High-dose intramuscular octreotide in patients with acromegaly inadequately controlled on conventional somatostatin analogue therapy: a randomised controlled trial

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Abstract

Objective: In acromegaly, 25–50% of patients respond inadequately to conventional long-acting somatostatin analogue (SSA) therapy. Response may be improved by increasing SSA frequency or dose. This study evaluated the biochemical efficacy and safety of high-dose octreotide in patients with acromegaly.

Design: A 24-week prospective, multicentre, randomised, open-label trial conducted from 12 December 2005 to 23 October 2007 in patients with persistently uncontrolled acromegaly despite ≥6 month conventional SSA therapy.

Methods: Patients with ≥50% reduction in GH levels during previous SSA treatment were randomised to high-dose (60 mg/28 days) or high-frequency (30 mg/21 days) octreotide i.m. injection. Primary end-points were week 12 and 24 reduction in serum IGF1 and GH from baseline. Secondary end points included IGF1 normalisation and tumour shrinkage rates, and safety/tolerability evaluations.

Results: Significantly, more patients (10 out of 11) achieved week 24 IGF1 reduction in the high-dose than the high-frequency group (8 out of 15; P < 0.05). In the high-dose group only, week-24 IGF1 values were significantly reduced (P = 0.02) versus baseline. Normalisation of IGF1 occurred only with the high-dose regimen (4/11; P = 0.02). Out of 14 patients experiencing adverse events, 5 reported drug-related gastrointestinal effects. No dose–response relationship was seen. Safety parameters were similar between treatment groups, apart from a slight decrease in HbA1c in the high-dose group only.

Conclusion: High-dose octreotide treatment is safe and effective (normalisation of IGF1 levels) in a subset of patients with active acromegaly inadequately controlled with long-term SSA. Individualised octreotide doses up to 60 mg/28 days may improve outcomes of SSA therapy.

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Introduction

Acromegaly is a rare chronic disease with elevated morbidity and mortality. Approximately, 25–50% of patients with this disease have an inadequate response to long-acting somatostatin analogues (SSAs). Current guidelines suggest switching those patients to other therapeutic modalities that are associated with higher costs and potential risks (1, 2). The pathophysiological basis of poor SSA response is unclear, but thought to be associated with tumour cell SS receptor expression and SSA-related factors such as dose and dosing intervals (3). Recent evidence has suggested that biochemical control can be improved by increasing the frequency of injection or the dose of SSA compared to recommended treatment schedules (4, 5). High-dose octreotide (Sandostatin LAR; Novartis Pharma AG) has been shown to be well tolerated in patients with neuroendocrine tumours (6).

The objective of this trial was to evaluate the safety and biochemical efficacy of high-dose (60 mg/28 days) versus high-frequency (30 mg/21 days) octreotide therapy in patients with persistently uncontrolled acromegaly despite ≥6 months’ conventional SSA therapy.
Methods

**Design overview**

This was a prospective multicentre, randomised, controlled and open-label study. Patients were enrolled from 12 December 2005 to 23 October 2007. The study duration was 25 weeks: 1 week screening and 24 weeks randomised treatment. Patients were randomised to one of two treatment arms in a 1:1 ratio. Study outcomes were measured at 12 and 24 weeks.

The protocol was approved by the ethical committee of the principal investigator (AG: Ethical Committee of Spedali Civili di Brescia on behalf of the National Health Authority) and by all local ethical committees of each participating centre. All patients gave their written informed consent to participate in the study.

The study was pre-registered at ClinicalTrials.gov under registration number NCT00372697.

**Setting and participants**

The trial was conducted in ten specialist endocrinology clinics in hospitals and universities in Italy. Patients screened for inclusion were ≥18 years old with biochemically active acromegaly, currently receiving i.m. injections of octreotide 30 mg/28 days or 20 mg/28 days (in a patient who previously refused uptitration), s.c. injections of lanreotide (Somatuline, Ipsen Biotech, Paris, France)-extended release (ER) 120 mg/28 days or i.m. injections of lanreotide-sustained release (SR) 90 mg (60+30 mg)/28 days for ≥6 months. Patients had a baseline (mean of three samples) GH level > 2 μg/l and insulin-like growth factor-1 (IGF1) levels above the upper limits of normal (ULN) for age and gender (7–9). A GH reduction of ≥50% with SSA therapy at baseline compared with pre-treatment values was also required to demonstrate SSA sensitivity.

