Geneva study (1). We agree that the Geneva score should not be used as the sole criterion to rule in or rule out pulmonary embolism. It should primarily be associated with a clinical probability assessment (1). In the sample we selected, alternative diagnoses, such as infection, pneumothorax, and iatrogenic event, were ruled out. In the patients with COPD who were selected according to the clinical criteria of severe exacerbation of unknown origin, we calculated the Geneva score to evaluate its diagnostic value. The prevalence of pulmonary embolism observed in patients with COPD was 9.2% (95% CI, 4.7% to 15.9%) in a low-probability group assessed by the Geneva score, similar to that observed in the Geneva study (10% [CI, 8% to 13%]) (1). A key question to consider is whether a 9% or 10% prevalence of pulmonary embolism in a low-probability group has a sufficient negative predictive value. We agree that the clinical suspicion of pulmonary embolism is particularly difficult in patients with COPD. However, missing 1 of 10 diagnoses of pulmonary embolism in the low-probability group could be deleterious in a population with poor respiratory condition at baseline.

Dr. Le Gal's and Dr. Righini's second comment concerns the modified Geneva score. We agree that this score was not prospectively evaluated and needs further validation. In our clinical practice, only 3% of patients with COPD admitted for severe exacerbation have had a recent surgical procedure. Surgery is included in the Geneva score (3 points) (1). In patients with COPD, cancer is much more prevalent (2) and was a risk factor for pulmonary embolism in our study. For this reason, we modified the Geneva score with a more relevant risk factor for patients with COPD. This score currently has no clinical value since it has not yet been validated in a prospective study.

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CLINICAL OBSERVATIONS**Lipohypertrophy in Acromegaly Induced by the New Growth Hormone Receptor Antagonist Pegvisomant**

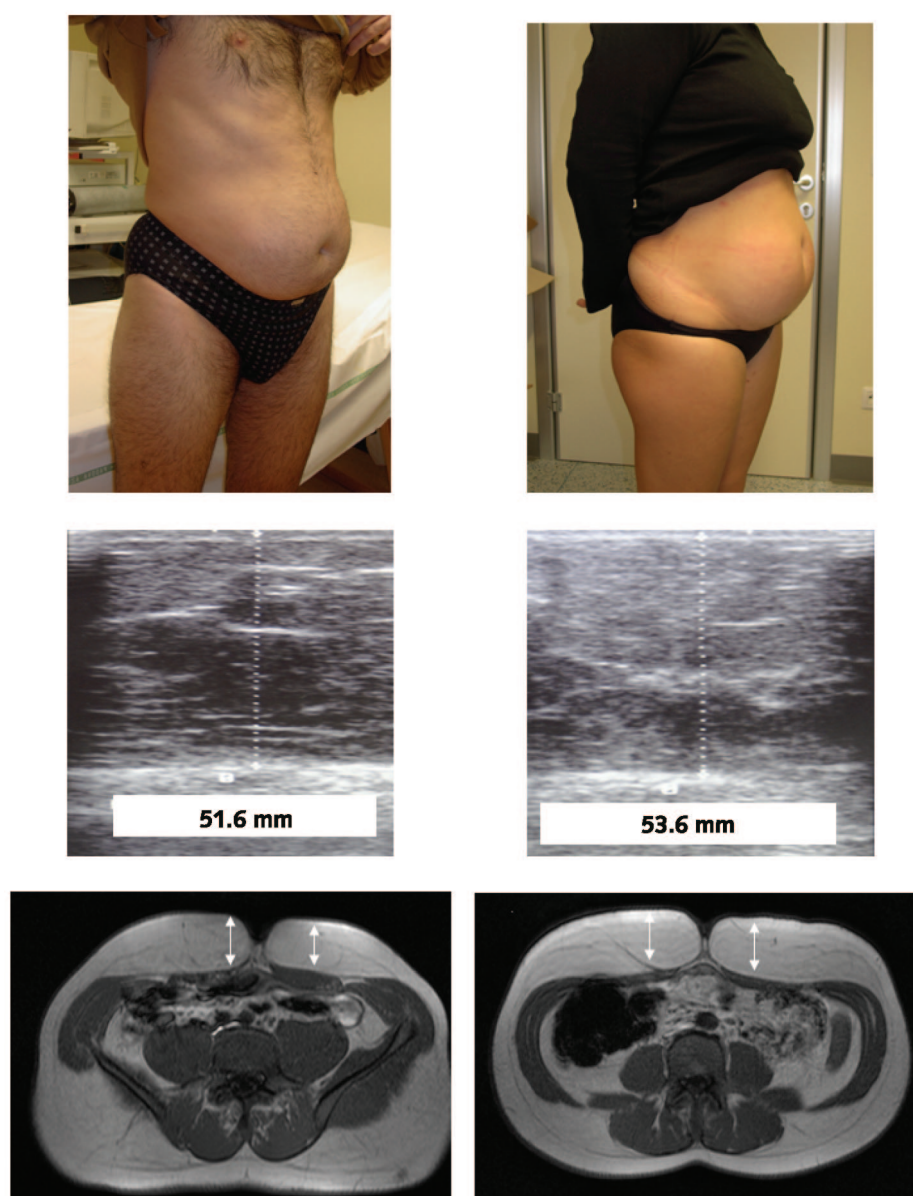
Background: Pegvisomant (Somavert, Pfizer, New York, New York) was recently released in Italy for the treatment of acromegaly. This drug binds to growth hormone receptors and blocks the binding of

