OPINION

Pre-surgical treatment with somatostatin analogues in patients with acromegaly: The case for

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BACKGROUND

Acromegaly has been largely considered a rare disease. However, prevalence and incidence has been reviewed in the last decade, particularly in Europe, and these patients seem theoretically more prevalent than previously thought (1). The more recent consensus guideline underlines that a significant progress has been made in the management of acromegaly when patients are referred to a multimodality team with specific experience in treating pituitary tumors; however, this is not yet a reality everywhere (2). Appropriate therapeutic strategy should include an integrated application of mainly surgery and medical therapy, with less use of radiotherapy, to achieve the goals and reduce cost-effectiveness of the management, which is, considering the emerging epidemiological data, still a rather unexplored important issue (3). This last consensus also recommends the tailored therapy by an experienced team as optimal approach, and, for the first time, medical treatment with somatostatin analogs (SSA) is equally considered as first-line treatment, in patient where surgical cure is unexpected (2). Successful medical treatment with SSA is based on the expression of specific receptors on tumors, indeed, clinical, biochemical, and tumor response is correlated with the amount of somatostatin receptor on adenoma cells (4, 5). Conversely, still debated is the role of pre-surgical treatment with SSA on either surgical outcome or peri-operative complications. Although the pre-operative medical therapy is certainly not contraindicated, its results still remain unclear at present. However, based on the data available in the literature, we should clearly distinguish the results of SSA given prior surgery on the pure surgical outcome from the more general clinical outcome of the patient and, perhaps, also on the general cost of the illness, including multimodality treatment.

DOES SOMATOSTATIN ANALOGUES PRE-TREATMENT IMPROVES SURGICAL RESULTS?

Few, and unfortunately, very heterogeneous studies have been performed along the last three decades aiming to answer the question whether pre-surgical SSA treatment may improve the operative outcome in acromegaly. As expected, conflicting results have been obtained. Beside the difference in the baseline study designs: prospective (only 2 randomized) vs retrospective, one study with data derived from a registry, different doses, as well as timing of the pre-treatment, different criteria and time for the assessment and definition of the disease control, and the use of different compounds, several other factors have affected the analysis and the results. Among these, the most important are the inclusion of patients with a microadenoma and of patients previously treated with medical and surgical therapies, or even with radiotherapy, the lack of matching for invasiveness or IGF-I concentration, reliance on single GH values rather than on a daily profile, as well as neurosurgeon(s) availability. However, even considering all these drawbacks, the major opinion (9 studies pro vs 5 contra, see Table 1) favor the use of SSA in a sort of neo-adjuvant schedule, or at least do not contraindicate this approach. In these studies indeed, either an improvement of the surgical results (6-14), or no beneficial effect (15-19) have been reported. Two additional studies (20, 21) are basically neutral, the first, on a rather large series, reporting an advantage in only selected patients with invasive tumors, the second presenting data derived from the analysis of the database of a register. However, both these latter studies were not in contrast with the pre-treatment scheme. These findings, together with some sensitive case reports, in my opinion, support the use of pre-treatment with SSA in acromegalic patients in the view of a potential surgical approach. Moreover, if confirmed, the increasing number of diagnoses of pituitary tumor, in general, will certainly impact on the standby list in neurosurgery referral centers, and consequently, for acromegaly, this issue will definitely favor the use of SSA in the pre-surgical setting, also to not leave the patient in clinically active disease for a long time.

Finally, nowadays, the diffuse availability of long-acting formulations of SSA and the forthcoming availability of new interesting compounds will strongly impact on the decision making and will certainly favor the multidisciplinary approaches to tailor the therapy in each single patient. Each patient with newly diagnosed acromegaly should be addressed to those pituitary units where both proven expert neuroendocrinologists, as well as dedicated neurosurgeons and neuroradiologists are available. In the meantime, these are the centers which should be
involved in an ideal prospective randomized controlled trial including a large number and variety of patients in both treatment schedules (pre-treatment with SSA vs untreated) that can definitively answer to the questions, particularly in terms of optimizing health care resource utilization.

DOES SOMATOSTATIN ANALOGUES PRE-TREATMENT IMPROVE SURGICAL COMPLICATIONS?

Cardiovascular, respiratory, and metabolic co-morbidities contribute to significantly enhanced mortality and increased morbidity in acromegaly. Indeed, large retrospective studies indicate an average 10-yr reduction in life expectancy, with at least a doubling of standardized mortality rates due particularly to cardiovascular, cerebrovascular, metabolic, and respiratory co-morbidities. However, overall, achieving a post-treatment GH level of less than 2.5 μg/l results in maintaining normal life expectancy rates.

Contraindications to surgery for acromegaly may include, beside the advanced age and general debility, many other commonly occurring co-morbidities, namely cardiovascular and metabolic alterations or respiratory disorders (22). Indeed, pre-operative evaluation in patients with acromegaly should consider a detailed assessment of clinical features, plus the airway evaluation by the anesthesiologist, as many acromegalic patients have significant tongue and airway edema that may require specialized intubation.

Other risks associated with transsphenoidal operations for acromegaly are related to the anatomical deviations, airway/laryngeal edema, and venous congestion, occurring frequently in this patients. Moreover, during the operation, the visualization can be limited by the mucosal edema, redundant tissue, hypertrophic nasal turbinates, thickened nasal bones, enlargement and tortuosity of the internal carotid arteries, and occasionally aneurismal formations (22). Recently, it has been also demonstrated that the efficacy of neurosurgery is affected by concentration of basal serum GH and IGF-I, GH at 120 min in oral glucose tolerance test, tumor size and invasiveness (23). Moreover, hypopituitarism as a consequence of surgery resulted more frequent in patients with macroadenoma, being found in 21% of patients with normal pituitary function prior to operation (23).

Despite this scenario, in the hand of a skilled surgical/anesthesiology team, overall morbidity rates associated with the transsphenoidal surgery can remain low, while mortality has been reported in less than 0.5% of patients. However, since treatment with SSA significantly and positively impact on the majority of these alterations, particularly at cardiovascular and respiratory levels, intuitively, a rather short-term pre-treatment period prior surgery with these drugs should further reduce the occurrence of operative complications and facilitate the anesthesiological procedures.

However, the only two prospective randomized studies, analyzing also the surgical complications in clinical trials, found no significant difference between patients pre-treated with SSA vs the untreated group (13, 14). Conversely, in 2 retrospective studies, a positive impact on the course of the surgical procedure with a shortened period of post-operative hospitalization was reported in SSA-pre-treated patients (9, 11). Despite these controversial results, the general feeling support the use of pre-surgical treatment with SSA in acromegly. In fact, already in a consensus document of the Polish Society for Endocrinology, a statement on this issue has been included, suggesting at least 3 months of treatment prior surgery in microadenomas, and 6 months in macroadenoma. Nevertheless, a large welldesigned study aiming to assess the anesthetic risk grades and cardiovascular status in the pre-treated and surgery only subgroups to determine whether SSA had a clinically relevant effect on overall pre-operative health status is strongly warranted to confirm this general view.

CONCLUSION

The controversial data of this delicate issue definitively require conclusive studies to address the question and solve the drawbacks and limits raised in the previous at-