Exclusion criteria were symptomatic cholelithiasis, unstable angina, sustained ventricular tachycardia, ventricular fibrillation or a history of acute myocardial infarction within the 3 months preceding study entry; liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis, or persistent alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase 2×ULN, total bilirubin 1.5×ULN or creatinine 1.5×ULN; radiotherapy for acromegaly; and surgery for acromegaly <3 months prior to study entry. Pregnant or lactating women or those of childbearing potential age and not practicing a medically acceptable method for birth control were also excluded.

**Randomisation and interventions**

Eligible patients were randomised to octreotide 30 mg administered every 21 days for 24 weeks (high-frequency group) or octreotide 60 mg administered every 28 days for 24 weeks (high-dose group). Octreotide 60 mg was administered as two 30 mg injections. Study regimens were chosen based on pharmacokinetic data from single dose pharmacokinetic profiles and multiple dose modelling (10).

Concomitant medication for complications of acromegaly, concomitant diseases or for treatment of adverse effects was allowed and recorded; however, concomitant use of medications capable of modifying GH or IGF1 secretion, such as dopamine agonists and pegvisomant, was not permitted.

Randomisation numbers were generated using a validated system that automated the random assignment of treatment arms to randomisation numbers in a 1:1 ratio. The system was reviewed by a Biostatistics Quality Assurance Group and locked after approval.

**Outcomes and follow-up**

The primary outcome measures were mean change in IGF1 and GH serum concentrations from baseline to week 24. The secondary outcome measures were the proportions of patients achieving IGF1 reduction ≥20% (to limit confounding effect of assay variability), IGF1 normalisation (according to pre-specified normal ranges for age), clinically relevant tumour shrinkage (tumour volume decrease of ≥20% versus baseline) and safety and tolerability evaluations.

Patients underwent evaluations at three time points during the study:

i. The baseline screening visit (T0) consisted of a complete clinical, biochemical and instrumental evaluation of acromegaly (acromegaly activity, general biochemistry, glucose homeostasis, gall bladder ultrasound, pituitary function, pituitary magnetic resonance imaging (MRI), visual field assessment, quality of life and electrocardiography). The disease activity was assessed by measuring serum GH (as an average concentration from three blood samples collected at 15-min intervals) and IGF1 concentration. Glucose homeostasis was assessed by the measurement of serum-HbA1c, fasting plasma glucose (FPG) and fasting plasma insulin (FPI). MRI was performed within 12 weeks prior to study entry according to a standardised procedure and evaluated by a neuroradiologist blinded to treatment. The adenoma size was evaluated and reported as tumour volume (mm³) calculated on the basis of the measures obtained by MRI on three axes according to the Di Chiro formula (11).

ii. The second evaluation was performed 12 weeks after starting study therapy (T1). At this point, the patients were evaluated for disease activity, general biochemistry, gall bladder ultrasound and pituitary function.

iii. The final visit occurred after 24 weeks of treatment (T2) when T0 evaluations were repeated.
Measurement of IGF1 and GH serum concentrations was centralised and performed using an automated immunometric assay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA). The interassay coefficients of variation (CV) ranges were 4.3–6.6% for GH and 4.7–8.1% for IGF1, while the intra-assay CV ranges were 3.0–4.4% for GH and 2.4–4.1 for IGF1. The sensitivity was 0.01 ng/ml for GH and 20 ng/ml for IGF1. Other biochemical parameters were measured locally using standard commercial assays. IGF1 and GH data were presented as median and range and mean ± s.d. unless otherwise specified.

**Statistical analysis**

Due to the exploratory nature of the study, sample size was not based on any statistical assumption. The safety population included all patients who received ≥1 dose of study medication. The intent-to-treat (ITT) population included all enrolled patients who received ≥1 dose of study medication and ≥1 post-baseline GH and IGF1 evaluation. The per protocol (PP) population consisted of all patients who fulfilled the inclusion and exclusion criteria and completed the treatment study phase or withdrew from the study for progression or death; or withdrew from the study for drug-related toxicity and had at least one key response evaluation.