endogenous growth hormone, thus decreasing serum concentrations of insulin-like growth factor I (IGF-I). Several studies reported that pegvisomant was safe and effective in more than 100 patients with acromegaly (1, 2). However, patients taking pegvisomant should be carefully followed for possible adverse effects, including increased baseline levels of growth hormone, pituitary tumor growth, hypoglycemia when taking antidiabetic drugs, functional growth hormone deficiency, and hepatitis (3). Local reactions were reported in 18 of 160 patients with acromegaly and were generally characterized as mild, erythematous, and self-limited (1, 2).

Objective: To describe 2 patients who developed focal lipohypertrophy while taking pegvisomant.

Case Report: A 35-year-old man (patient 1) and a 38-year-old woman (patient 2) began treatment with subcutaneous pegvisomant, 10 mg daily (1 mL), rotating the injection site around the umbilical area. Neither patient was taking concomitant medications. After 1 month, both patients began to report marked abdominal distention not related to bowel or abdominal abnormalities. According to the patients' IGF-I values, pegvisomant treatment was effective (Table), and levels of liver enzymes remained in the normal range. On clinical examination after a second month of treatment, the distention (soft, homogeneous, and associated with a marked thickening of subcutaneous tissues) was clearly visible (Figure, top). Anthropometric variables at baseline and after a second month are reported in the Table.

Figure. Clinical and radiographic features of patient 1 (left) and patient 2 (right) after 2 months of treatment with pegvisomant.



Top. Photographs of the abdominal area. **Middle.** Ultrasonography of the subcutaneous tissue accumulation. **Bottom.** Magnetic resonance imaging (T1-weighted axial images) centered at the umbilical level and showing marked thickening of subcutaneous fat tissue (arrows).

Table. Changes in Levels of Insulin-Like Growth Factor-I and Anthropometric Measures in 2 Patients Who Developed Lipohypertrophy While Taking Pegvisomant

Variable	Patient 1		Patient 2	
	Baseline	Month 2	Baseline	Month 2
Insulin-like growth factor-I level, $\mu\text{g/L}$	1432	750	1329	721
Weight, kg	87.5	86.5	71.5	71.6
Waist circumference, cm	96	99	87	94
Hip circumference, cm	110	106	103	101

Abdominal ultrasonography (Figure, middle) and magnetic resonance imaging (Figure, bottom) confirmed a focal accumulation of subcutaneous adipose tissue without increased visceral fat depots.

Discussion: Local modification of subcutaneous adipose tissue depots after hormonal injections is not a new concept and has been reported with insulin, which is able to induce both lipoatrophy and lipohypertrophy. There is a strong pathophysiologic association between growth hormone and adipose tissue depots, especially in the abdominal area. It is well known that growth hormone can be lipolytic and that patients with growth hormone deficiencies present with increased abdominal fat. Moreover, in acromegaly, blockade of growth hormone action by pegvisomant is associated with reversal of the inhibition of 11- β -hydroxysteroid dehydrogenase 1, possibly affecting omental fat cortisol concentrations, adipocyte differentiation, and visceral fat distribution (4). Therefore, pegvisomant may be able to induce subcutaneous lipohypertrophy at the abdominal site by growth hormone inhibition or by unknown direct mechanisms when injected in the same area for a prolonged time. The IGF-I values in our 2 patients suggest that transient growth hormone deficiency may have been a cause of focal hypertrophy.

Conclusion: Pegvisomant appeared to induce lipohypertrophy in 2 patients after a month of therapy. We recommend avoiding abdominal injection of pegvisomant and carefully rotating injections to other parts of the body to prevent this complication. Our observations stress the necessity of paying close attention to newly released drugs, notwithstanding previous well-organized clinical trials (1, 2). Lipohypertrophy was not reported in premarketing and postmarketing studies of pegvisomant or in recent reviews (1–5).

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CORRECTION

Correction: Book Notes: *The Health Care Mess: How We Got Into It and What It Will Take To Get Out*

In the 4 April 2006 issue, the name and affiliation of a book reviewer were inadvertently omitted from his review (1). *The Health Care Mess: How We Got Into It and What It Will Take To Get Out* was reviewed by William Rifkin, MD, from Yale University School of Medicine, New Haven, Connecticut.

Reference

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