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ORIGINAL ARTICLE

How to improve effectiveness of pegvisomant treatment in acromegalic patients

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Abstract
Purpose Pegvisomant (PEGV) treatment in acromegaly patients resistant to somatostatin analogues is less effective in the real life than in clinical trials. This is a multicenter, observational, retrospective, longitudinal study. The aim was to detect characteristics which improve long-term PEGV effectiveness.
Methods 87 acromegalic patients treated with PEGV have been enrolled in seven referral Italian centres. PEGV was administered for up to 4 years, at doses up titrated until IGF-1 normalization or to ≥ 30 mg/day. The rate of patients who reached IGF-1 normalization at last visit has been calculated.
Results IGF-1 was normalized in 75.9% of patients after 1 year and in 89.6% at last visit. Disease control was associated with lower baseline GH, IGF-1 and IGF-1 xULN and was more frequent when baseline IGF-1 was < 2.7 × ULN ($p < 0.02$). PEGV dose was dependent on baseline IGF-1 > 2.7 × ULN ($p < 0.05$) and doses > 1.0 mg/BMI/day were administered more frequently when baseline IGF-1 was > 2.0 × ULN ($p = 0.03$). PEGV resistance was associated with higher BMI ($p = 0.006$) and was more frequent when BMI was > 30 kg/m^2 ($p = 0.07$). There were no significant differences between patients treated with monotherapy or combined treatment. IGF-1 normalization, PEGV dose and rate of associated treatment were similar between males and females. PEGV effectiveness was independent from previous management. Diabetic patients needed higher doses of PEGV than non-diabetic ones.
Conclusions PEGV effectiveness improves when up titration is appropriate. Higher PEGV doses at start and a more rapid up-titration are necessary in patients with obesity and/or IGF-1 > 2.7 × ULN.

Keywords Acromegaly · Pegvisomant · IGF-1 · Pituitary · Resistance

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Introduction

Acromegaly is a rare disease due to the excess of GH produced, in almost all cases, by a pituitary tumour [1, 2]. According to the most recent guidelines, neurosurgery approach is considered the treatment of choice and is recommended at least in patients with intrasellar microadenomas, non-invasive macroadenomas or visual impairment [3]. Nonetheless, the cure rate of surgery is inversely related to the tumour size and serum GH levels [4]. For this reason,

medical management is mandatory in patients not cured by surgery, but it is also preferred in patients with poor surgical prognosis. First line medical treatment is usually represented by somatostatin analogues (SSa), Octreotide or Lanreotide, that are able to normalize serum GH and IGF-1 levels in about 23–25% of patients and shrink the pituitary tumour in about 30–40% of cases [5–7]. The most advanced radiosurgery techniques could be useful in several cases with resistant acromegaly, but the risk of hypopituitarism and cerebrovascular events is very high [4].

When the SSa fail to control acromegaly, GH-receptor antagonist Pegvisomant (PEGV) is an alternative choice for the treatment of acromegaly [5]. Indeed, PEGV is indicated in all patients who are resistant or intolerant to other pharmacological treatments. They account for more than 20% of all acromegalic patients [8]. PEGV treatment is safe but can lead to essentially two adverse events: lipohypertrophy on the injection site and hepatotoxicity [9]. Liver toxicity can be observed above all in patients with multi-therapies or previous episodes of liver disease [10]. Several observational studies showed that PEGV is effective in less than seventy percent of acromegalic patients, despite previous clinical trials reported higher efficacy rate [8, 11–15]. It has been proposed that an inadequate dose titration, poor compliance to daily injections, suboptimal selection of patients or technical problems related to IGF-1 assay could justify a lower effectiveness of PEGV treatment in real-life experiences, while a true ''biochemical resistance'' has not been ruled out yet [8]. At present, factors associated with a better outcome of PEGV therapy are not well known, despite some studies reported that younger subjects, women, diabetic and/or non-irradiated patients need higher doses of the drug or are less responders to the treatment [16, 17]. However, the limitation of most studies is the sub-optimal dose titration of PEGV in many patients and the cross-sectional design of the studies.

In this collaborative study, we investigated factors and patients' characteristics associated with the effectiveness of long-term PEGV treatment in a group of acromegalic patients treated with appropriate dose titration of the drug and longitudinally evaluated, in order to suggest the correct approach to treatment of patients with resistant acromegaly.