Sign test or signed rank test (depending on the symmetry of data distribution) for paired data and the test on median were applied to GH and IGF1 median values respectively for comparison of values at the end point versus baseline and between groups. The Fisher’s exact test was used for comparison of proportions. Statistical significance was accepted at \( P < 0.05 \). Baseline characteristics were analysed for their ability to predict IGF1 normalisation.

**Role of the funding source**

Financial support for the study was provided by Novartis Farma S.p.A. The funding source was involved in the study design, data analysis and editorial support.

**Results**

**Baseline clinical characteristics and patient demographics**

In total, 42 patients with biochemically active acromegaly were screened in the ten participating centres. Seven patients had elevated GH (>2 μg/l) but normal...
IGF1 values, six had normal GH and elevated IGF1 and one patient refused to participate in the study. Therefore, 28 patients were enrolled in the study and comprised the safety population. Patient disposition throughout the study is shown in Fig. 1. Patients (14 male and 14 female) had a median age of 50.5 years (range: 27–79). Previous therapy included either octreotide (n = 24: 23 had received 30 mg/28 days and 1, randomised to the high-frequency group, had previously received 20 mg/28 days refusing up titration), lanreotide ER 120 mg/28 days (n = 3) or lanreotide SR 90 mg/28 days (n = 1), for at least 6 months prior to baseline (with the exception of the one patient treated with lanreotide SR who had received treatment for only 5 months). All enrolled patients had a mean baseline GH level ≥ 2 μg/l and IGF1 levels above the ULN for age and gender (7, 8). Table 1 shows the clinical and demographic characteristics of the 28 patients randomised to the two therapeutic schemes. Out of the 28 patients, 2 (one in each arm) were withdrawn from the study at baseline (T0) due to protocol violations. One patient had received concomitant treatment with a dopamine agonist and one patient had IGF1 levels below the ULN range when rechecked in the central laboratory. Therefore, 26 patients (11 randomised to the high-dose group and 15 to the high-frequency group) completed the study and were evaluated at T1 and T2 (the ITT and PP populations were the same). Out of these 26 patients, 13 had previously undergone neurosurgery for their GH-secreting adenoma.

**Efficacy**

**Serum IGF1 concentrations** In patients receiving high-dose octreotide, a significantly greater number of patients (10 out of 11, 91%) achieved a reduction (of any magnitude) in serum IGF1 concentration at 24 weeks than those in the high-frequency group (8 out of 15, 53%; P < 0.05). In the high-dose group, the median serum IGF1 concentration at week 24 was significantly lower (P = 0.02) than baseline (Table 2), whereas the median serum IGF1 at the end of the study in the high-frequency group was not significantly lower than baseline. The between-group difference in IGF1 median levels at week 24 was not significant. The percentage IGF1 change at the end of the study versus baseline was statistically significant in the high-dose group (−27%, P = 0.02), but not in the high-frequency group (−5%, P > 0.05). The between-group difference did not achieve statistical significance (P = 0.08). In the high-frequency group, week 12 IGF1 level decreased from baseline (P = 0.06), but week 24 IGF1 levels were unchanged relative to the 12 week time point (Table 2), whereas in the high-dose group, a progressive decrease in IGF1 levels was observed throughout the study.

