Consensus

French consensus on the management of acromegaly

Consensus français sur la prise en charge de l'acromégalie

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Foreword

This text sums up the proposals resulting from a preparatory meeting held with the participation of a number of experts pro-

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posed by the *Club de l'hypophyse* (French Pituitary Club), at the request of the *Société française d'endocrinologie* (French Endocrinology Society). These proposals were then discussed during a plenary session of the *Club français de l'hypophyse* on 22 June 2007 and corrected according to the comments made at that time. A synthetic version was then submitted to the various members of the study group, whose corrections have been taken into account in this final version. Finally, the text was put online on the website of the *Société française d'endocrinologie* in September of 2007, thus making possible further amendments.

The recommendations are sometimes very general and cannot necessarily be applied to all patients, for whom a multidisciplinary case discussion is mandatory. Some treatments that have not received a marketing authorization for certain indications are referred to in the context of a physiopathological logic or of one relating to practical management, in order to offer a state-of-the-

art document. Their prescription involves the sole liability of the prescriber and does not commit either the *Club de l'hypophyse* or the *Société française d'endocrinologie*.

1. Growth hormone-insulin-like growth factor1 (GH-IGF-I): what measurements?

1.1. Measurement of growth hormone (GH)

Three international standards were previously used for the calibration of the techniques used to measure GH, among which the standard 98/574 (recombinant GH), has been recommended by the *Société française de biologie clinique* (French Society of Clinical Biology) in 2004 [1] and by the EC experts in 2006 [2]. Manufacturers marketing GH measurement kits must now use this standard. Quality control is carried out by Afssaps. The manufacturers are also invited to use 22K recombinant GH as a working standard, and, due to a well-identified "matrix" effect, GH-free human serum for the dilution of the international standards when recalibrating. At this writing, this recommendation is unfortunately not applied by all. The French biology experts have requested that, before these Recommendations are enforced by all, the results be expressed in IU, with $1\,ng = 3\,\mu IU$, if the 98/574 standard is used (all other equivalence factors should be banned!). GH must be measured in serum (sampled in a dry tube) and not in plasma.

However, despite these recommendations, even though an improvement may be noted, the measurement of GH is far from producing univocal results according to the method used. Depending on the kits used, when measurements are carried out on serum pools having a known GH concentration, the results may vary between one and 1.5-fold [3]. A study of compliance with recommendations conducted by Afssaps in 2007 also found major discrepancies when measurements were performed on one and the same sample, not only from one kit to another, but also from one laboratory to another, even when the same kit was used [4,5]! For more details regarding this French survey, please contact http://afssaps.sante.fr/htm/10/dm/inddm.htm!

Most of the kits presently used in France allow very sensitive measurements (IRMA, ICMA, IFMA, etc.). Their detection limit is 0.1–0.2 μg/l (0.3–0.6 mIU/L). The GH values which will be indicated later on in this text, particularly when discussing diagnostic or therapeutic thresholds, will be based on these very sensitive methods of measurement. A list of the main kits for the measurement of GH offered in France, together with their detection limit, is given in Appendix 1.

1.2. Measurement of insulin-like growth factor1 (IGF-I)

The measurement of IGF-I involves even more difficulties [6]:

- the first difficulty concerns the separation between IGF-I and IGFBP:
  - gel filtration is the reference method, but it takes a long time and is complicated to apply on a routine basis and must

be reserved for (very) special cases in (very) specialized laboratories,
  - the acid-ethanol extraction technique is simpler, but does not always eliminate all the IGFBP,
  - the technique involving the displacement of IGF-I by an excess of IGF2 is simple and fast, but of uneven quality. It is the most attractive in connection with automation;
- the laboratory must be required to express the results according to the age-adjusted normal range (decade by decade). Laboratories often do not establish their own reference range. Careful, many laboratories use the standards established by Brabant [7], who used a Nichols kit, which has unfortunately been taken off the market. These should therefore no longer be used. The concern about intermethod variability is important when evaluating acromegaly: thus, a study showed that in spite of excellent correlation between the four methods tested, a number of discrepancies were observed when it came to classifying blood samples as either normal or pathological [8,9];
- finally, in each age bracket, the distribution of the IGF-I values is not Gaussian, which makes it difficult to express the results in the form of a Z-score, even though correction formulas are proposed. Lastly, we must not lose sight of the fact that the intra-individual variance of IGF-I is much smaller that the variance in the normal population of the same age. Each individual is "clamped" to an individual normal value, around which he or she will evidence very little variation over time. As a result, the definition of the normal value for an individual does not always correspond to the normal value for the population of the same age [10,11].

An initiative that would prove useful to all could consist in:

- contributing to the standardization of GH measurements by checking with the laboratories to which we send samples in order to make sure that they use kits whose quality is acknowledged;
- establishing IGF-I standards at the national level according to age, on the basis of samples from normal individuals of all ages measured by means of the different techniques.

2. Diagnosis of acromegaly

2.1. Two different clinical situations must be considered

2.1.1. Moderate clinical suspicion

For instance, the patient is seen for another reason and the clinical aspect causes the clinician to raise the possibility of the diagnosis.

In this case, the diagnostic procedure is aimed especially at ruling out acromegaly.

A measurement of IGF-I and a single measurement of GH are advised.

When faced with a normal serum concentration of IGF-I and a GH concentration less than 0.4 μg/l (< 1.2 mIU/l), the diagnosis is ruled out [12].

If such is not the case, a GH measurement during oral glucose tolerance test (OGTT) is recommended (see below).

2.1.2. Strong clinical presumption

The objective is different and aims at asserting acromegaly [13].

A very high concentration of IGF-I is sufficient for the diagnosis of acromegaly. OGTT is not necessary, but is nevertheless of value in order to indicate, prior to treatment, the GH level and nadir (except in diabetics).

