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EDITORIAL

Optimal use of pegvisomant in acromegaly: are we getting there?

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Several consensus statements on the medical management of acromegaly are available [1–4]. In fact, acromegaly due to growth hormone (GH)-secreting pituitary adenoma although quite rare is a serious clinical condition due to a concomitance of factors: surprisingly persistent diagnostic delay which leads to high prevalence of macroadenomas at diagnosis and in turn to difficult surgical radicality [5]; severe complications affecting multiple GH/insulin-like growth factor 1 (IGF-1) target organs with impaired quality of life and increased mortality risk [6–11]; biological aggressiveness/invasiveness of the neoplasm [12] and variability of the GH and IGF-1 responses to medical treatment [1–3]. In fact, use as recommended of conventional treatment tools (surgery, somatostatin receptor ligands—SRLs, and even radiotherapy) may lead to "cure" of the disease [13–16] which, however, despite their appropriate and also combined use may not be adequately controlled in a relevant part of acromegaly patients [17, 18]. Therefore, the advent of pegvisomant, which acts at the tissue level blocking the GH receptor and GH action, in the clinical scenario more than a decade ago has been surrounded by many hopes and expectations for a potential global control of acromegaly [19]. However, despite accumulating clinical experience and ad hoc designed surveillance studies specific guidelines for pegvisomant in acromegaly are limited [20], and its use appears still not always to be optimal. Why? In this issue of Endocrine, Grottoli et al. report data from acromegaly patients who have been included in the Italian Acrostudy registry [21] a world-wide non-interventional, post-marketing surveillance study initiated in 2004 not only to monitor mainly the safety but also outcomes of pegvisomant in clinical practice [22]. This single country experience (which adds to the long-term one obtained in Germany) [23] performed on a relevant number of patients (>300) with a long-term follow-up period (>4 years) offers some hints that may help to elaborate on this topic. First of all, although the surveillance study is global in its design data reported come prevalently from centers that have large experience with this treatment modality. In fact, despite patients being enrolled in 25 different sites more than a half were enrolled in 6 centers. This aspect, which is somewhat expected since current indications for pegvisomant use are focused on acromegaly patients "resistant to other treatments," has double implications: on one side, this means that use of the drug is still likely confined to difficult long standing (mean duration of acromegaly before pegvisomant start was 8 years) acromegaly patients who are seen in very selected institutions, and therefore, most endocrine centers have a very limited experience with the drug; on the other side, this implies that Acrostudy data are really the best available reflecting the practice of endocrinologists with the largest experience with this treatment. Interestingly, slightly less than one quarter of the patients in this Italian experience were only treated medically before starting pegvisomant [21]. In fact, the main safety issue with pegvisomant so far, that greatly limited its use in clinical practice, has been the concern of a potential tumor (re)growth. Bases for this concern ranged from the concept that the pituitary was not the target of treatment to potential Nelson syndrome-like effect on the GH-secreting tumor of the negative feed-back induced by the lowering of IGF-1

