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FIRST REPORT ON PERSISTENT REMISSION OF ACROMEGALY AFTER WITHDRAWAL OF LONG-TERM PEGVISOMANT MONOTHERAPY

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Running Title: Acromegaly remission after Pegvisomant monotherapy.

ABSTRACT

The GH-receptor antagonist pegvisomant (PEG) **reduces peripheral** IGF-1 synthesis and is used **to treat** acromegaly patients resistant or intolerant to somatostatin analogues (SSA). Medical therapy is generally life-long in patients with acromegaly, **since** disease remission is very uncommon after SSA discontinuation and has never been reported after PEG withdrawal. Here, we report for the first time the cases of two acromegaly patients treated with PEG monotherapy for many years because of resistance to SSA, who persistently maintained normal serum IGF-1 **levels** after PEG withdrawal. The **first patient** autonomously discontinued PEG treatment after 8 years, while in the **second** case we stopped the treatment after 11 years, because slight hypertransaminasemia occurred. After PEG discontinuation, in both cases IGF-1 values remained persistently normal and GH during OGTT regularly suppressed. To date, both patients are still in remission. **Therefore,** we suggest that PEG could exert unknown antitumoral effects in pituitary tumor cells and that long-term PEG treatment can induce acromegaly remission in some patients.

INTRODUCTION

Acromegaly is a rare endocrine disease, due to growth hormone (GH) and insulin like growth factor 1 (IGF-1) overproduction by a pituitary tumor, and associated with increased morbidity and mortality [1]. **The aims of treatment are to** normalize GH and IGF-I levels, to shrink the tumor mass, to ameliorate the systemic comorbidities, to improve quality of life, and to reduce the mortality rate [2]. Pituitary surgery is the mainstay of treatment because it is a rapid and potentially curative approach, but medical and/or radiation therapy can be used when neurosurgery is contraindicated or unsuccessful [3]. First-generation somatostatin analogues (SSA) represent the first-line medical therapy, being effective in more than 50% of patients [4], while pasireotide, a second-generation multireceptor-targeted SSA, has recently demonstrated efficacy in patients not adequately controlled by first-generation SSA [5]. Pegvisomant (PEG), a genetically engineered

antagonist of GH receptor, is an alternative second-line therapy in patients resistant or intolerant to SSA. It normalizes IGF-1 levels in 60-90% of patients [6-10]. Nevertheless, consistent with the mechanism of action, PEG does not reduce GH levels and tumor mass.

Medical therapy is generally **intended** as a lifelong approach. Indeed, permanent remission of acromegaly after SSA withdrawal **is** rarely **observed, while it** has **never been** reported after PEG discontinuation [11-13]. Here, we report the first two cases of SSA-resistant acromegaly patients **with persistently controlled disease** after withdrawal of long-term treatment with PEG.

Case n. 1

In 1994, a 34-year-old female with acromegaly (IGF-1 3.8 ULN [upper limit of normal] and GH nadir 8 μg/L during oral glucose tolerance test [OGTT]) due to a 7-mm pituitary adenoma was initially treated with transsphenoidal surgery. Because of persistently elevated GH and IGF-1 levels, daily subcutaneous injection of octreotide acetate was initially prescribed, and switched to octreotide LAR after a couple of years, at a dosage rapidly increased up to 30 mg/ 4 weeks. In consideration of persistently high IGF-1 levels, PEG 10 mg/day was added in June 2005, achieving IGF-1 normalization (ULN 0.66). In November 2005, a head-magnetic resonance imaging (MRI) showed a 3-mm pituitary tumor remnant. In the same month, Octreotide LAR was stopped and over the following years acromegaly was adequately controlled by PEG monotherapy. In 2007, a new head-MRI confirmed a tumor remnant of 2 mm. In November 2016, considering the normalization of IGF-1 levels and the occurrence of slight hypertransaminasemia, PEG therapy was withdrawn. Three and 6 months after PEG discontinuation, GH and IGF-1 values were within the normal range. In May 2017, a head-MRI showed a 10 mm partially cystic pituitary adenoma, but IGF-1 continued to be in the normal range and GH was regularly suppressed during OGTT (GH nadir 0.29 μg/L).

To date, acromegaly is still in remission (**Fig. 1**).