Patients and methods

Patients

Overall, 135 SSa-resistant acromegalic patients were treated with PEGV by seven endocrinological Italian units during a 8-year period. Among them, 87 patients (41 males, mean age 47.9 ± 13.7 years) have been enrolled in this study, while 48 cases were excluded because of being treated with PEGV for less than 12 months (no. 8), the dose-titration of PEGV was still inadequate at last visit (no. 28), or they had been enrolled in previous clinical trials (no. 12). The length between the diagnosis of acromegaly and PEGV start was 9.6 ± 7.9 years, during which the patients underwent transsphenoidal surgery (no. 52), radiotherapy (no. 22) and/or SSa (all patients). The duration of PEGV treatment was 35.1 ± 14.2 months (range 12-48 months). In 41 patients PEGV was associated with SSa during the study period. Patients have been longitudinally evaluated from the start of PEGV treatment to the last visit. Twenty-four out of 87 patients were not enrolled in previous retrospective, cross-sectional studies [17, 18].

Methods

This is a non-interventional, retrospective, longitudinal, multicentre study. In all patients, acromegaly was diagnosed according to the most recent guidelines, and resistance was defined according to the last consensus statements [5, 19, 20]. Acromegaly has been defined "controlled by PEGV" when IGF-1 felt $\leq 1 \times$ ULN value during treatment. In this study serum IGF-1 measurement was not centralized, but the assay was performed in all patients with the same commercial kit (Immulite 1000 Immunoassay System, SIEMENS). PEGV dose is expressed as mg/day and as mg/BMI/day. Pituitary imaging was evaluated in all patients before PEGV start, after 6 months of treatment and every year by contrast-enhanced 1.5 Tesla MRI. An informed, written consent has been obtained from all patients.

Statistical analysis

Numerical data are expressed as mean ± SD and categorical variables as number and percentage. p values were considered significant at a level of < 0.05. The non-parametric Mann-Whitney U Test has been used to evaluate IGF-1 levels and IGF-1 $\times$ ULN values, which did not present normal distribution as verified by Kolmogorov–Smirnov test. The value of 1.0 mg/BMI/day PEGV dose was identified as the cut-off used for statistical analysis. A multivariate logistic regression (stepwise method) has been used in order to evaluate association between patient characteristics and treatment outcomes.

Results

The characteristics of the 87 acromegalic patients enrolled in the study are shown in Table 1.

PEGV treatment, alone or in combination with SSa, induced IGF-1 normalization in 66 out of 87 cases (75.9%) at the end of the 1st year, in 53/69 (76.8%) at the end of

Table 1 General features of the 87 acromegalic patients at baseline

No. of patients	87
Gender (M/F)	41/46
Mean age (years)	47.9 ± 13.7
Tumour size (Macro/microadenoma) no.	69/18
Hypersecretion of other hormones no.	8 (PRL no. 7, TSH no. 1)
GH at T^0 (ng/ml)	10.5 ± 12.8
IGF-1 at T^0 (ng/ml)	614.1 ± 304.8
IGF-1 xULN at T^0	2.1 ± 0.9
BMI at T^0 (kg/m^2)	28.1 ± 0.5
Treatment with SSa	39 (44.8%)

T^0 PEGV start, *SSa* somatostatin analogues

the 2nd year, in 40/54 (74.1%) at the end of the 3rd year, in 31/37 (83.8%) at the end of the 4th year and in 78/87 patients (89.6%) at last visit, overall (Fig. 1). The data analysis was performed on a number of cases decreasing year by year because not all patients completed the 4-year observation. None of them was operated/irradiated, lost to the follow-up or died during the study period. Treatment caused significant decrease of serum IGF-1 levels and IGF-1 × ULN values in both controlled and uncontrolled patients (Table 2). Serum IGF-1 levels and IGF-1 × ULN values were significantly higher in uncontrolled than in controlled cases, both at baseline ($p < 0.05$ and $p < 0.05$, respectively) and at last visit ($p < 0.05$ and $p < 0.05$, respectively) (Table 2). Disease control was more frequent in patients with baseline IGF-1 < 2.7 × ULN values ($p = 0.005$). Linear regression analysis demonstrated that acromegaly control was associated with lower serum GH ($p = 0.05$), IGF-1 levels ($p < 0.05$) and IGF-1 × ULN ($p < 0.01$) values at baseline.