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[24]. Data published so far have been re-assuring on this issue. In fact, several long-term evaluations reported an increased tumor size during pegvisomant in 5–7 % of patients [25–29] percentage which was even lower when centralized image re-evaluation was performed [22, 26]. Tumor growth, observed more frequently during the first year of treatment, in the current view may prevalently reflect the disease natural history [29] or the consequence of SRL discontinuation [26]. Absence of previous irradiation and shorter duration of pre-pegvisomant SRL therapy were associated with increased risk of growth [30]. In the Italian experience number of patients who experienced increased pituitary tumor volume, symptomatic in one case, was reported to be slightly higher than in other studies (8.8 %) [21]. This may be due to the enrollment of patients who were not previously treated by surgery or radiotherapy. At least partially related to this issue does appear to be the high percentage of patients (>50 %) that in the study was on combined pegvisomant + SRL treatment [21]. Based on this experience and on available data pegvisomant could be considered as "primary" medical therapy only when surgery and radiation can not be performed and SRL may not be effective as in patients with acromegaly and McCune Albright syndrome [31] or in case of infrequent but possible clear-cut intolerance to SRLs [20]. Otherwise, optimal use of pegvisomant concerning tumor safety should take into account the history of the adenoma (aggressiveness/invasiveness), previous tumor response to treatments including SRLs [32, 33] and tumor volume at start of treatment [34]. Moreover, all patients treated with pegvisomant should undergo regular sellar MRI to screen for potential tumor growth and likely a more intensive MRI follow-up protocol should be followed in non-irradiated patients [20]. Another safety issue that so far limited the use of pegvisomant is liver toxicity. An elevation of liver transaminase levels generally mild and transient was reported in about 5–8 % of patients in surveillance studies [35] percentage which was observed to be higher when pegvisomant was combined with SRLs [36]. The Italian experience is somewhat re-assuring concerning this aspect [21]. In fact, despite the high prevalence in the study population of combination therapy pegvisomant + SRLs elevation of liver enzymes, particularly of severe degree, was a quite infrequent occurrence. Based on this observation and available literature, only the presence of liver dysfunction contraindicates pegvisomant use [20]. However, not only a monthly monitoring of serum transaminases is necessary in the first 6 months of treatment, but also afterward a careful evaluation of liver function (quarterly for next 6 months, and then semi-annually) is required [34]. An adjustment of this time schedule could be discretional in case of combination treatments with SRLs. Discontinuation of treatment is mandatory for cases of severe liver toxicity (acute hepatitis, one case in Italian experience, and transaminase increase >5 times upper limit of normal, three cases in this same report) [20, 21]. Less clear is the recommended behavior in the more frequent cases of mild transaminases increase without liver failure: in the case pegvisomant is continued intensive (weekly) monitoring of liver function is mandatory [20]. Although the Italian Acrostudy, as the global one, is a surveillance study mainly focused on safety issues some aspects concerning the efficacy of pegvisomant as it is currently used in clinical practice may be of interest. Normalization of IGF-1 levels for age is the main goal of pegvisomant treatment [1–3]. In clinical trials, this end point was obtained in more than 90 % of patients [37, 38] leading to the concept that at an adequate dose virtually all patients with acromegaly should be controlled by this drug coherently with the specificity of its mechanism of action [19]. However, the percentage of subjects reaching biochemical control was reported to be lower and somewhat limited to two thirds of the treated subjects in practically all "real life" observational studies [22, 23]. Interestingly, also in the Italian experience only 60 % of patients normalized IGF-I levels at the end of the first year of therapy; this figure slightly increased to 70 % after 5–6 years of treatment [21]. Main explanations so far for this discrepancy have been clinicians being unable or not prepared to adequate dose titration as well as technical problems with the IGF-1 assay [39]. However, since most of the patients were concentrated in few very experienced centers these appear to be unlikely events. In fact, it seems quite clear from the study of Grottoli et al. [21] that independently of the existence of a true "biochemical resistance" to pegvisomant, as observed with SRLs [40] there really exists a spectrum of biochemical responses to pegvisomant in clinical practice which varies from the best possible outcome with even over-suppression of IGF-1 with low doses of the drug to the non-normalization of IGF-1 even with up-titration of drug to maximal allowed doses (30 mg/day). The Italian experience suggests that male gender [21] (and not female as reported by other studies) [30, 41] elevated body weight and baseline IGF-1 levels are predictors for increased dose requirement and consequently an increase in starting dose and/or a quicker dose up-titration could be considered in these instances. Grottoli et al. [21] did not investigate the potential role of d3GHR polymorphism in conditioning the effectiveness of pegvisomant treatment. However, this has been shown to modify receptor sensitivity to GH [42] and, although not consistently across studies, the response to pegvisomant [43, 44]. Therefore, since in approximately half of the acromegaly population the wild type receptor is found [42] it can not be excluded that molecular variants of the GH receptor may play a role in this wide spectrum of