In this case:

- increased IGF-I concentration and unsuppressed GH/OGTT concentration: acromegaly is certain;
- increased IGF-I concentration and suppressed GH/OGTT concentration: moderate acromegaly is probable (depending on the clinical context, discuss pituitary imaging, do not treat and repeat the tests several months later, with the performance of a GH profile if necessary);
- normal IGF-I concentration and unsuppressed GH/OGTT concentration: moderate acromegaly is probable (depending on the clinical context, discuss pituitary imaging, do not treat and repeat the tests several months later, with the performance of a GH profile if necessary);
- normal IGF-I concentration and suppressed GH/OGTT concentration: no acromegaly (diagnosis ruled out).

2.2. In practice

2.2.1. The performance of a GH measurement

The performance of a GH measurement during OGTT, if the IGF-I concentration is normal, therefore depends on the level of presumption of the disease.

The GH threshold at nadir during OGTT (75 g) is set at 0.3 μg/l (0.9 mIU/l) in the case of an ultrasensitive GH measurement (ultrasensitive measurements are those used in practice in France at present: their detection threshold is around 0.05 μg/L, i.e., 0.015 mIU/l). When less sensitive measurement techniques were used (RIA), this threshold of 0.3 μg/l (0.9 mIU/l) was equivalent to a threshold of about 1 μg/L [14,15]: this explains why the diagnostic thresholds for acromegaly have changed, decreasing from 1 to 0.3 μg/l (3 mIU/l à 0.9 mIU/l).

Let us keep in mind, however, that in the great majority of cases the diagnostic threshold for acromegaly is not a problem: thus, in the entire series reported in the *Registre français de l'acromégalie* (French Acromegaly Register), only two patients out of 192 had a GH nadir less than 1 μg/l [5]!

Finally, OGTT presents the added value of screening for a disturbance in glucose tolerance.

2.2.2. Tests not advised for diagnosis

These tests are as follows:

- GH under TRH;
- 24-h GH profile;
- urinary GH.

These tests are not advisable for the diagnosis of acromegaly on account of the absence of precisely defined standards and of the frequent overlap between normal individuals and acromegalic patients.

2.2.3. Unanswered question

Must glycemia increase up to a certain value in order to allow the interpretation of the GH/OGTT measurement? There is no answer to this question, for during OGTT not only glycemia is involved, but perhaps also other signals (ghrelin, gastro-enteropancreatic peptides, etc.). In practice, therefore, no glycemic threshold need be reached in order to allow the interpretation of the test and therefore it is the GH nadir, whatever the time at which it occurs in the course of the test, that is taken into account. Some authors go even further and state that the GH nadir observed during an OGTT is the same as if a saline solution had been administered [16], thus implying that the standardization of the samples is more relevant to the diagnosis than glucose intake.

2.2.4. The interpretation of IGF-I is delicate in various situations [17]

Hepatic or renal insufficiency, uncontrolled diabetes, malnutrition, anorexia, estrogen treatment, pregnancy, puberty, etc. (Appendix 2).

2.2.5. The case of the diabetic patient

The diagnostic procedure in a diabetic patient, particularly if diabetes is uncontrolled, is poorly documented.

It must be recalled that uncontrolled diabetes is associated with a state of relative resistance to GH; hence a tendency to overestimate GH (which is higher than it would be in the absence of diabetes) and to underestimate IGF-I (which would, therefore, be higher in the absence of diabetes). Thus, it is possible to imagine the situation of an authentic acromegalic patient suffering from uncontrolled diabetes with elevated GH measurements and a normal IGF-I measurement, who, once his diabetes is brought under control, experiences a fall in his GH level and a rise in his IGF-I level [18]. Therefore, it is always useful as a first step, when the diabetes is uncontrolled, to begin by bringing it under control before attempting to make a diagnosis of acromegaly!

Apart from an obvious lack of control, in a diabetic who is only weakly hyperglycemic, OGTT is best avoided. Therefore, repeated samplings will often be preferred (GH profile), without a suppression test, even though a study has shown that the normality thresholds during OGTT are the same in individuals evidencing normal glucose tolerance, in those with glucose intolerance and in diabetics [19]. The absence of hypoglycemia (which is liable to stimulate the secretion of GH) induced by the hypoglycemic treatment must also be checked during the test. As for the number, frequency or duration of the samples required to establish the GH profile, no data are available at present. A minimum number of samples is desirable: six samples, taken every 15 to 20 min. In the absence of undetectable levels (< 0.3 μg/l), the diagnosis of acromegaly is probable.

2.3. Special cases

2.3.1. Measurement of GHRH

This must be performed in order to search for an ectopic secretion of GHRH when dealing with authentic acromegaly, but when the MRI shows a pituitary gland whose aspect is normal or hyperplastic, without any actual intrasellar lesion suggesting a pituitary adenoma.

2.3.2. Genetic tests

When there is a family history of acromegaly and/or in a young patient presenting acromegalic gigantism, the existence of a mutation of the AIP gene should be explored [20,21].

In cases of primary hyperparathyroidism or of gastropancreatic endocrine tumors, one must look for a multiple endocrine neoplasia type 1 (NEM1) [22] and test the menin gene.

Acromegaly can also be part of McCune-Albright syndrome [23] or of Carney complex [24].

3. Evaluating the complications present at diagnosis

When a diagnosis of acromegaly is made, in order to detect the complications associated with the condition [25,26], the following tests are advisable [27].

3.1. Evaluation of the impact of acromegaly

3.1.1. Metabolic

- look for diabetes or glucose intolerance: fasting glycemia, OGTT and HbA1C;
- dyslipidemia: evaluation of any lipid abnormalities.

3.1.2. Cardiopulmonary

- repeated blood pressure measurements (using a Dynamap®, for example);
- ECG;
- echocardiography, with a precise measurement of diastolic function (E/A ratio), of the LVEF, of the thicknesses of the interventricular septum and of the posterior wall, and an evaluation of the condition of the valves;
- ECG Holter and blood pressure Holter tests are prescribed when the history is suggestive or when there is a clinical or ECG indication (although recommended by some international articles, these tests are not systematically performed in France);
- systematic screening for sleep apnea syndrome. Polysomnography is the reference test. A severe SAS, i.e. one requiring breathing assistance, is found in 65% of patients (Cortet-Rudelli C, unpublished data). The institution of continuous positive airways pressure (CPAP) ventilation at night is recommended when the apnea-hypopnea index is above 30 or when there are multiple micro-awakenings. One must beware of a falsely reassuring test in the case of patients who did not sleep during the recording. Otherwise, ventilation polygraphy shall be prescribed. Neither oxymetry nor evaluation of the Epworth score are sufficiently specific.

