Shrinkage of pituitary adenomas with pasireotide

The value of T2-weighted signal intensity (T2WSI) of pituitary tumours on MRI in predicting tumour characteristics and response to somatostatin analogues is receiving increasing attention.[1,2] We read with interest the recent Correspondence in *The Lancet Diabetes & Endocrinology* by Eva C Coopmans and colleagues[3] regarding pasireotide long-acting release (PAS-LAR) treatment in patients with acromegaly and the relationship between increased T2WSI on MRI and stronger reductions in insulin-like growth factor-1 (IGF-1) concentrations.[3] The authors suggest that increased T2WSI reflects underlying necrosis or cystic degeneration of the adenoma and might indicate an antitumour effect of PAS-LAR. Although increased T2WSI was associated with improved hormonal control, significant decreases in tumour volume did not occur within the 36 weeks of PAS-LAR treatment, which could call into question the existence of the suggested antitumour effect.

We believe, however, that strong evidence of an antitumour effect of PAS-LAR does exist, which leads to clinically meaningful tumour regression and hormonal control in some patients who were treated long term with PAS-LAR. The best molecularly characterised form of resistant acromegaly is due to germline mutations in *AIP*, which cause tumours at a younger age that are larger and more invasive.[4] Patients with germline mutations in *AIP* also have significantly lower hormonal reductions following treatment with first-generation somatostatin analogues and rarely exhibit significant tumour shrinkage.[4] Recently, we reported a dramatic shrinkage of pituitary tumours in two patients with resistant acromegaly caused by germline mutations in *AIP*, following long-term treatment (8–11 years) with PAS-LAR.[5] In one patient, PAS-LAR treatment was even associated with disappearance of the tumour residue; no regrowth occurred more than 18 months after PAS-LAR treatment was stopped and the patient's IGF-1 concentrations remained normal. These results, along with other reports of significant tumour shrinkage and hormonal control in patients with severely resistant acromegaly with negative or unknown *AIP* mutation status, argue that PAS-LAR may indeed have an antitumour effect.[6–8]

Increased T2WSI can occur with first-generation somatostatin analogues in a minority of patients;[9,10] tumour necrosis or cystic degeneration is very rare in patients with acromegaly who receive octreotide or lanreotide. Only tissue-based pathology can confirm whether necrosis, cystic degeneration, or some other molecular change is causing the increased T2WSI in some patients receiving PAS-LAR. Nevertheless, PAS-LAR can lead to dramatic tumour regression in acromegaly, which is surely the most clinically relevant measure of any antitumour effect. The identification of genetic, molecular, or clinical characteristics that are associated with a better PAS-LAR response could assist in personalised medical treatment of acromegaly.

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1 Heck A, Ringstad G, Fougner SL, et al. Intensity of pituitary adenoma on T2-weighted magnetic resonance imaging predicts the response to octreotide treatment in newly diagnosed acromegaly. Clin Endocrinol (Oxf) 2012; 77: 72–78.

2 Potorac I, Petrossians P, Daly AF, et al. T2-weighted MRI signal predicts hormone and tumor responses to somatostatin analogs in acromegaly. *Endocr Relat Cancer* 2016; **23:** 871–81.

3 Coopmans EC, van der Lely AJ, Schneiders JJ, Neggers SJCMM. Potential antitumour activity of pasireotide on pituitary tumours in acromegaly. *Lancet Diabetes Endocrinol* 2019; **7:** 425–26.

4 Daly AF, Tichomirowa MA, Petrossians P, et al. Clinical characteristics and therapeutic responses in patients with germ-line AIP mutations and pituitary adenomas: an international collaborative study. *J Clin Endocrinol Metab* 2010; **95:** E373–83.

5 Daly A, Rostomyan L, Betea D, et al. AIP-mutated acromegaly resistant to first-generation somatostatin analogs: long-term control with pasireotide LAR in two patients. *Endocr Connect* 2019; **8:** 367–77.

6 Chiloiro S, Giampietro A, Bianchi A, et al. Acromegaly can be cured by first-line pasireotide treatment? Endocrine 2019; **64:** 196–99.

7 Amarawardena WKMG, Liyanarachchi KD, Newell-Price JDC, Ross RJM, Iacovazzo D, Debono M. Pasireotide: successful treatment of a sparsely granulated tumour in a resistant case of acromegaly. *Endocrinol Diabetes Metab Case Rep* 2017; **2017:** pii 17-0067.

8 Yamamoto R, Robert Shima K, Igawa H, et al. Impact of preoperative pasireotide therapy on invasive octreotide-resistant acromegaly. *Endocr J* 2018; **65:** 1061–67.

9 Bonneville F, Rivière L-D, Petersenn S, et al. MRI T2 signal intensity and tumor response in patients with GH-secreting pituitary macroadenoma: PRIMARYS post hoc analysis. *Eur J Endocrinol* 2018; published online Dec 1. DOI:10.1530/EJE-18-0254.

10 Potorac I, Bonneville J-F. Acromegaly. In: Bonneville J-F, Bonneville F, Cattin F, Nagi S, eds. *MRI of the pituitary gland*. Cham, Switzerland: Springer, 2016: 97–105.

Authors' reply

We thank Adrian F Daly and colleagues for their comments on our Correspondence[1] and appreciate the opportunity to further discuss our proposed antitumour activity of pasireotide long-acting release (PAS-LAR) on pituitary tumours in acromegaly. Daly and colleagues raise the point that although increased T2-weighted signal intensity (T2WSI) was associated with improved hormonal control, a significant decrease in tumour volume did not occur with nine months of PAS-LAR treatment. This could call into question the existence of the suggested antitumour effect of PAS-LAR.

We agree with Daly and colleagues that besides T2WSI, there are