responses to pegvisomant. Treatment with pegvisomant has, similarly to SRLs [45, 46], many positive effects on acromegaly comorbidities. However, the Italian study did not report data in this regard [21]. Particularly, it would have been interesting to have detailed information on glucose metabolism since, due to its favorable effects [47] and to SRL variable or even negative effects [48], diabetes mellitus difficult to control (not infrequent in this population) may represent an indication to pegvisomant use [20]. Finally, modalities of pegvisomant administration (timing, mono vs combination with SRL therapy) seem to be issues on which still clinical practice is not homogeneous. Pegvisomant is indicated for daily administrations. However, regimens with less frequent injections are reported to be effective in some instances [49] and in the global Acrostudy report [22] daily injections were not used by 12 % of endocrinologists, a similar and even slightly higher figure reported by Grottoli et al. [21]. This may be related to an attempt to limit the burden of injections for the patient or the potential side effects of the drug. Nevertheless, one other possible reason is that it may be a cost-saving practice in some centers. Certainly, direct costs of life-long pegvisomant therapy are higher than any other standard treatment modalities. However, we need to take into account that controlling appropriately acromegaly, which anyway is a quite rare disease, has an heavy positive cost-saving impact [50]. Moreover, when pegvisomant is used it is generally the last chance to obtain full biochemical control of the disease [51]. Therefore, at least in principle, the real cost-effective approach with pegvisomant is that allowing to reach the treatment target and therefore the correct scheme of administration should be applied to all patients. Only in those patients, less than 4 % in the Italian experience [21], particularly good responders to pegvisomant dose under-titration may allow to go beyond the daily schedule of administration. Furthermore, starting with very low-dose regimens of the drug seems not to be motivated by safety issues (e.g., liver toxicity appears to be not dose-dependent) [22, 35] and it may cause a relevant delay in reaching the objective of normalizing IGF-1. This in turn, may have a particularly negative clinical impact in the course of a disease which is generally advanced in the candidates to pegvisomant therapy and, as we well know, may be life-threatening [52]. Use of pevisomant is indicated in monotherapy. However, combining pegvisomant with SRL treatment, which generally means continuing patients on SRLs and adding on pegvisomant, has become a widespread practice [5] although still "off-label" for some regulatory agencies [20]. In fact, Grottoli et al. [21] report that only about 40 % of patients started pegvisomant in monotherapy. What are the reasons behind this choice? We already mentioned that this may be a choice to prevent tumor volume increase which however, as concordantly reported by many studies, is as infrequent occurrence during pegvisomant.treatment and therefore does not justify a generalized combination approach. Nevertheless, in carefully selected patients (non-operated and non-irradiated, residual adenoma with a potential of mass effects, proven significant shrinkage effects by SRLs) this approach may be clinically indicated. On the other hand, always in terms of side effects the potential price to be paid to the combination approach is the increase in liver toxicity which has to be taken into account when choosing this treatment option. Again, costs may be another reason behind this approach. In fact, combination with SRLs has been reported to be effective while allowing use of low and much refracted (weekly) doses of pegvisomant [53]. The rationale behind this observation is not only based on the different and synergic mechanisms of action (central for SRLs and peripheral for pegvisomant) but also includes reduced clearance of pegvisomant, control of GH hypersecretion, and improved liver action of the drug [54]. This biochemical synergic effect may add on the potential protective effect of SRLs on tumor growth. While all these considerations, corroborated by some clinical findings, are reasonable, convincing evidence for a superiority in terms of clinical results with at least equal risk of side effects of the combination approach versus pegvisomant monotherapy is still lacking [55, 56]. Therefore, instead of a generalized type of approach it is currently possible to personalize treatment based on the characteristics of the patient response to SRLs [57]. In fact, as reported in recent guidelines [3, 20] in the case of no response to maximal SRLs doses [58] (no or very limited change in GH and IGF-1) there is little significance in continuing with SRLs and patients should be switched to pegvisomant monotherapy. In partial responders to SRLs combination therapy can be considered and this choice has to be balanced between expected results and possible side effects of the two treatments alone or in association. In conclusion, after almost 15 years from the publication of seminal trials on the beneficial effects of pegvisomant in acromegaly many steps forward have been made in understanding how to use it in a complex disease like this. Thanks to surveillance studies we know now that pegvisomant is not only highly effective but also substantially safe when used relatively long-term in acromegaly patients. However, waiting for specific widely accepted recommendations for its clinical use [20] there remains a quite large variability in the clinical community on the patient choice and treatment modalities often based on not so strongly motivated perception of this treatment being limited by risk of side effects and costs. The numerical power of surveillance studies [21–23] may help to overcome these

current barriers and the critical evaluation of their results will likely contribute to reach the objective of an optimal use of pegvisomant in acromegaly.

Conflict of interest A.G. is consultant for Ipsen, Novartis and Pfizer.

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