**Table 1 Clinical and biochemical characteristics of patients at baseline.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>High-dose octreotide 60 mg/28 days</th>
<th>High-frequency octreotide 30 mg/21 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>51 (27–79)</td>
<td>50 (32–78)</td>
</tr>
<tr>
<td>Sex, n female/male</td>
<td>4/8</td>
<td>10/6</td>
</tr>
<tr>
<td>Duration of disease, median months (range)</td>
<td>53 (11–144)</td>
<td>42 (7–210)</td>
</tr>
<tr>
<td>Previous surgery, n yes/no</td>
<td>6/6</td>
<td>7/9</td>
</tr>
<tr>
<td>Time from surgery, median months (range)</td>
<td>34 (9–135)</td>
<td>19 (4–124)</td>
</tr>
<tr>
<td>Previous treatmenta</td>
<td>Octreotide 11 (91.7)</td>
<td>14 (87.5)</td>
</tr>
<tr>
<td></td>
<td>Lanreotide SR 1 (8.3)</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td></td>
<td>Lanreotide ER 2 (16.7)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>Duration of previous treatments, median months (interquartile range)</td>
<td>Octreotide 52 (18–76)</td>
<td>38 (17–72)</td>
</tr>
<tr>
<td></td>
<td>Lanreotide SR 28 (28–28)</td>
<td>5 (4–5)</td>
</tr>
<tr>
<td></td>
<td>Lanreotide ER 10 (5–14)</td>
<td>6 (6–6)</td>
</tr>
<tr>
<td></td>
<td>Serum GH values, median μg/l (range)</td>
<td>5.7 (2.0–14.2)</td>
</tr>
<tr>
<td></td>
<td>Serum IGF1 values, median μg/l (range)</td>
<td>469 (198–756)</td>
</tr>
<tr>
<td></td>
<td>Tumour volume, median mm3 (range)</td>
<td>377.0 (0–13 115)</td>
</tr>
<tr>
<td></td>
<td>Abnormal ECG, n (%)</td>
<td>5 (42)</td>
</tr>
<tr>
<td></td>
<td>Gallstones/sludge, n (%)</td>
<td>5 (42)</td>
</tr>
<tr>
<td></td>
<td>Serum HbA1c values, median % (range)</td>
<td>5.95 (5.4–8.2)</td>
</tr>
</tbody>
</table>

ECG, electrocardiograph; HbA1c, glycosylated haemoglobin; IGF1, insulin-like growth factor-1.

*The sum of patients is more than 12 (high-dose) and 16 (high-frequency), because two patients in the high-dose group and three patients in the high-frequency group received different treatments. The percentage is calculated on the total number of patients in each group.

Individual baseline and week 24 IGF1 data and normal age-related ranges are shown in Fig. 2. By week 24, normalisation of serum IGF1 concentration occurred significantly more frequently in the high-dose group (4 out of 11, 36%) than in the high-frequency group (0/15; P = 0.02). In the high-dose group, 5 out of 11 patients (46%) and in the high-frequency group 4 out of 15 (27%) achieved an IGF1 decrease of >20% versus baseline, and an IGF1 decrease >50% versus baseline was achieved in three patients in the high-dose group (27%) compared with one in the high-frequency group (7%).

No baseline clinical or biochemical factors (including baseline IGF1, Fig. 2) were predictive for either IGF1 normalisation or decrease in IGF1 levels in the high-dose group.

**Serum GH concentrations** Median serum GH levels at week 24 were not significantly lower versus baseline in either the high-dose group or in the high-frequency group.
group (Table 2), and between-group differences in changes in GH median levels were not significant. The percentage change in GH levels at the end of the study versus baseline was statistically significant in the high-dose group (−28%, P<0.05), but not in the high-frequency group (+6%, P>0.05); the between-group difference did not achieve statistical significance (P=0.08). In three patients in the high-dose group and in none of the high-frequency group, GH dropped below 2 μg/l by the end of the study (P=0.06).

Only 2 out of 11 (18%) patients in the high-dose group and none in the high-frequency group achieved a combined normalisation of IGF1 and GH values (P=0.17 for between-group difference).

**Tumour volume** Tumour volume did not change significantly in either group. In one patient in the high-frequency group, a modest (<20%) increase in tumour volume was observed. The proportion of patients experiencing tumour shrinkage throughout the study was comparable in the two groups (14% in the high-frequency group versus 11% in the high-dose group).

**Safety and tolerability**

Overall, 14 patients (50%) experienced an adverse event. No dose–response effect was noted. Of these, drug-related gastrointestinal (GI) adverse events were reported in 5 out of 28 patients (17.9%); all were mild to moderate and transient in nature and included diarrhoea (n=5), flatulence (n=2) and abdominal pain (n=2). In addition, one patient experienced asymptomatic coelitis deemed to be related to the study drug. The incidence of GI adverse effects was not significantly different between study groups. A slight decrease in median HbA1c was observed in patients in the high-dose group (5.65% (range 5.3–6.4) at 24 weeks versus 5.95% (5.4–8.2) at baseline), but not in the high-frequency group (5.95% (5.2–10.1) at 24 weeks versus 5.95% (5.0–8.6) at baseline). No significant changes versus baseline were observed in FPI, FPG or blood pressure. Non-significant increases in the prevalence of gallstones or gall bladder sludge were observed in both groups (high dose: 25 vs 45%; high frequency: 25 vs 44% for baseline and week 24 respectively).

