Effects of long-term combined treatment with somatostatin analogs and pegvisomant on cardiac structure and performance in acromegaly

Renata S. Auriemma, Ludovica F.S. Grasso, Mariano Galdiero, Claudia Pivonello, Ciro Salzano, Mariarosaria Negri, Cristina de Angelis, Annamaria Colao, Rosario Pivonello

Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Università Federico II di Napoli, Naples, Italy

OBJECTIVES

Somatostatin analogs (SA) are known to revert acromegalic cardiomyopathy mainly in young patients with short disease duration[1], whereas pegvisomant (PEG) reportedly improves cardiac structure and performance in patients resistant to SA[2]. To date, no data are available on the effects of long-term combined treatment with SA and PEG on cardiovascular complications. The current study aimed at investigating the effects of long-term SA+PEG on cardiac structure and performance in acromegaly.

METHODS

Thirty-six acromegalic patients (14 men, 22 women, aged 52.3±10.2 yrs) proven to be resistant to long-term high dose medical treatment with SA monotherapy entered the study. Resistance to SA monotherapy was defined as a serum IGF-I level of greater than 1.3 times x ULN measured 28 days after the last SA injection. After long-term SA monotherapy (range 6-156 months) octreotide LAR dose ranged 30-40 mg/28 days and lanreotide dose ranged 120-240 mg/28 days. In all patients PEG was added at the starting dose of 10 mg/day, with an overall weekly dose of 70 mg. Dose adjustment by ±10 mg/day was carried out every 3 months on the basis of IGF-I levels. Final PEG dose ranged 30-280 mg/week. Weight, body mass index (BMI), systolic (SBP) and diastolic (DBP) blood pressure, IGF-I, fasting glucose (FG), fasting insulin (FI), HOMA-IR, glycated haemoglobyn (HbA_{1c}) and lipid fractions were evaluated at diagnosis (T0), after long-term (median 36 months) SA (T1), and after 12 (T12) and 60 (T60) months of combined treatment with SA and PEG, with last follow up (LFU) being performed after a median time of 78 months (range 60-144 months). At each time point all patients underwent echocardiography to evaluate ejection fraction (EF), Left ventricular mass index (LVMi), early (E) to late or atrial (A) peak velocities ratio (E/A) and isovolumic relaxation time (IVRT). Left Ventricular (LV) hypertrophy was defined as LVMi>135 g/m^2 in men and >110 mg/m^2 in women. LV diastolic dysfunction was defined as E/A lower than 1 or 0.5 for patients younger or older than 50 yr, respectively, and/or as IVRT longer than 92 (30 yr of age), 100 (30–50 yr of age), or 105 msec (>50 yr of age). LV systolic dysfunction was defined as ejection fraction (EF) lower than 50%.

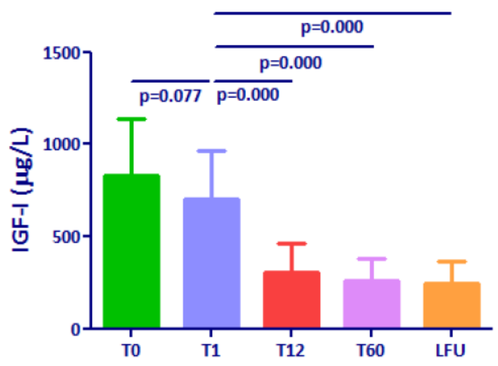

Fig. 1: IGF-I levels at study entry (T0), after long-term SA (T1), after 12 (T12) and 60 (T60) months of combined treatment with SA and PEG, and at last available follow-up (LFU).