PEGV administration was started at a daily dose of 10 mg in 82 patients, of 15 mg in two cases and at the dose of 10 mg for 6 days a week in other three cases. Overall, the mean PEGV daily dose was higher at last visit than at start ($p < 0.02$). Dose was significantly dependent on baseline IGF-1 × ULN when values were > 2.7 × ULN ($p < 0.05$). Moreover, both mean PEGV mg/day dose and mean PEGV mg/BMI/day were higher in the uncontrolled than in the controlled patients at last visit ($p < 0.02$) (Table 2). The probability of using PEGV daily doses > 1.0 mg/BMI was six times higher in patients with IGF-1 > 2.0 × ULN values ($p = 0.03$, OR 5.935). At baseline, PEGV was associated with SSa (Octreotide LAR 30 mg or Lanreotide 120 mg every 28 days) in 39 patients, and 30 of them continued this association until the last visit. In other two cases, controlled at the last visit, SSa were associated 3 years after PEGV start. At last visit, 30 out of 78 patients with controlled and 2 out of 9 cases with uncontrolled disease were treated with PEGV and SSa (38.5 vs. 22.2%, *p* NS) (Table 2). The rate of disease control was similar between patients in monotherapy or combined treatment (48/55 and 30/32, respectively; *p* NS). Moreover, mean PEGV dose was similar between patients treated by monotherapy or by association in the controlled group (15.3 ± 5.6 vs. 15.0 ± 6.9 mg/day, *p* NS), while this comparison was not applicable in the uncontrolled one due to the small patients' cohort.

Concerning the maximum PEGV doses, seven patients were treated with 30 mg/day at the end of the first year, seven with 30 mg/day at the end of the second year, seven with 30 mg and two with 40 mg daily at the end of the third year, and seven with 30 mg and one with 40 mg daily at the end of the fourth year of observation. Overall, 13

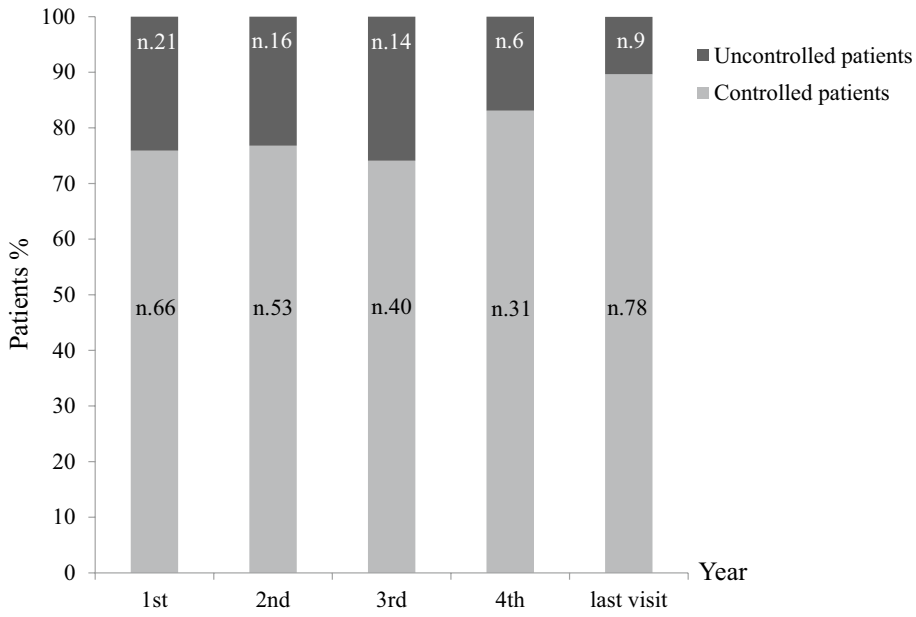

Fig. 1 Number of patients with controlled and uncontrolled disease at the end of each year during PEGV therapy

Table 2 Clinical, biochemical and radiological characteristics of acromegalic patients with controlled and uncontrolled disease