**Discussion**

This randomised, controlled study shows that high-dose octreotide controls IGF1 levels in a subset of patients with acromegaly inadequately controlled with conventional SSA including maximum labelled dose regimens. From baseline to week 24, both the decrease and the percentage reduction in median IGF1 values were greater with high-dose octreotide than with high-frequency octreotide, although neither parameter achieved significance. The high proportion of patients (91%) reporting a decrease in IGF1 concentration and the 36% normalisation rate observed with high-dose octreotide, despite the relatively short-term duration of the study, indicates that patients inadequately controlled with conventional SSA doses may improve biochemically with higher doses.
Pharmacokinetic and pharmacodynamic studies in patients with acromegaly have established that current octreotide regimens do not control acromegaly optimally in all patients (4, 12). Our data suggest that high-dose octreotide may provide increased beneficial effects. In fact, by increasing octreotide dose, a sustained decrease in IGF1 can be achieved in some patients. These findings may be explained based on the hypothesis that octreotide at higher doses could exert its activity via receptor subtypes other than SSTR2 for which the molecule has a lower affinity, such as SSTR5 (13). Indeed, in vitro and in vivo studies have suggested the importance of SSTR5 in mediating GH inhibition (14, 15). Alternatively, elevated octreotide concentration may lead to SSTR2 upregulation or interfere with receptor metabolism (16).

Our results may have important clinical implications. Octreotide is the most widely used medical treatment for acromegaly; it is effective in more than 50% of patients, is well tolerated and has high compliance rates based on monthly i.m. injections (1, 7, 8, 15). However, in patients not achieving optimal IGF1 control on conventional SSA therapy, current guidelines recommend other treatment modalities (pegvisomant and/or radiosurgery in the case of post-surgical treatment or surgery for those receiving primary medical treatment) (1). Although alternative treatment modalities show higher efficacy rates than the high-dose octreotide regimen used in this study, they are generally associated with increased cost as well as potential side effects and inconvenience to the patient (9, 17–19). Therefore, our present demonstration that high-dose octreotide is effective in normalising/reducing serum IGF1 levels in some patients and was associated with a low rate of adverse events, in both the post-surgical and primary medical settings, warrants further investigation to confirm our findings and to identify those patients who benefit from octreotide dose escalation. If confirmed, high-dose octreotide therapy could be a viable option for the treatment of acromegaly in some patients uncontrolled on conventional SSA therapy. In fact, it could be suggested that before a patient that is not fully controlled on conventional dose SSA is switched to other therapeutic modalities, high-dose octreotide should be explored in patients with a proven response to these drugs, since it has more than a 35% probability of achieving normalisation of IGF1 and can decrease IGF1 in most patients (>90%). We were not able to demonstrate any predictive role of clinical and/or biochemical baseline characteristics on high-dose octreotide efficacy. It could be expected that patients with lower baseline IGF1 levels were more likely to achieve IGF1 normalisation during high-dose octreotide treatment; however, this was not the case in our study. From these data, one can infer that the observed amelioration of IGF1 control with high-dose octreotide may be more than a simple amplification effect and even patients with relatively low sensitivity to conventional SSA doses may benefit from high-dose treatment. Our study also showed a decrease in GH levels in some patients treated with high-dose octreotide. Although the percentage change in median GH levels at the end of the study versus baseline was statistically significant in the high-dose group, the median reduction in GH did not reach statistical significance and only two of the four patients with normalised IGF1 achieved GH levels <2 µg/l at study end. The greater reduction in IGF1 may be consistent with the emerging evidence of direct effects of octreotide on IGF1 (20, 21), which in our study could have been amplified with respect to conventional regimens (22) by the high doses used or by the arbitrary nature of the threshold for ‘safe’ GH levels based on mortality studies, which did not correct for possible interference of spontaneous GH secretory activity (23, 24).