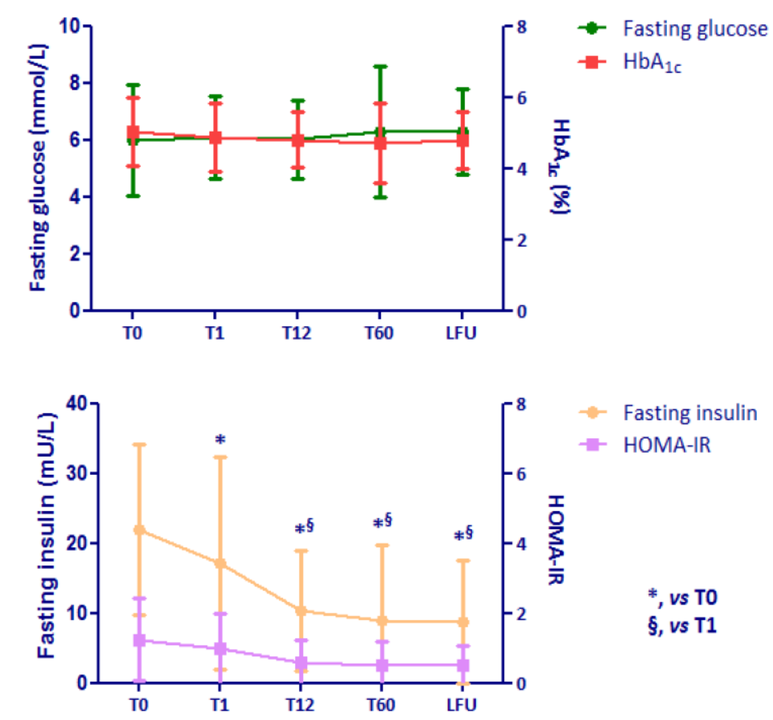

Fig. 2: Fasting glucose, HbA_{1c}, fasting insulin and HOMA-IR at study entry (T0), after long-term SA (T1), after 12 (T12) and 60 (T60) months of combined treatment with SA and PEG, and at last available follow-up (LFU).

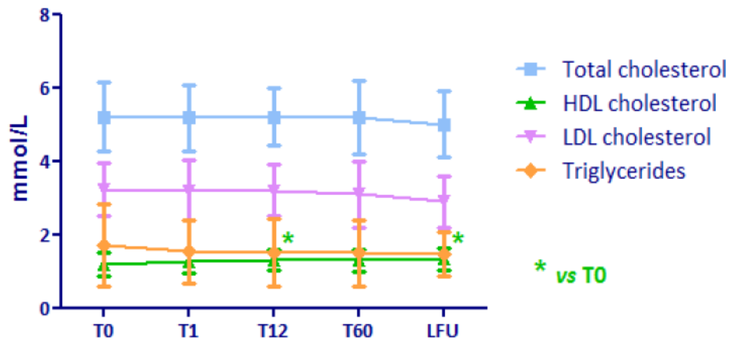

Fig. 4: Total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides at study entry (T0), after long-term SA (T1), after 12 (T12) and 60 (T60) months of combined treatment with SA and PEG, and at last available follow-up (LFU).