	Controlled patients	Uncontrolled patients	*P*
Patients no.	78	9	
Male gender (no.)	36	5	NS
Tumour size (M/m) no.	64 (82.0%)/14	5 (55.5%)/4	NS
BMI at T^0 (Kg/m^2)	27.4 ± 4.5	32.3 ± 6.3	**< 0.05**
GH at T^0 (ng/ml)	9.6 ± 11.4	16.5 ± 20.5	NS
IGF-1 at T^0 (ng/ml)	593.1 ± 284.2	867.7 ± 405.1	**< 0.05**
IGF-1 × ULN at T^0	2.0 ± 1.8	3.0 ± 1.3	**< 0.05**
PEGV starting dose	10.1 ± 0.8	10.0 ± 0.0	NS
SSa at T^0 (no.)	35 (44.9%)	4 (44.4%)	NS
Months of PEGV	39.8 ± 22.5	41.7 ± 25.3	NS
PEGV mean daily dose at T^1 (mg)	15.1 ± 6.1	31.2 ± 3.5	**< 0.02**
PEGV dose increase	< 0.05	< 0.05	
PEGV dose/BMI at T^1 (mg/die)	0.5 ± 0.2	0.9 ± 0.1	**< 0.02**
SSa at T^1 (no.)	30 (38.5%)	2 (22.2%)	NS
IGF-1 at T^1 (ng/ml)	195.4 ± 62.3	457.9 ± 250.9	**< 0.05**
IGF-1 × ULN at T^1	0.7 ± 0.2	1.9 ± 1.1	**< 0.05**
IGF-1 reduction (ng/ml)	< 0.02	< 0.05	NS
IGF-1 × ULN reduction	< 0.02	< 0.05	NS

T^0 PEGV start, *SSa* somatostatin analogues, T^l last visit

Table 3 Clinical and biochemical differences of male and female patients during PEGV treatment

	Males	Females	*p*
Patients no.	41	46	
Disease control at T^1	36 (87.8%)	42 (91.3%)	NS
IGF-1 at T^1 (ng/ml)	243.05 ± 147.7	204.3 ± 85.8	**NS (0.07)**
IGF-1 × ULN at T^1	0.9 ± 0.6	0.8 ± 0.3	**< 0.05**
PEGV mean daily dose	17.5 ± 7.8	16.5 ± 8.1	NS
SSa association no.	13	19	NS

T^l last visit, *SSa* somatostatin analogues

patients (6F/7 M) were treated with PEGV daily dose of 30 mg (no. 11) or 40 mg (no.2), at last evaluation.

Patients with higher BMI showed a lower probability of reaching disease control ($p = 0.006$). Indeed, IGF-1 normalization was more frequent in patients with BMI < 30 kg/m^2 ($p = 0.07$). Linear regression analysis demonstrated that acromegaly control was associated with lower BMI at baseline ($p < 0.01$) and at last evaluation ($p < 0.01$).

According to gender, the percentages of disease control, the mean PEGV dose and the rate of patients managed with associated treatment were similar (*p* NS) (Table 3). At last visit, serum IGF-1 × ULN values, but not IGF-1 levels, were significantly lower in females than in males (Table 3). Only 17 out of 47 women were ≤ 45 years old at last visit.

Before PEGV start, 52 out of 87 patients had undergone TNS and then had been treated with SSa, 22 had undergone TNS followed by SSa treatment and radiotherapy (RX), and 13 had been treated only with SSa. At last visit, the rates of disease control were not significantly different among these three groups (*p* NS) (Table 4). On the basis of the multivariate analysis, disease control was not associated with a specific previous management, while it was significantly associated with lower GH levels (*p* 0.05) and IGF-1 × ULN ($p < 0.05$) at baseline and BMI at baseline ($p < 0.02$) and at last evaluation ($p < 0.02$) only in the first group.

Sixteen out of the 87 patients were affected by type 2 diabetes and treated with oral antidiabetic agents and/or insulin. At last visit, acromegaly was controlled by PEGV in 14 of them and in 64 out of the other 71 non-diabetic patients (87.5 vs. 90.1%, *p* NS). The PEGV doses were higher, but not significantly, in diabetic than in non-diabetic patients (17.7 ± 7.03 vs. 16.7 ± 8.2 mg/die, respectively, *p* NS).