Case n. 2

In 1990, a 33-year-old female with acromegaly (IGF-1 levels 4.9 ULN and GH nadir 20 μg/L during OGTT) due to a 12-mm pituitary adenoma was successfully treated with transsphenoidal surgery. Nevertheless, acromegaly recurred in 1998 and therefore lanreotide treatment was started. At that time, head-MRI documented an empty sella. In 1999, lanreotide was switched to octreotide LAR, progressively increased up to 30 mg/4 weeks. In 2005, because of persistently increased IGF-1 levels, PEG 10 mg/day was added to SSA, achieving IGF-1 normalization (0.06 ULN). In September 2006, octreotide LAR was stopped and over the following years biochemical control of acromegaly was maintained with PEG monotherapy. In 2013, patient autonomously stopped PEG treatment and was lost to follow-up for almost one year. When the patient returned in July 2014, biochemical evaluation revealed normal IGF-1 levels and GH regularly suppressed during OGTT (GH nadir 0.14 μg/L). Periodic evaluation performed over the following four years confirmed remission of acromegaly (**Fig. 1**).

DISCUSSION

Transsphenoidal surgery is the first-line therapy in acromegaly patients [3], while medical treatment with first-generation SSA is indicated when surgery is unfeasible or not curative. When first-generation SSA are ineffective or not tolerated, PEG or, more recently, pasireotide can be used. Medical therapy is frequently life-long since persistent remission of acromegaly after SSA treatment discontinuation is a very uncommon event, while remission after PEG therapy withdrawal has never been reported [11-13]. For this reason, radiotherapy is advisable in selected cases. PEG has been shown to be effective in the vast majority of acromegaly patients [6-10], especially when an appropriate **drug up-titration** is performed [14]. PEG treatment has been proven to be safe, since a very low incidence of tumor size increase, liver enzyme elevations, and lipodystrophy at the injection site have been reported [15, 16].

In this study, we report - for the first time - persistent remission of acromegaly after discontinuation of long-term PEG treatment. **In both cases remission occurred after menopause, therefore excluding a potential involvement of oestrogen secretion.** None of the patients underwent pituitary radiotherapy, while pituitary tumor apoplexy - as a possible explanation for remission - can be excluded on the basis of clinical history and MRI findings. Indeed, one patient has been found with an empty sella after neurosurgery, whereas in the other one the pituitary adenoma was still visible at the last follow-up imaging. Especially in **the** latter case, it is difficult to speculate on the exact mechanism underlying the normalization of GH secretion despite the persistence of the pituitary tumor. Nevertheless, in this regard, Cuny et al. [17] showed that PEG inhibits - in vitro - GH and PRL secretion in primary cultures of human GH(/PRL)-secreting tumors, without impacting on cell proliferation or viability. **However, this short-term in vitro evidence cannot explain how the effect could persist for a long time after PEG discontinuation. Moreover, the** authors explained that these findings could **apply** in vivo since the pituitary gland, which is not enveloped by the brain-blood barrier, is potentially attainable by PEG. Some indirect evidences would also suggest that PEG is able to cross the capillary wall of anterior pituitary. Indeed, a PEG analog injected in the cerebroventricular space in rats triggered a hypothalamic feedback [18]. Moreover, it is known that monoclonal antibody ipilimumab, a molecule bigger than PEG, is able to cross the capillary wall and cause hypophysitis [19]. Nevertheless, to date, the effects of PEG on the pituitary gland are unclear and the complex mechanisms of drug action still need to be elucidated.

Overall, we treated with PEG monotherapy 18 patients with acromegaly, and 8 of them were treated for more than 5 years. In our experience, remission of acromegaly after PEG withdrawal occurred in 11% of patients, **while drug's discontinuation led to the increase of IGF-1 levels in the other cases**.

In conclusion, we report, for the first time, persistent biochemical remission of acromegaly in two patients resistant to SSA, after discontinuation of long-term PEG monotherapy. Although we are aware that an extended follow-up of these patients is mandatory to rule out recurrences and we

cannot provide a clear pathophysiological explanation of the reported event, our observation could shed new light on the effects of long-term PEG treatment in acromegaly patients.

Compliance with ethical standards

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Conflict of Interest:

Salvatore Cannavò: advisory board Pfizer, advisory board Novartis.

Francesco Ferraù: research grant from Pfizer.

The other authors declare that they have no conflict of interest.

Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent:

Informed consent was obtained from all individual participants included in the study.

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Fig 1. Treatment timeline in case 1 and case 2.

OCT = Octreotide
LAN= Lanreotide

PEG= Pegvisomant

TNS = Trans-naso-sphenoidal

HIGHLIGHTS

- Pegvisomant (PEG) is used in acromegaly resistant to somatostatin analogues.
- The known action of PEG is the decrease of IGF-1 synthesis in peripheral tissues.
- Remission in patients with medical-treated acromegaly is very uncommon.
- This is the first report of acromegaly remission after long-term PEG monotherapy.
- PEG could exert unknown antitumoral effects in pituitary tumor cells.