3.1.3. Digestive

Colonoscopy is advisable upon diagnosis in adults, including young patients, as early as 20 to 30 years of age, since polyps may be found even before the age of 40 (20% polyps) [28,29].

3.1.4. Thyroid

- TSH, free T3, free T4, in order to detect associated hyperthyroidism;
- thyroid ultrasonography (US) when a goiter is present. This test should be readily prescribed in view of the increased risk of goiter, nodules and thyroid cancer [30,31].

3.1.5. Other recommended tests

- abdominal and renal US in order to search for gallstones or renal calculi in patients treated with somatostatin analogs (SA);
- bone X-rays (oriented) in the case of rheumatological problems;
- measurement of blood and urinary phosphorus and calcium (including a measurement of PTH in case of hypercalcaemia);
- osteodensitometry to measure bone mineral density, if hypogonadism is present;
- search for a carpal tunnel syndrome (clinical examination, documented by electromyography if present clinically);
- stomatological evaluation.

3.2. Evaluation of the pituitary impact of the pituitary lesion and search for associated hypersecretion

- search for a pituitary deficiency: measurement of plasma cortisol and possibly stimulation test, fT4, fT3 and TSH, testosterone or estradiol, FSH, LH;
- measurement of prolactin, free alpha subunit of gonadotrophins.

3.3. Evaluation of the psychological impact

A quality of life questionnaire (AcroQol) exists and can be offered to the patient. The clinician shall judge whether it should be used and what solutions can be given to the problems thus raised (psychological and sexual problems requiring attention or a specific referral to a psychologist or psychiatrist). This is not a criterion for evaluation of the activity of the disease.

4. Imaging: initial evaluation and follow-up

4.1. Initial imaging tests

4.1.1. Initial MRI
4.1.1.1. Method. Pituitary MRI with 2–3 mm sections, in spin echo (better than gradient echo), with T1 and T2 coronal sections (the adenoma is sometimes hypo-intense in T2), with gadolinium injection.

In 72 to 86% of cases, macroadenomas are found [13,32,33]. The dimensions of the lesion shall be measured at the level of the subcallosum plane and perpendicular to the subcallosum plane.

Some adenomas may appear necrotic (hence the value of T2 sequences).

4.1.1.2. Prognostic value of the initial MRI.
This allows the pinpointing of the healthy pituitary and the evaluation of the tumor invasion, particularly at the level of the cavernous sinus [34].

Some information will be important and decisive as regards the choice of treatment, i.e. surgery versus medical treatment: size greater than 15 mm, invasion, major suprasellar expansion, necessity of surgery in case of compression of the chiasma [35].

3T MRI may allow a better anatomical approach of the cavernous sinus.

4.1.2. Other initial tests

- there is no longer any indication for a brain CT-scan;
- the captation of the pituitary adenoma at Octreoscan®, which should theoretically allow the prediction of the hormonal and tumoral response to octreotide, has yielded disappointing results (an overall correlation between the intensity of captation and the response was found in two of the three studies, but the positive predictive value is poor), and therefore there is no indication for this test in acromegaly [36–38];
- in case of an orientation toward an ectopic secretion of GHRH, a thoracic CT-scan and an Octreoscan® are necessary [13].

4.2. MRI during follow-up

- the postoperative control MRI must be performed between three and six months after surgery (it is of no use at all before three months);
- the subsequent follow-up depends on the status of the patient:
  ○ no indication for the repetition of the MRI in a patient who is biologically cured,
  ○ MRI within three to six months of the initiation of treatment with SA in a patient not cured by surgery (the reduction in tumor volume occurs early; 80% of patients respond as early as the 6th month [39,40]),
  ○ yearly MRI in patients not controlled by SA,
  ○ increase the interval to two years (if not more? since the risk of growth in tumor volume under treatment with SA is extremely small) if the patient is well controlled. In patients with good control showing a reduction in tumor volume in the first MRI, this test is not worth repeating annually,
  ○ generally speaking, MRI supervision is justified only if there is reason to fear an expansion of the tumor, which would justify further surgery or another type of treatment, such as radiotherapy.
- special case of patients treated with pegvisomant. At present MRI is rather widely recommended for the follow-up of patients with a tumor remnant who are treated with pegvisomant. An increase in the size of the tumor volume was observed in 3 to 5% of patients [41,42], keeping in mind that the patients treated with pegvisomant are often those resistant

to SA, i.e. those who have potentially more aggressive tumors whose spontaneous evolution would probably have been the same [43]. In some cases, the increase in tumor volume is associated with the interruption of the SA simultaneously with the beginning of pegvisomant treatment [44].

4.3. Calculating volumes

Various methods are used for calculating of the volume of an adenoma; the best one seems to be the volume index. It is especially used for purposes of clinical research, in order to judge the antitumor effectiveness of the treatments.

In practice, however, since the evaluation of volumes is difficult, individual comparison between the measurements of the various diameters is more frequently used. Therefore, it is recommended, to the extent that this is possible, that the explorations be performed in the same place and by the same neuroradiologist for a given patient, so that the imaging procedures and machines used will be the same.

In practice, especially if the explorations are not carried out in the same plane, with the same protocol, it is often more relevant to gauge the evolution of the tumor volume in relation to the neighboring structures rather than by relying on measurement figures. This also leads us to stress the fact that multidisciplinary consultation meetings (among neuroradiologists, neurosurgeons, and endocrinologists) are essential.

4.4. Peroperative imaging (MRI in the operating room)

This allows an evaluation of the quality of the removal during the operation and seems to increase the success rate, but is available in only very few centers.