Pituitary MRI did not show clinically relevant changes of tumour size in all cases. A slight increase of AST and ALT and lipodistrophy, localized in the injection site, were evident in five and in two cases, respectively.

Discussion

Our study suggests that only 10% of acromegalic patients are resistant to PEGV if dose titration is appropriate. Indeed, the disease was controlled in 74–77% of cases during the first years of treatment, and up to 90% at last visit. This percentage is dramatically higher than in other studies performed in a real-life setting [11, 21–23]. In the paper of van der Lely et al. [11], reporting the results of global

Table 4 Characteristics of patients divided into three groups on the basis of the previous management (before PEGV start)

	Group A	Group B	Group C	*p*
Patient no.	52	22	13	
Previous treatments	Tx + SSa	Tx + SSa + Rx	SSa	
Gender M/F (males %)	22/30 (42.3%)	11/11 (50%)	8/5 (61.5%)	NS
Mean age at diagnosis (year)	37.5 ± 13.1	39.4 ± 12.2	49.5 ± 17.7[a]	**< 0.05**
macro/microadenomaM/m (M %)	42/10 (80.7%)	20/2 (90.9%)	7/6 (53.8)[a]	**< 0.05**
Active disease duration (years)	8.7 ± 8.3	14 ± 7.6[b]	6.3 ± 4.6	**< 0.02**
GH (T^0) ng/ml	13.3 ± 15.2[c]	7.1 ± 7.3	5.6 ± 4.9	**< 0.02**
IGF-1 (T^0) ng/ml	669.3 ± 345.9[c]	558.1 ± 214.7	490.9 ± 187.9	**0.05**
IGF-1 (T^0) xULN	2.2 ± 1.0	2.1 ± 0.8	2.0 ± 0.7	NS
BMI at T^0 (kg/m^2)	27.9 ± 5.9	28.9 ± 3.4	27.7 ± 3.7	NS
Mean starting dose PEGV (mg/day)	10.1 ± 0.7	10.2 ± 1.1	9.7 ± 0.5[d]	**0.05**
Disease control at T^1 (no.)	46	20	12	NS

Tx Neurosurgery, *SSa* Somatostatin analogues, *Rx*, Radiotherapy, T^0 PEGV start, T^1 last visit

[a]Group C versus A and B

[b]Group B versus A and C

[c]Group A versus B and C

[d]Group C versus B

Acrostudy, IGF-1 levels were normalized in 63% of cases after 5 years of treatment [11]. More recently, this percentage of effectiveness has been confirmed by Chanson et al. [22] in the French arm of the same registry, while it was slightly higher in the Spanish group of patients [22, 23]. In the present study, 94% of patients started PEGV treatment at a daily dose of 10 mg, which was increased progressively until IGF-1 normalization or the achievement of a dose of at least 30 mg/day. The mean dose administered at last visit in uncontrolled patients was significantly higher than in the controlled ones. In other studies, mean PEGV doses administered in uncontrolled patients were similar to or slightly higher than doses administered to controlled cases during all the treatment period and the majority of apparently resistant patients were probably treated with suboptimal dosages [11, 21–23]. However, in a previous study reporting the Italian Acrostudy experience we demonstrated that only 57% of cases treated by skilled centres reached disease control at last visit, despite the mean PEGV dose was significantly higher in uncontrolled compared to controlled patients [18].

Our study demonstrates that obesity is a predictor of PEGV resistance, both at treatment start or at the last evaluation. Indeed, IGF-1 normalization was more frequent in patients with BMI < 30 kg/m^2. The relationship between PEGV responsiveness and body weight or BMI was previously evaluated by us and other authors [17, 24]. In this study we have preferred to analyse the role of BMI instead of body weight because the former is associated with the metabolic status better than the latter and involves factors such as drug absorption, distribution, clearance and interaction with ghrelin and leptin which can influence its effectiveness [25]. We also demonstrated that a better response to PEGV is associated with lower serum GH and IGF-1 levels and IGF-1 × ULN values at baseline, confirming several reports [17, 26, 27]. In addition, we suggest that IGF-1 levels under 2.7 × ULN at baseline identify a group of patients with higher probability to reach disease control. On the contrary, patients with IGF-1 over 2.0 × ULN values have a six times higher probability to need PEGV doses higher than 1.0 mg/BMI/day. Therefore, we can argue that PEGV should be started at higher doses and titration should be performed faster when IGF-1 levels are over this cut-off at baseline. This indication is in accordance with old and recent guidelines which recommend the use of higher doses of PEGV in patients with a more aggressive disease or obesity [8, 27, 28].

