Subcutaneous octreotide as a therapeutic option for refractory chronic cough: subjective response pattern and adverse effects from a retrospective single-centre case series

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To the Editor:

Refractory chronic cough (RCC) is a common and challenging clinical problem, now recognised as a hypersensitivity of the afferent vagus and its central projections. Despite thorough clinical appraisal and diagnostic tests, treatment strategies based upon the current international cough management guidelines are limited [1, 2]. For example, in the Manchester tertiary cough clinic, 78% of referrals with chronic cough were identified as RCC [3]. While hypersensitivity of the vagus may be the root pathological mechanism producing the heightened cough reflex and has inspired the development of antitussive agents such as the P2X3 receptor antagonist, gefapixant, these promising agents have yet to be widely approved by regulatory authorities [4]. The majority of patients do not respond to existing therapies such as low-dose morphine, and remain "refractory". Thus, repurposing of existing licensed medicines is an attractive option.

Three-quarters of patients with RCC exhibit disorders of oesophageal motility on high-resolution oesophageal manometry (HROM) [5]. Octreotide is a synthetic somatostatin analogue, which can help regulate gastrointestinal motility and restore normal gastrointestinal transit with its antisecretory ability. We have previously reported some preliminary data of our experience using octreotide in bronchorrhoea [6] and intractable chronic cough [7]. Both reports showed favourable effect in improving cough symptoms. Here we update our experience on new patients initiated since June 2019.

Patients in this retrospective case series were attending the Hull cough clinic, Hull University Teaching Hospitals NHS Trust (Hull, UK) and were initiated on 50 µg octreotide subcutaneous injection in a nurse-led clinic from June 2019 to December 2022. The dosage was adjusted when necessary (range from 50 to 100 µg). Medical records of all patients initiated within this time frame were reviewed. Follow-up details and treatment outcomes were categorised. Data of demographics, spirometry, HROM and patient-reported questionnaires, including Symptom Assessment Score (SAS; scoring cough frequency, intensity, wheeze, breathlessness, and sputum; maximum total score 45) and Hull Airway Reflux Questionnaire (HARQ; a verified measure of extra-oesophageal reflux), were collected and analysed.

This audit was conducted following review by the Hull University Teaching Hospitals NHS Trust clinical audit committee. Informed consent had been obtained from all patients prior to the initiation of octreotide.

Data were expressed as mean±SD. Student–Newman–Keuls test was used to make pairwise comparisons among follow-ups. Statistical analysis was conducted *via* SPSS 21.0 (Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

21 patients (20 females; mean age 61±13 years; mean body mass index 30±6 $kg \cdot m^{-2}$; mean cough duration 14±12 years) were initiated on 50 µg octreotide *s.c.* Their mean baseline forced expiratory volume in 1 s was 2 L (83.5% predicted); forced vital capacity was 3 L (95.5% pred) and fractional exhaled nitric oxide was 21±15 ppb. 16 patients had complete HROM results and oesophageal dysmotility was found in 13 out of 16, including ineffective motility in nine patients, failed contraction in three and fragmented swallow in one.

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Therapeutic antitussive effect of octreotide on intractable cough https://bit.ly/3mVMEc6

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Nine patients discontinued in 5±6 weeks post-initiation due to adverse gastrointestinal effects (n=5), no improvement (n=3) and noncompliance (n=1). One patient died, the cause of death being unrelated to the treatment. The remaining 11 (52.4%) patients self-reported cough improvement. These patients' baseline data were comparable to those of patients who discontinued octreotide (p=0.65). Their HARQ scores fell from 49±17 to 21±15 (p=0.01) and SAS fell from 30±10 to 13±11 (p=0.01) in 4 months (figure 1). Among them, two had stopped the increased dose of injection (100 µg) due to the resolution of cough at 6 and 25 weeks. Both subsequently had a recurrence of cough (at 7 and 4 months, respectively) and re-initiated on 50 µg octreotide; one discontinued in a further week due to intolerable palpitations and restlessness. Thus, 10 patients remained on octreotide treatment, with half of them prescribed the increased dosage of 100 µg to maintain the antitussive effect.