5. Criteria defining good control and cure

5.1. Epidemiological data

Acromegaly remains associated with excess mortality, which, however, probably tends to decrease in the most recent studies, reflecting better treatment of comorbidities and most likely more aggressive treatment objectives [45]. Recent epidemiological studies relating patient mortality and the control of acromegaly are based essentially on GH concentrations [46–51] and, more rarely, on IGF-I concentrations [48], probably because of the reliability of the measurement, of the often very heterogeneous nature of the methods of measurement and of the small number of patients on which the studies were performed. They have made it possible to give an idea of the concentrations which it is desirable to achieve in order to allow a reduction in the excess mortality of acromegalic patients.

5.2. The objective of acromegaly treatment

The ideal treatment objective (which can be called a "cure") is to restore a normal dynamic to the somatotropic axis, defined by the normalization of the response of the serum concentration

of GH/OGTT and the normalization of that of IGF-I. This is not possible with any treatment presently available, aside from surgery.

On the other hand, it must be recalled that the sole fact of lowering GH concentrations significantly improves the patients.

5.3. The criteria defining cure or control vary according to the type of treatment

Several situations may be encountered, for which the criteria defining cure (or good control) differ.

5.3.1. After surgery

The sample for the measurement of IGF-I must be taken at least three months after surgery.

The criteria defining a "cure" (if one considers that a patient is not cured unless he presents the same secretion characteristics as a normal individual) are:

- an average GH concentration below 2.5 μg/l (7.5 mIU/l) *and*
- a GH concentration nadir during OGTT below 0.4 μg/L (1.2 mIU/l) (new ultrasensitive measurements);
- an IGF-I concentration which is normal for the patient's age.

When these objectives are not attained, the patient is not considered to be cured. However, if the IGF-I concentration remains normal and the GH concentration during OGTT remains below 1 μg/l (3 mIU/l), the disease will most likely not be progressive. Indeed, according to a recent study, patients whose GH nadir was between 0.4 and 1 μg/L (between 1.2 and 3 mIU/l) did not develop any major complications of their disease, nor any obvious recurrence in the longer term (6.5 years) [52]. Monitoring is, however, required.

If the IGF-I concentration is high, if the GH concentration does not drop below 1 μg/l (3 mIU/l), the patient is considered to be uncontrolled and additional treatment is necessary.

5.3.2. With somatostatin analogs injected monthly

5.3.2.1. Measurement of the GH and IGF-I concentration.
The first measurement of the GH and IGF-I concentration must be performed after a steady state in the concentration of the analog has been achieved, (that is, after four injections at the earliest). The evaluation must be carried out when the SA has finished acting (that is, just before an injection).

5.3.2.2. Quality of the control of patients under SA.
Should or should not the GH be measured during OGTT in order to evaluate the quality of the control of patients under SA? In fact, very little difference is generally observed between the average GH concentration and the concentration obtained during OGTT, and there is no consensus regarding the value of using OGTT:

- according to some authors, the advantage of OGTT lies in the fact that it is a standardized test, used in most published studies in order to establish the criteria defining good control [53], but others consider that it does not contribute much,

since under treatment with an analog, suppression is already at a maximum!

- if an OGTT is performed, what nadir should be chosen? Until 2004, the nadir required for good control was set at 1 μg/l (3 mIU/l) [12]. In 2005, in connection with the publication of the recommendations of a group of experts, a threshold value of 0.4 μg/L (1.2 mIU/l) was proposed, taking into account the widespread use of very sensitive measurements of GH [54]. At present, according to the studies, the target nadir varies (0.14 to 0.4 μg/L, i.e. 0.42 to 1.2 mIU/l). But we may ask what the actual value of thus bringing down the threshold used to define good control may be. In fact, according to a recent study, patients whose GH nadir was between 0.4 and 1 μg/L (between 1.2 and 3 mIU/l) do not have any major complications of their disease, nor any obvious recurrence in the longer term (6.5 years) [52]. Therefore, a threshold of 1 μg/l (3 mIU/l) is perhaps still relevant;
- if one chooses to simply measure GH without OGTT, repeated measurements are advisable in order to evaluate control under SA.

5.3.2.3. Practical attitude recommended under somatostatin analogs.
If the IGF-I concentration is elevated, with an average concentration of GH that is abnormal (above 2.5 μg/L, 7.5 mIU/l) or cannot be suppressed by OGTT, the patient is uncontrolled.

If the IGF-I concentration is normal and the average GH concentration is below 2.5 μg/L (7.5 mIU/l), the patient is considered to be well controlled.

Otherwise, and not exceptionally [55]:

- the IGF-I concentration is normal, but the GH concentration is elevated or unsuppressed (for instance, between 0.4 and 1 μg/L – between 1.2 and 3 mIU/l – with an ultrasensitive measurement): this may be an end-of-dose effect; the patient will then be considered to be well controlled;
- the IGF-I concentration is moderately elevated (between +2 and +3DS) and the average GH concentration is below 2.5 μg/l (7.5 mIU/l) and suppressible: no change in treatment is considered necessary if the patient's condition does not suggest any progression of the disease, but this point is debated.

5.3.3. Control of acromegaly treated with pegvisomant

The GH concentration rises and therefore no longer reflects the control of the acromegaly, and this is also true of GH during OGTT. The adjustment of the treatment must therefore be carried out on the sole basis of the IGF-I measurement.

Care must be taken when switching from treatment with a SA to pegvisomant, as the IGF-I concentration may be transitorily normalized on account of the action of pegvisomant combined with the remanent effect of the SA. Following the gradual elimination of the analog, the IGF-I concentration may then rise, which requires a secondary increase in the dose of pegvisomant.

5.3.4. Cure of acromegaly

Generally speaking, the term "cure" is used with caution in connection with acromegaly, for it means that the patient's

somatotropic axis has returned to normal and remains so in the long term. This situation is encountered only after surgery allowing a total and selective removal of the microadenoma or following etiologic treatment of an ectopic secretion of GHRH. All patients considered to be cured must be followed up on a lifelong basis.