RESULTS

At T1, SA induced a slight but not significant decrease in IGF-I (p=0.077, *Fig. 1*), whereas FI (p=0.004, *Fig. 2*), HOMA-IR (p=0.013, *Fig. 2*), EF (p=0.013, *Fig. 3*), E/A (p=0.001, *Fig. 3*) and IVRT (p=0.000, *Fig. 3*) significantly improved. At T12 IGF-I (p=0.000, *Fig. 1*), FI (p=0.001, *Fig. 2*), HOMA-IR (p=0.000, *Fig. 2*), HDL (p=0.05, *Fig. 4*), EF (p=0.002, *Fig. 3*), LVMi (p=0.000, *Fig. 3*), E/A (p=0.006, *Fig. 3)* and IVRT (p=0.000, *Fig. 3*) significantly improved compared to T0, with FI (p=0.001, *Fig. 2*), HOMA-IR (p=0.000, *Fig. 2*), LVMi (p=0.000, *Fig. 3)* and E/A (p=0.006, *Fig. 3*) further improving compared to T1. At T60, IGF-I (p=0.000, *Fig. 1*), FI (p=0.001, *Fig. 2*), HOMA-IR (p=0.000, *Fig. 2*), EF (p=0.018, *Fig. 3*), LVMi (p=0.002, *Fig. 3*), E/A (p=0.049, *Fig. 3*) and IVRT (p=0.014, *Fig. 3)* significantly ameliorated compared to T0, with IGF-I (p=0.000, *Fig. 1*), FI (p=0.027, *Fig. 2*), HOMA-IR (p=0.009, *Fig. 3*), LVMi (p=0.049, *Fig. 3*) and E/A (p=0.005, *Fig. 3*) further improving compared to T1. MetS prevalence significantly reduced as compared to T1 (p=0.034). At LFU IGF-I normalized in 83.3% ; IGF-I (p=0.000, *Fig, 1*), FI (p=0.000, *Fig. 2*), HOMA-IR (p=0.000, *Fig. 2*), HDL (p=0.031, *Fig. 4*), EF (p=0.035), LVMi (p=0.000, *Fig. 3*), E/A (p=0.02, *Fig. 3*) and IVRT (p=0.001, *Fig. 3*) significantly improved compared to T0, with IGF-I (p=0.000, *Fig. 1*), FI (p=0.000, *Fig. 2*), HOMA-IR (p=0.000, *Fig.2*), LVMi (p=0.000, *Fig. 3*) and E/A (p=0.005, *Fig. 3*) further ameliorating as comaperd to T1. MetS prevalence significantly reduced as compared to T1 (36.1%, p=0.034). PEG dose significantly correlated with LVMi at T12 (r=0.575, p=0.000, *Fig. 5*) and T60 (r=0.403, p=0.037, *Fig. 5*). At multiple regression analysis, PEG dose was the best predictive factor of LVMi (t=2.8, p=0.001) at T12, and of EF (t=2.59, p=0.021) and of ΔLVMi (t=2.79, p=0.01) at T60.