Tumour shrinkage is an emerging feature of SSA treatment (25). We did not observe any substantial changes in tumour volume in either group; this may be because several patients had already undergone surgery, making neuroradiological evaluation of the sella more difficult (25). In acromegaly, volumetric and biochemical responses can be dissociated (3), particularly in patients receiving long-term SSA therapy, since shrinkage is particularly evident in the first year of treatment (25).

Generally, SSA treatment is well tolerated at conventional doses; substantially higher doses have not been studied in patients with acromegaly. Areas of potential interest are general safety, glucose metabolism and potential effects relating to the hepatobiliary tract (15, 26). In our study, no patients withdrew from the study due to clinically or biochemically relevant adverse effects. Furthermore, as previously shown in open-label studies in patients with neuroendocrine tumours (6), our study found no statistically significant adverse effects, including glucose metabolism. These data demonstrate that, at least during the study period, the tolerability profile of high-dose octreotide (60 mg/28 days) or high-frequency octreotide (30 mg/21 days) does not differ from that of the conventional maximal dose regimen.

There are some potential limitations to be considered in the interpretation of our findings. First, the number of enrolled patients was limited due to disease rarity, relatively high rate of disease control with conventional SSA treatment and stringent entry criteria. Due to the rarity of the disease, randomised controlled studies in acromegaly are difficult to undertake and are very rarely performed successfully (20, 27). The study design and patient selection based on elevated GH and IGF1 levels produced a reasonably homogeneous population. Therefore, despite the small number of patients enrolled, the IGF1 end-point, a clinically reliable parameter to evaluate acromegaly disease activity (8), was satisfied, thereby emphasising the clinical relevance of the study. The relatively small number of patients may have
prevented identification of significant predictors of high-dose octreotide efficacy and may be insufficient to assess the safety of high-dose octreotide adequately. The 24-week study period was selected as the shortest period in which sustained biochemical and clinical effects of treatment could have occurred (3). Moreover, it was deemed unethical to prolong a hitherto unproven study treatment beyond this period. It is possible that a higher proportion of patients, particularly in the high-dose group, will achieve IGF1 normalisation with longer treatment durations, as previously shown for conventional treatment (28); however, this was not investigated in this study. Another potential limitation is that the minimum 6-month duration of previous conventional SSA therapy may be too short to consider a patient inadequately controlled by conventional doses of SSA, since prolonging treatment to 4 years has been shown to increase IGF1 normalisation rates (28). However, although we considered this 6-month minimum pre-study period clinically relevant to therapeutic decision making, in terms of predicting long-term outcomes and switching to other therapeutic modalities (3, 28), most of the enrolled patients did have much longer periods of pre-study SSA treatment than 6 months. Moreover, the observed effect was not shown to be dependent on baseline IGF1.

The study did not allow the effect of frequency to be clearly differentiated from the effect of the higher dose, since the high-dose group received a total of 360 mg octreotide and the high-frequency group received only 240 mg, both over 24 weeks. Further studies with identical total doses are required to show whether the frequency of dosing may have an impact. Finally, patients with proven partial sensitivity to SSAs were selected; this choice was based on ethical considerations, assuming that patients with very low or no response to conventional regimens would have a low probability of benefitting from a high-dose SSA regimen versus other treatment modalities. However, that the observed effect was not dependent on baseline IGF1 suggests that the findings may also be relevant for patients unresponsive to conventional SSA therapy.

In conclusion, our findings suggest that high-dose octreotide appears to be well tolerated and may be effective in normalising IGF1 in a subset of patients with acromegaly previously inadequately controlled on SSA therapy. However, before individualised high-dose octreotide can be recommended in the post-surgical and primary medical settings, larger clinical studies are required to confirm the dose and frequency required for optimal biochemical effect and the clinical benefit to risk ratio, and to compare the efficacy and safety of this treatment with alternative treatment modalities including new SSAs with broader receptor-binding profile. Such studies should also attempt to identify those patients who would benefit most from the various treatment options.

Declaration of interest
Professor Andrea Giustina is a consultant for Ipsen, Italfarmaco and Novartis and has received lecture fees from Pfizer, Ipsen and Italfarmaco. The remaining authors have no conflicts of interest.

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