6. Presurgical treatment with somatostatin analogs

6.1. Purposes of pretreatment

The purpose of presurgical treatment is a multiple one:

- to improve the conditions of anesthesia, i.e. to facilitate intubation and reduce the risk of complications *via* an improvement in comorbidities (arterial hypertension, diabetes) [56];
- to make the tumor tissues softer which may simplify the removal of the pituitary adenoma, particularly when dealing with an enclosed, non-invasive adenoma [57]. However, this remains controversial [58];
- to improve the effectiveness of surgery in terms of remission of the disease, but here again there is a conflict of opinions (see below).

6.2. Results

6.2.1. Effect on the results of surgery

- some studies find presurgical treatment to be of value, by evidencing improved cure rates in pretreated patients, except in the case of invasive macroadenomas. Among those studies, Stevenaert et al. report cure rates increasing from 74 to 94% with presurgical treatment for microadenomas and from 61 to 89% for enclosed macroadenomas [57]. Such results were also found by Barkan et al. [59], Abe et al. [60] (although they were not significant in this study) and Colao et al. [56], with even an improvement in the cure of invasive macroadenomas (from 29 to 54%);
- conversely, two studies contradict such an effect of presurgical treatment on cure rates [58,61];
- thus, since it has not been proven that pretreatment improves the cure rate achieved with surgery, and in view of its cost, it does not seem that it should be systematically recommended in the hope of improving the effectiveness of surgical treatment.

6.2.2. Pretreatment may be indicated under the following circumstances

- at risk patients with comorbidities (sleep apnea, severe hypertension, heart failure, etc.), in order to improve pre- and perioperative comfort (this can be discussed with the anesthesiologist, noting that some of them who are used to the intubation conditions of acromegalic patients consider specific preparation to be unnecessary);
- when there are progressive complications of acromegaly (sleep apnea syndrome, cardiac problems, diabetes); it seems

wise to control hypersecretion through medical treatment at least three months before surgery;
- when dealing with a non-invasive adenoma, in the hope of a regression of tumor volume, so as to facilitate removal, remembering, however, that there is no formal proof of an improvement in the effectiveness of surgery.

7. The place of surgery

Tumor removal, generally by a transsphenoidal approach, is the fastest way of bringing down GH and IGF-I concentrations in acromegalic patients. The transcolumellar approach, rather than the supralabial one, has now come into general use. Nevertheless, normalization is achieved in only about 40 to 70% of cases [62–65]; the results depend on the size of the tumor (microadenomas have a much better chance of being cured), the preoperative GH concentrations (the lower the GH concentration, i.e. less than $10\,\mu g/l$–30 mIU/l, the higher the success rate) and the experience of the surgeon. Endoscopic techniques are now used in most expert centers [66,67]. They seem to allow the same results to be achieved, probably with fewer side effects.

The importance of experts centers within which one or two neurosurgeons experienced in this pituitary surgery operate a large volume of tumors of this type is stressed by all [68,69]. The rate of surgical complications (diabetes insipidus, rhinorrhea due to CSF leakage, anterior pituitary insufficiency, etc.), although usually low, is clearly related to the experience of the surgeon and to the volume of cases he operates.

The surgical result is evaluated on the third postoperative month. In the absence of a cure following surgery, or when surgery is impossible or contra-indicated, supplementary treatment with radiotherapy and/or medical treatment are resorted to.

8. Place of dopaminergic agonists

Dopaminergic agonists, which represent the historic treatment used for over 30 years, are now infrequently prescribed in France. According to the studies published, they may allow the normalization of IGF-I in 20% of patients [70–73]. Sometimes the GH concentration is significantly reduced, but without normalization of the IGF-I concentration. No predictive criterion of effectiveness emerges from the literature.

However, mixed prolactin-GH adenomas respond better to dopaminergic agonists.

It is not known whether, in the future, the cases of valve disease reported in patients with Parkinson's disease treated with high doses of dopaminergic agonists [74] will lead to a restriction of the use of such drugs in this indication, at least at high doses.

In view of its low cost and ease of treatment (oral intake), this treatment can be attempted in two situations:

- mixed GH-PRL adenoma and low-secreting adenoma;
- persistence of a moderate elevation of IGF-I concentrations (<1.3 times the upper limit of normal for the patient's age)

under treatment with SA (i.e. as a second-intention treatment in patients who are insufficiently sensitive to SA; they should then be associated with SA).

9. Place of somatostatin analogs

First-generation SA (octreotide and lanreotide) especially bind the sst2 and (to a lesser degree) sst5 somatostatin receptor subtypes [13,75]. The new analogs presently under development, including SOM230, have an identical affinity for sst2 and sst5.

SA have many valuable features, including effectiveness, rapid action, good tolerance, lack of interference with anterior pituitary function, no tachyphylaxia, but a major drawback, i.e. cost.

9.1. Results of treatment with SA

- the effectiveness of SA as regards hormonal control is between 64 and 74% during the first months [76]. A time-dependent effect is suggested by several recent studies [33,77]; thus, during follow-up (which lasted a total of 84 months in the study performed by Cozzi et al. and 18 years in the study carried out by Maiza et al.), IGF-I concentration may continue to drop whereas the same dose of SA is continued;
- the antitumor effect of SA is observed in 50 to 70% of patients [40,78]. On the average, when patients are treated de novo, the reduction in tumor volume has been reported to reach 40%;
- let us stress that effectiveness varies from one study to the next, probably due to differences in the duration of treatment, in the selection of the patients, in the existence or absence of a history of surgery or radiotherapy. Finally, the expression of the receptor subtypes by the tumor probably also plays a role.

9.2. Side effects

SA may result in digestive complaints (which are generally transitory), gall bladder abnormalities (stones, sludge, etc.) which exceptionally lead to complications, an elevation in glycemia (which is, however, compensated by the drop in insulin resistance which in turn is connected with the hypersecretion of GH), alopecia, and rarely hypothyroidism and bradycardia.