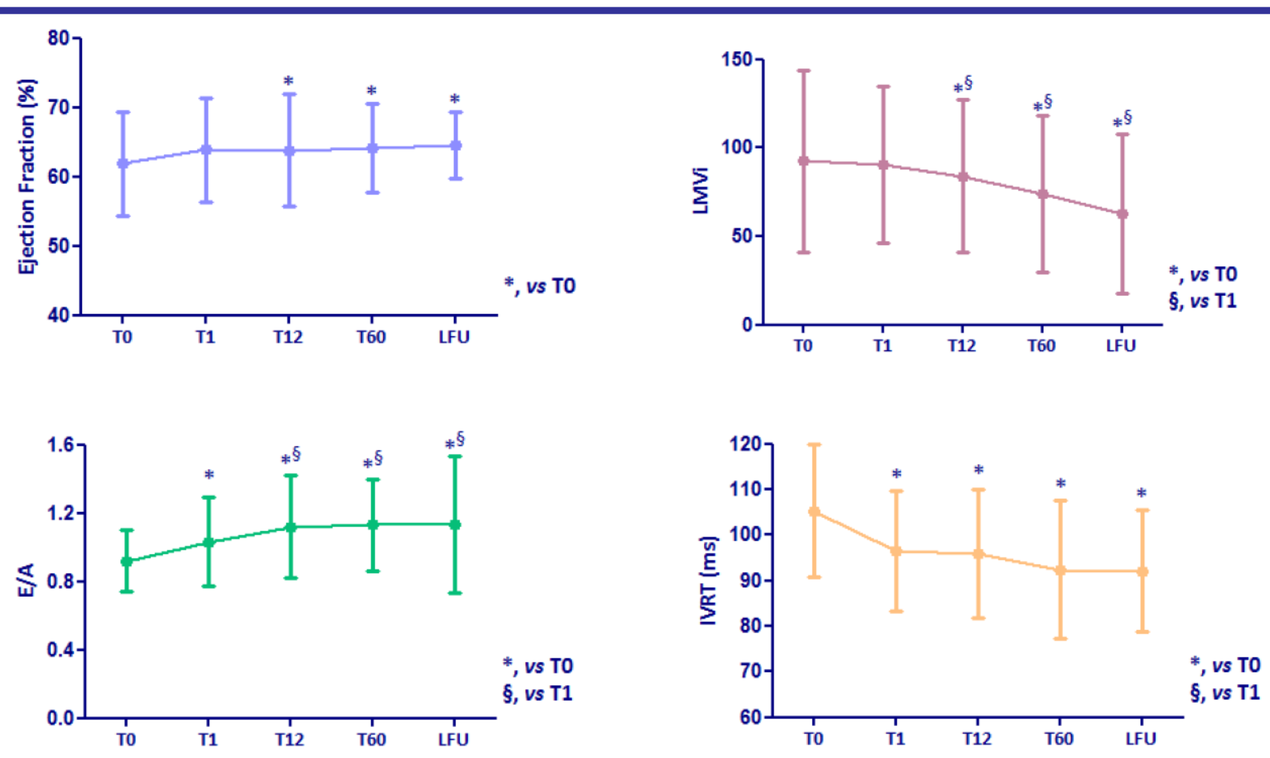

Fig. :3 Ejection fraction, LVMi, E/A and IVRT at study entry (T0), after long-term SA (T1), after 12 (T12) and 60 (T60) months of combined treatment with SA and PEG, and at last available follow-up (LFU).

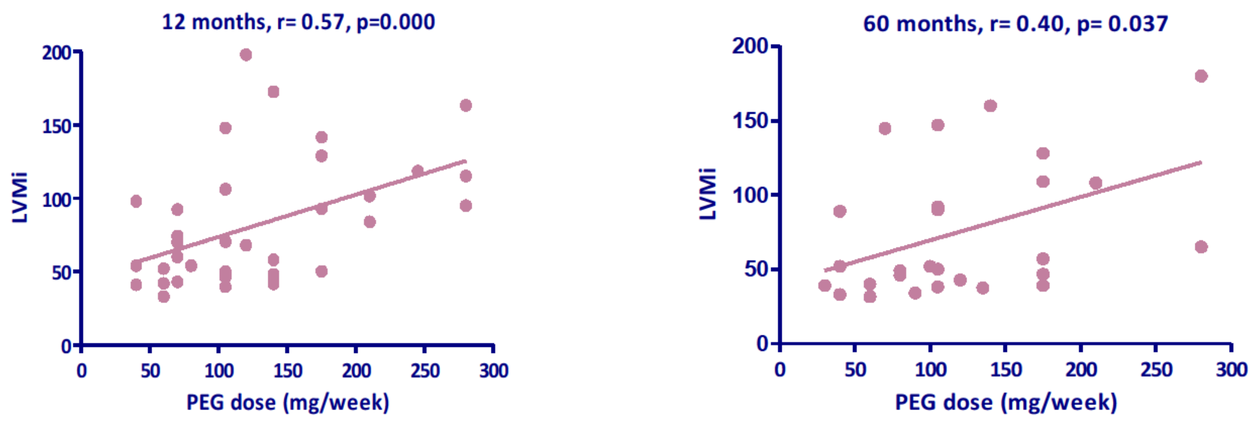

Fig. 5: Correlation between LVMi and PEG dose at 12 (T12) and 60 (T60) months of combined treatment with SA and PEG.

CONCLUSIONS

The results of the current study demonstrate that long-term PEG addition to SA improves cardiac structure and performance, particularly diastolic dysfunction, in acromegalic patients resistant to SA, therefore representing a valid therapeutic strategy in acromegalic patients with left ventricular hypertrophy and diastolic dysfunction.

References

1. Colao A, *et al* 2003 Reversal of acromegalic cardiomyopathy in young but not in middle-aged patients after 12 months of treatment with the depot long-acting somatostatin analogue octreotide. Clin Endocrinol 58: 169–176
2. Pivonello R, *et al*. 2007 Treatment with growth hormone receptor antagonist in acromegaly: effect on cardiac structure and performance. J Clin Endocrinol Matab, Feb;92(2):476-82

17 ECE
8--GP-19
Pituitary basic and neuroendocrinology
ROSARIO PIVONELLO
DOI: 10.3252/pso.eu.17ece.2015
Poster presented at: ECE2015 16–20 May 2015 DUBLIN, IRELAND 17th EUROPEAN CONGRESS OF ENDOCRINOLOGY