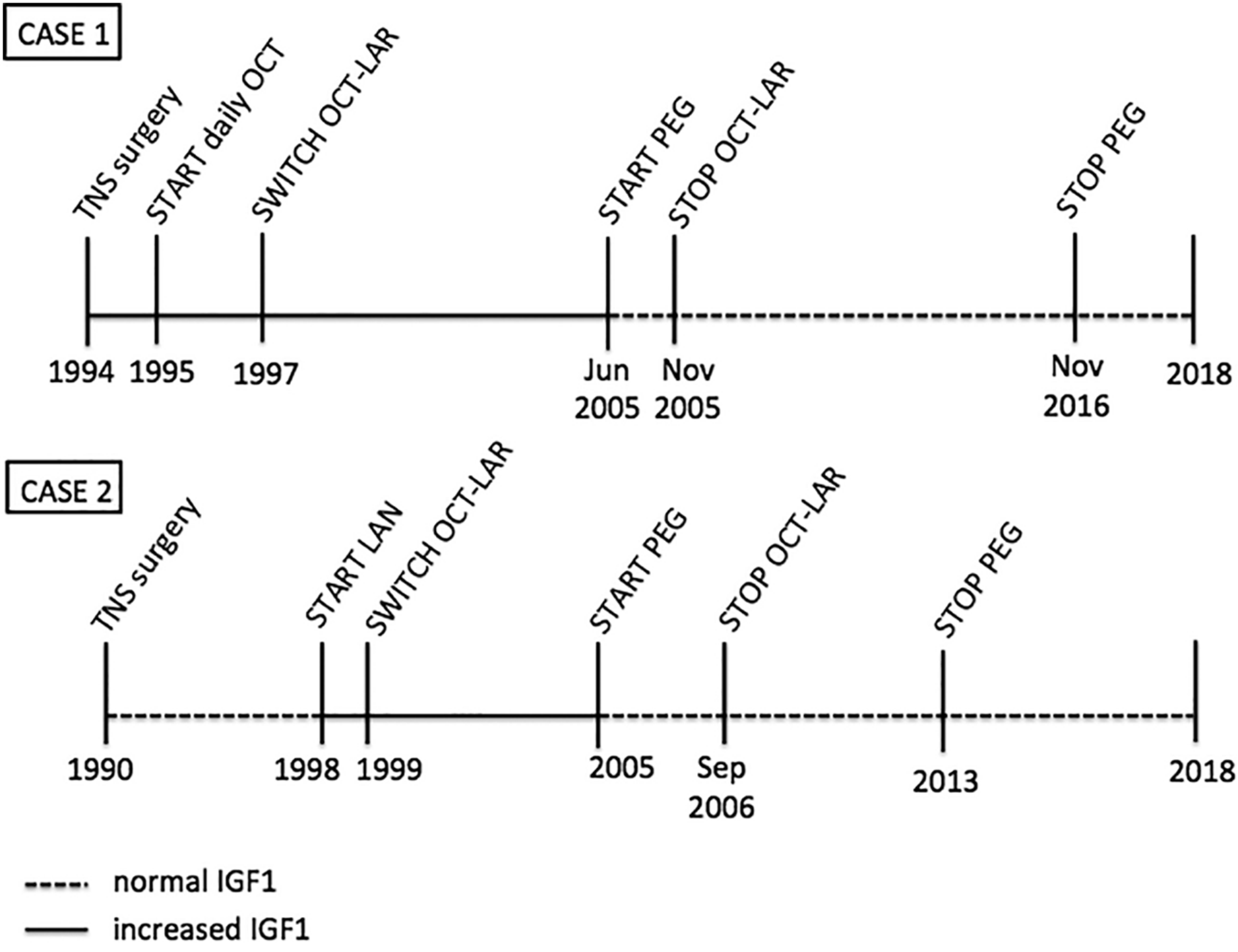
CASE 1
TNS surgery
START daily OCT
SWITCH OCT-LAR
START PEG
STOP OCT-LAR
STOP PEG
1994
1995
1997
Jun 2005
Nov 2005
Nov 2016
2018
CASE 2
TNS surgery
START LAN
SWITCH OCT-LAR
START PEG
STOP OCT-LAR
STOP PEG
1990
1998
1999
2005
Sep 2006
2013
2018
normal IGF1
increased IGF1

Figure 1