Digestive side effects are sometimes significant during the first three to six months, while they are exceptional after three years of treatment [79]. Some symptomatic biliary complications (particularly choleocystitis and migration of a stone) may be observed following the interruption of treatment and may even be more frequent after the drug is discontinued than under treatment [80].

9.3. Indications

SA may be given:

- in the first intention in an acromegaly patient not operated on because he presents an invasive macroadenoma not affecting

the optic chiasma, when the patient refuses surgery or when it is contraindicated;
- in the second intention, in a patient not cured by surgery (see treatment algorithm at the end of the article – Figure 1).

The indication of SA as preoperative treatment is discussed in a specific subchapter.

9.4. Adjusting the treatment

The first GH/IGF-I test must be performed during the fourth month, at end of a dose, i.e. either just before (≤ 3 days) or rather, if possible, on the day of the fourth injection and of course before it. Subsequent tests will be performed under the same conditions if the doses of SA are increased.

If the patient is well controlled, the time between injections may be increased and/or the doses may be decreased [81–83].

If the patient is inadequately controlled in spite of maximum treatment, one of the questions raised is how long the treatment must be continued in the hope of achieving "time-dependent" effectiveness. The interval between two injections can also be shortened. Sometimes, especially when the IGF-I concentration has decreased significantly but still remains just above the upper limit of normal, it may be worthwhile to associate a dopaminergic agonist (preferably cabergolin) with the SA (see above). Under certain circumstances (tumor risk, for instance), SA may also be associated with a GH receptor antagonist [84–88] (see below). Finally, if effectiveness proves inadequate, it may be worthwhile to propose surgical reduction of the tumor or of its residue (if possible) in order to recover satisfactory sensitivity to SA, due to the lower levels of GH/IGF-I achieved after surgery [32,89].

There is no tachyphylaxia.

It is useless to prolong the treatment beyond three months when a patient evidences resistance to SA (that is, a lack of response, defined by a decrease of less than 15–20%).

9.5. Value of the acute test

It consists of following the change in concentration of GH every 20 min–1 h after a subcutaneous injection of 100 µg of octreotide.

Some physicians use the acute test in order to verify whether certain patients are totally resistant. This test would rather be useful prior to surgery, particularly when choosing whether to institute treatment with SA for three months in order to facilitate surgery (in case of response) or propose surgery immediately (in the absence of a 50% drop in GH after the test) [5].

For others, the only indication of an acute test is to check tolerance, particularly digestive tolerance.

However, prior to operation, in a patient who is not cured, even if he does not respond to octreotide administered acutely, treatment with SA shall always be attempted for a few months before going on to a third-intention treatment such as radiotherapy.

10. Place of the GH antagonist

10.1. The effectiveness of the GH antagonist has been demonstrated

This is the medical treatment whose effects on the symptoms are the most rapid and constant. In the clinical trials, at 12 weeks of treatment, the percentage of patients normalized is as high as 90% [41,90]. However, this percentage is lower (closer to 70%) in day-to-day clinical practice [42,91].

In the long term, the biological effectiveness persists, but the presence of antipegvisomant antibodies is noted in a few patients; however, this does not seem to attenuate the effect of the treatment.

As regards glucid homeostasis, pegvisomant does not have the suppressive effect of SA on insulin secretion, which may be an advantage in diabetic patients. Glycemia may improve, with even a risk of hypoglycemia in treated diabetics, which requires the clinician to check whether antidiabetic drugs are still indicated [92–94].

10.2. Side effects

Some cases of increase in the tumor volume have been observed while the patients were treated with pegvisomant [41]. The patients had not undergone radiotherapy. There is no demonstration of a causal link between treatment with pegvisomant and the increase in the volume of the tumor. The natural evolution of such tumors must be taken into account [42,43]; some of them, when they require treatment with pegvisomant, are already known to be resistant to SA and thus more liable to be aggressive. It must also be remembered that, when SA have been effective in reducing the tumor volume, their interruption (with a view to their replacement by pegvisomant) may lead to a rebound effect with reexpansion of the tumor (see the paragraph on MRI), which is then erroneously ascribed to pegvisomant.

Some cases of drug-induced hepatitis have been reported, some of which regress without requiring the interruption of the treatment [95]. Liver function tests are therefore necessary before treatment is instituted, and this must be repeated shortly, i.e. two weeks to a month after treatment is begun, and then every six months.

10.3. Indications

Since this is a third or fourth intention treatment, it is indicated:

- in case of inadequate response to surgery or radiotherapy;
- in case of resistance to SA (no normalization of IGF-I) and/or SA intolerance [96,97]:
  - it is then used alone, to replace SA,
  - association with somatostatinergic medication is used when dealing with a tumor syndrome (headaches or regrowth of the adenoma residue when the SA is discontinued), according to variable methods. Pilot studies have

suggested the possibility of administering pegvisomant on a weekly basis in such cases (at this time, no approval for use by national agencies has been obtained for these new methods) [85,88].

10.4. Practical methods and adjustment of the dosage

The medication is administered at an initial dose of 10 mg daily (some recommend a loading dose of 80 mg on the first day). The effectiveness of the treatment is judged as early as the first month by measuring the IGF-I level. The dosage is then increased 5 mg at a time until the IGF-I level becomes normal.

10.5. Monitoring the treatment

- monitoring the GH concentration is not called for, the more so since some methods used to measure GH recognize pegvisomant [98]. Monitoring is performed by measuring IGF-I every four to six weeks, for the purpose of obtaining a normal concentration of IGF-I, while avoiding too large a drop in the IGF-I level;
- monitoring includes regular liver function tests and a pituitary MRI on the sixth month, then every six months or every year;
- the monitoring of glycemia must be reinforced in diabetic patients treated with oral hypoglycemic agents or insulin (risk of hypoglycemic episodes).

11. Place of radiotherapy

Pituitary radiotherapy must involve an irradiation of 45 Gy in order to be effective.

Serious side effects have been reported with "conventional" fractioned radiotherapy: an excess of cerebral vascular accidents (CVA) [99], occurence of second tumors (meningiomas, brain tumors) [100]. The relative risk of CVA-related mortality is increased (RR = 1.67, $p = 0.02$) [46].