Of all patients initiated on octreotide, eight reported adverse events, six of whom experienced gastrointestinal symptoms, including stomach cramps (n=6), diarrhoea (n=5), reduced appetite (n=1) and nausea (n=1). Other adverse effects included headache (n=2), palpitations (n=1), itching legs (n=1), restlessness (n=1) and kidney pain (n=1).

In this study, we demonstrated that over half of patients with RCC who had previously failed our usual treatment strategies successfully responded to octreotide *s.c.* injections. These are patients with RCC who all scored above the upper limit of normal of 14 on the HARQ. High prevalence of oesophageal dysmotility (in >80% of patients with full HROM data) was observed. These data support our previous findings that the likelihood of gastrointestinal dysmotility increased with higher HARQ scores [5].

Octreotide has long been used in palliative care to manage symptoms and difficult-to-manage conditions caused by excessive secretions [8]. The exact mechanism of its action on RCC remains unclear. We speculate that the benefit may come through the interaction with motilin, which can improve oesophageal dysmotility and decrease airway reflux, as evidenced by the use of octreotide as a prokinetic agent [9]. In addition, the reduced mucus production in the gastrointestinal tract due to the inhibition of gastrin release from G-cells may lead to a shorter exposure of the oesophageal mucosa to refluxates (mainly gaseous and nonacidic). These consequently reduce cough by breaking the vicious cycle mediated through the gut–lung axis. Additionally, the capacity of octreotide to reduce gastric stretch may help to calm the irritated vagal nerves. Our observations build on the previously reported improvement in respiratory symptoms in patients with bronchorrhoea [6, 10, 11].

The major limitations of this report are its retrospective noncontrolled design, the absence of objective cough counting data, and the small sample size. In addition, placebo effect cannot be excluded. However, all patients in this case series had undergone multiple failed treatment strategies, which could lend credence to the significant improvement highlighted within this report.

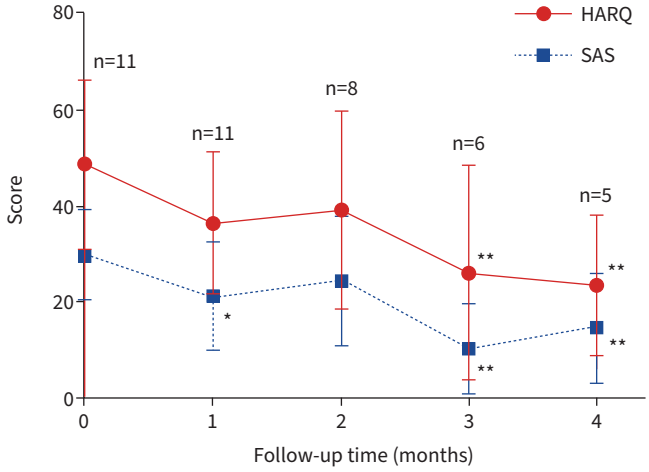

FIGURE 1 Changes over time in Hull Airway Reflux Questionnaire (HARQ) scores and Symptom Assessment Score (SAS) of patients with complete treatment. At 0 months, n=11; 1 month, n=11; 2 months, n=8 (one patient stopped the treatment due to cough improvement, and two patients lacked questionnaire data); 3 months, n=6 (two patients lacked questionnaire data); 4 months, n=5 (one patient lacked questionnaire data). Data are presented as mean±SD (within-group). *: p<0.05; **: p≤0.01 compared with baseline.

Octreotide subcutaneous injections as a treatment for RCC may be burdensome, painful, and possibly associated with adverse effects. However, we suggest that it is a treatment option in the absence of any other currently available therapy in patients with intractable cough and oesophageal dysmotility. A randomised placebo-controlled trial should be conducted to determine biomarkers to inform patient selection and to confirm or refute our findings in this disease with distressing morbidity.

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