In almost 37% of our patients PEGV was associated with SSa from the start to the last visit. The percentage of patients who controlled the disease was similar in the group treated with combined therapy or with PEGV alone. Indeed, IGF-1 normalization was reached in almost 94% of the former and in 88% of the latter one. Our data are in accordance with those of Trainer et al. who, however, reported IGF-1 normalization only in 56% of patients treated with monotherapy and in 62% of those treated with combined therapy [29]. Recently, Bianchi et al. [30] suggested that combined treatment was less effective than monotherapy, but this result was probably due to the fact that more aggressive cases were enrolled in the group treated with the first option [30]. In the majority of our cases the combined treatment was preferred to monotherapy because of the persistence of a pituitary tumour remnant which was at risk of increasing in size or because the patient refused surgery. Nevertheless, MRI performed

over the time did not demonstrated relevant changes of tumour volume in any case. These data, as well as those about other adverse events, are in line with other previous studies [17, 18, 21, 23, 31].

In our study the effectiveness of PEGV was not influenced by gender, despite IGF-1 levels were lower in females at last visit. This result is indirectly in accordance with a previous study published by us, which demonstrated that females need a lower mean PEGV dose than males, while Marazuela et al. showed the opposite [16, 17]. Other authors did not find differences in IGF-1 levels between males and females at the end of treatment, but women required higher PEG-V dose to control acromegaly [26].

We have evaluated also the role of the previous management on the effectiveness of PEGV. The percentages of controlled patients, as well as the mean PEGV doses, were similar regardless of the previous treatment performed. Other authors showed that previous radiotherapy was associated with a better response or with the requirement of lower doses of PEGV [16, 26]. In our experience, PEGV effectiveness is associated with lower GH levels, IGF-1 × ULN values and BMI only in the group of patients treated with surgery and somatostatin analogues, while these associations are lost in other groups treated also with radiotherapy or with drugs alone. No previous data are available on this topic, which in our opinion represents a crucial point because up to a quarter of patients treated with PEGV were not previously operated [17].

Our study confirms that disease's control needs higher PEGV doses in diabetic patients than in non-diabetic ones, despite the difference was not significant. The relative resistance to PEGV in patients with obesity and/or diabetes mellitus was also reported by other authors [32]. It is probably related to the effects of high portal insulin concentration on the availability of hepatic GH receptors. Indeed, several years ago Leung et al. [33] demonstrated that insulin increases the total cellular content of hepatic GH receptors in a concentration-dependent manner, by up-regulating receptor mRNA expression in a human hepatoma cell line HuH7 model [33]. Insulin also inhibits surface translocation of GH receptor, but this effect is evident only at very high insulin concentration [33]. On the contrary, the percentage of controlled patients was similar in the two groups [34]. This suggestion is in contrast with previous evidences probably because we evaluated only treated-to-target patients.

This study has some limitations, concerning for instance the multicenter, retrospective design and the non-centralized IGF-1 assay. Moreover, some information about patient management is lacking, e.g. the reasons of PEGV doses > 10 mg/day at start in some cases or the length of dose up-titration. Nevertheless, this study is one of the few which report on a longitudinal analysis of biochemical parameters during real-life, appropriately up-titrated PEGV treatment.

In conclusion, our study suggests that appropriate PEGV titration allows IGF-1 normalization in up to 90% of acromegalic patients, but obesity and IGF-1 values > 2.7 × ULN are predictors of resistance to the drug. In addition, patients with IGF-1 values > 2.0 × ULN have a six-times higher probability to need PEGV daily doses higher than 1.0 mg/BMI, so patients with a more aggressive disease should start therapy at higher doses and titration should be faster.

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Compliance with ethical standards

Conflict of interest SP, AA, MRA, GA, AB, MCZ, LDM, EG, FM, CM and LT nothing to disclosure. SG, PM consultants for Pfizer. AG consultant for IPSEN, Novartis and Pfizer. SC consultant for Pfizer, Novartis and Italfarmaco, MR consultant for Italfarmaco.

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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