The alternatives to conventional fractioned radiotherapy available in France are fractioned stereotactic radiotherapy, linear particle accelerator (LINAC), radiosurgery (gamma-knife) where, in this case, the dose is administered in a single session.

Effectiveness as regards GH control increases with the time elapsed following treatment:

- out of 884 patients treated with conventional fractioned radiotherapy, the GH concentration was below 2.5 µg/l and the IGF-I concentration was normalized in 22% of the patients at two years, 36% at five years and 53% at 10 years [101]. The results reported by Barrande et al. (128 patients) are quite similar [102] and go against the assertions of Barkan et al. [103];
- the gamma-knife results of good control in 21% of patients at two years and 28% at five years [104];
- with fractioned stereotactic radiotherapy, control was obtained in 24% of patients at five years [105].

Whatever the technique used, the initial GH concentration is predictive as regards the results (and especially the time required

to obtain them): thus, no patients are normalized when the GH concentration is greater than 30 ng/ml (90 mIU/l), whereas 100% of them are when it is less than 10 ng/ml.

Ultimately, the results, in terms of effectiveness in controlling the hypersecretion of GH, are quite similar regardless of the study and technique, and appear to be somewhat disappointing. Better results were expected with treatments that targeted the pituitary more specifically. Theoretically, conventional radiotherapy, which includes the whole tumor, should produce better results than the gamma knife, since somatotropic adenomas can invade the dura mater, but no study confirms this hypothesis. Conversely, the results of the gamma-knife could be expected to be better since this technique is usually used for smaller tumors which secrete less GH.

Pituitary deficiencies secondary to stereotactic radiotherapy or to the gamma-knife are quite frequent (as high as 30% at 10 years), as in the case of conventional radiotherapy. Moreover, Castinetti reports two transitory neurological episodes (gamma-knife) [104]. No CVA-type secondary effect or second tumor has been (for the time being?) reported following gamma-knife treatment.

To sum up, a gamma-knife radiotherapy is advised when there is a tumor remnant located at a distance from the chiasma (more than 5 mm), together with resistance to SA. A small adenomatous remnant located in the cavernous sinus is considered by all to be an ideal indication for stereotactic radiotherapy.

Medical treatment (SA or dopaminergic agonist) is pursued initially following radiotherapy, with repeated interruptions for purposes of reevaluation. Opinions vary as to the advisability of discontinuing SA transitorily at the time of radiotherapy (in order to improve the results of the radiotherapy).

In practice, many physicians concerned about the side effects of conventional radiotherapy remain little inclined to propose radiotherapy in the second intention and more readily discuss pegvisomant now that a drug that can be used in cases of failure of SA treatment or SA intolerance is available.

12. Follow-up

Follow-up is guided by the monitoring of three parameters:

- damage to brain structures: MRI evaluation shall be performed annually when there is a remnant (preferably every six months, at any rate initially, under treatment with pegvisomant). As stated above, it will be less frequent (every two years, if not more) when the patient is well controlled by SA;
- damage to pituitary function, which may persist or appear after surgery, and which must be reevaluated annually in patients treated by radiotherapy;
- complications of the disease. The frequency of regular reevaluation of course depends on the control of GH hypersecretion:
  ○ when the disease is out of control, an evaluation of the complications, identical to the one carried out at the time of the diagnosis (see above) is renewed each year (except for digestive follow-up: see below),

  ○ when the disease is under control, screening tests (colonoscopy, PSA, mammogram, etc.) are advised with the same frequency as in the general population. Otherwise, the tests are repeated annually,
  ○ when the patient is cured, a visit appears necessary every year for five years, and then every two years on a lifelong basis, with a measurement of IGF-I at each visit,
  ○ whether or not the acromegaly is under control, psychological follow-up (changes in the face), dental problems and fertility problems must be kept in mind;
- special case of digestive follow-up (colon polyps). Since 14 to 20% of patients will experience a recurrence of polyps, colonoscopy shall be performed as part of follow-up, with a few nuances [106]:
  ○ at three years, when a polyp was present and when IGF-I concentration remains high,
  ○ at five years, when no polyp was seen upon initial exploration, but when IGF-I concentration remains poorly controlled,
  ○ conversely, when the initial colonoscopy was normal and the IGF-I concentration was normalized as soon as treatment was begun, screening identical to that performed in the general population appears to be sufficient (i.e. either repeat the test after the age of 50 in a patient diagnosed when young, or monitor via Hémocult®).

13. Treatment algorithm

Any algorithm, because it aims to be schematic, is open to discussion [26,107]. In difficult cases, it appears essential that the treatment decision be the result of a multidisciplinary meeting (endocrinologists, neurosurgeons, neuroradiologists, and even radiotherapists).

A suggested decisional treatment algorithm is proposed in Fig. 1.

The first intention treatment for microadenomas is surgery (Fig. 1A).

One of the important questions is the place of surgery in the treatment of macroadenomas. It shall be proposed in the first intention if the chances of a cure are sufficient (50%? 70%?). Some elements do in fact provide reason to believe that surgery will result in a cure (size under 10–15 mm, adenoma located at a distance from the cavernous sinus, weakly secreting adenoma, etc., and, obviously the experience of the surgeon). This discussion can, by the way, be conducted with the patient.

Macroadenomas not dealt with surgically are treated medically (Fig. 1B). Surgical treatment may be proposed secondarily (tumor reduction surgery) if medical treatment is ineffective.

When SA are effective, two attitudes shall be discussed:

- either long-term medical treatment (Fig. 1A and B);
- or radiotherapy in order to attempt to wean the patient secondarily from his or her medical treatment.
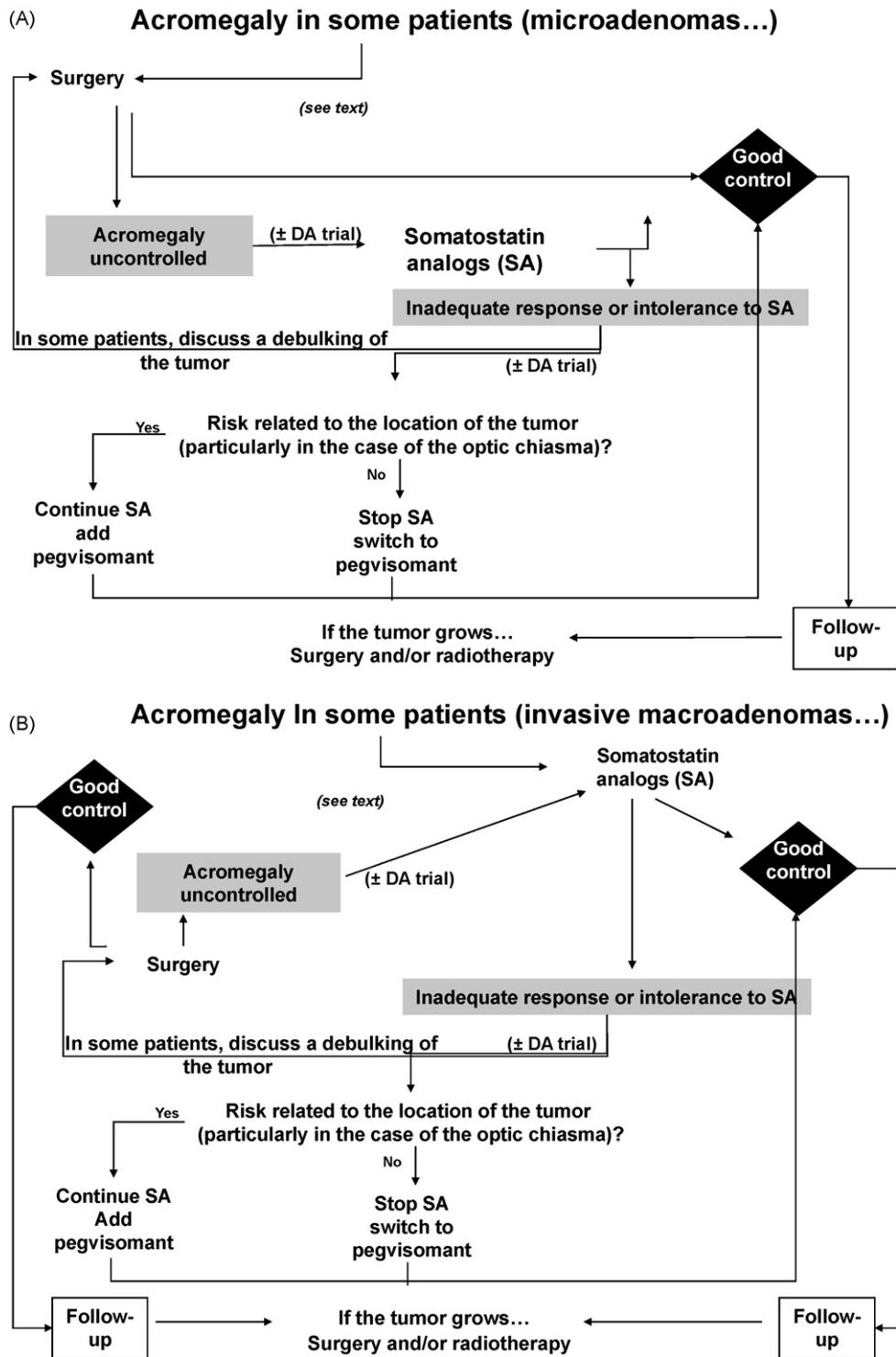
Fig. 1. Therapeutic strategy in acromegaly according to the adenoma size. The choice between radiotherapy and pegvisomant is controversial. DA: dopaminergic agonists.

Stratégie thérapeutique dans l'acromégalie en fonction de la taille de l'adénome. Le choix entre radiothérapie et pegvisomant est controversé. DA : agonistes dopaminergiques.

When the patient is partly controlled by SA (moderately elevated IGF-I and/or discordance of GH figures), various options shall be discussed (Fig. 1A and B):

- reduce the interval between injections;
- associate SA and dopaminergic agonist;

- propose tumor debulking surgery in order to reduce the concentrations of GH/IGF-I and hope that a second attempt at SA treatment will prove more effective.

In cases of SA resistance or intolerance, the choice between radiotherapy and pegvisomant is controversial (Fig. 1A and B).

But for many physicians, radiotherapy is rather recommended as the last resort. On the contrary, when dealing with a very aggressive adenoma, which continues to progress in spite of surgery and administration of SA, radiotherapy shall be resorted to earlier.

Appendix 1. The various GH measurement kits available in France in 2008

The limit of detection in mU/l is given for each kit.

Beckman Coulter	Access Ultrasensitive hGH	QE	0.009 mU/L
Beckman Coulter	Irma GH (Immunotech)	BO	0.1 mU/L
Brahms France	hGH-Irma (Biosource)	AM	0.2 mIU/L
Diasorin SA	HGH-CTK/Irma	B9	0.12 mIU/L
Diasorin SA	Liaison hGH	S8	0.15 mU/L
DPC France	Immulite & Immulite 2000 & Immulite 2500 hGH	SA	0.03 mU/L
Perkin Elmer Instruments	Delfia/AutoDELFIA hGH	KC	0.03 mU/L
CIS Bio International	RIA gnost (CT)	BN	0.03 mU/L
Tosoh Bioscience	AIA Pack/STAT AIA Pack HGH	DL	0.21 mU/L

Appendix 2. Physiological and pathological situations in which the interpretation of IGF-I levels is difficult

Physiological and pathological situations	Direction of variation of IGF-I
Pregnancy	Increases
Puberty	Increases
Hepatic insufficiency	Decreases
Fasting and undernutrition	Decreases
Severe intercurrent illnesses	Decreases
Renal insufficiency	Decreases
Hypothyroidism	Decreases
Uncontrolled diabetes	Decreases
Oral Estrogen treatment	Decreases

French version

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