PROGRESS IN THE TREATMENT OF PITUITARY ADENOMAS

Josef Marek

REZUMAT
În prolactinoame, agonistii dopaminergici reprezintă prima linie de tratament, cau mai eficientă dintre acesta fiind cabergolina. În acromegalie, costul tratamentului medical, care trebuie să dureze toată viața, impiedică folosirea pe scară largă a analogilor de somatostatină și a agonistilor de hormon de creștere. În multe centre tratamentul de elecție pentru adenomele acromegale este cel chirurgical. Dacă adenomul nu este îndepărtat complet prin intervenția chirurgicală, este utilizată iradiera tumorii restante prin radiochirurgie. La toți pacienții cu acromagile tratamentul trebuie să fie strict individualizat. În boala Cushing tratamentul de elecție este cel chirurgical. Radiochirurgia este cel mai eficient în tratamentul tumorilor restante secretoare de ACTH. Tratamentul medical este doar adjuvant și se adresează în principal pregătirii preoperatorii a pacientului sau acoperirii intervalului dintre intervenția chirurgicală și efectul maxim al radiochirurgiei. Tratamentul adenomelor secretoare de TSH necesită de obicei combinarea metodelor chirurgicală, radioterapică și medicală, cu anolog de somatostatină. Neurochirurgia rămâne singura metodă eficientă de tratament a adenomelor mari, nefuncționale, în special a celor care vin în contact cu tractul optic. În tumorile nefuncționale mai mici de 30 mm în diametru radiochirurgia este eficientă în prevenirea creșterii în 99,5% dintre ele și determină reducerea dimensiunilor lor în 64% din cazuri.

Cuvinte cheie: adenom pituitar, acromegalie, boală Cushing, adenom nefuncțional, tratament

ABSTRACT
In prolactinomas dopaminergic agonists represent the first line treatment, cabergoline being the most effective among them. In acromegaly the cost of the lifelong medical treatment hinders the vast use of somatostatin analogues and growth hormone antagonist. In many centres surgery remains the first line treatment of acromegalic adenoma. If an adenoma is not completely removed by surgery, it is useful to irradiate the remnant by radiosurgery. In all patients with acromegaly the treatment should be individually tailored. In Cushing’s disease the neurosurgery is the treatment of first choice. In treating the tumorous remnants of ACTH secreting adenomas radiosurgery has the best results of all hormonally active adenomas. Medical therapy is only adjunctive one, mostly to prepare a patient for surgery or to cover the interval between surgery and the full effect of radiosurgery. The treatment of TSH secreting adenoma necessitates usually the combination of surgery, radiotherapy and medical treatment by somatostatin analogues. Neurosurgery remains the only effective treatment of large functionless adenomas, especially those with contact to the optic pathway. In functionless tumours smaller as 30 mm in diameter radiosurgery is effective in preventing of growth in 99.5% of them and results in diminishing their size in 64%.

Key Words: Pituitary adenoma, prolactinoma, acromegaly, Cushing’s disease, functionless adenoma, treatment

The review is aimed to summarize the recent trends in the treatment of pituitary adenomas.

1. Prolactinomas.
Options for the treatment of prolactinomas are: mere observation, medical therapy with dopaminergic agonists (DA), surgery and radiotherapy. Medical therapy affords the greatest benefit-to-risk ratio and is generally considered the primary therapy of choice. Microprolactinomas which do not cause any symptoms, such as microprolactinomas in postmenopausal women, probably need not to be treated. The only concern which is not solved up-to-date, is a possibility that high prolactin levels may promote the development of mammary carcinoma.1 Symptomatic prolactinomas should be treated. Most prolactinomas found in women are microadenomas. Some surgical centres prefer to treat microprolactinomas with microsurgical techniques and claim the success, i.e., the normalisation of serum prolactin, in about 70% cases.2 A recurrence of about 17% of microprolactinomas is reported, what means an overall long-term prolactin normalisation in 53%. DA can achieve the restoration of normal prolactin.
in microprolactinomas in up 95%. The main objection against the medical therapy is the length of the treatment, which must be sometimes prolonged up to menopause. However, there is a subset of patients with microprolactinomas (26%) that can maintain normoprolactinaemia after drug withdrawal if the treatment is prolonged sufficiently. Approximately 20% of pregnant women become normoprolactinaemic after delivery.

In large macroprolactinomas the role of medical therapy increases. Prolactin is normalised by surgery in about 10-40% of patients with a high recurrence rate. The overall long-term cure is estimated to 0–20%, meanwhile DA achieve normal serum prolactin in up to 80% patients with macroprolactinomas. Besides normalising hyperprolactinaemia, DA reduce size of prolactinomas in about 80% of treated patients. This regression is because of involution of the rough endoplasmatic reticulum and Golgi apparatus followed by vacuolisation and fragmentation of cells. 80% of responders show shrinkage of more than 25% of volume and some adenomas disappear completely. In “normal responders” the maximal regression is seen in 6-12 months of treatment, but there is a group of “slow responders” with maximal regression up to 36 months. However, degenerative changes with pseudocystic formation may continue for many years. The extent of tumour size reduction does not correlate with the extent of reduction of prolactin levels.

Among DA two drugs are used worldwide: bromocriptine and cabergoline. Bromocriptine was the first drug used since more than 30 years ago. In comparison, cabergoline showed: 1) to be better tolerated, 2) to have higher affinity to D2 receptors and hence better effects even in some bromocriptine resistant adenomas and 3) to have a long biological half-life permitting the administration once or twice weekly. It is possible to administer both drugs also by intravaginal route. In some countries other DA are used such as pergolide, quinagolide, lisuride and terguride. They have no advantage in comparison with cabergoline.

Because of possible side effects, the doses of all DA should be increased gradually. For large prolactinomas it is better to start with cabergoline which is more effective. The switch from bromocriptine to cabergoline in resistant cases is possible, but the results are worse than in patients where cabergoline is started as a primary therapy. Usual doses with bromocriptine are up to 7.5 mg daily and with cabergoline up to 4 mg weekly. In resistant cases the dose should be increased – with bromocriptine to 20 mg. The highest dose reported with cabergoline was 21 mg/week. With tumour shrinkage the amount of DA can be reduced, usually to a low maintenance dose. Men with prolactinomas have usually low testosterone levels because of hyperprolactinaemia. With the decrease of prolactin levels, testosterone has a tendency to normalise, but the normalisation may be slow. Such patients are usually given testosterone analogues as a replacement therapy. Testosterone is aromatised to estrogens and estrogens stimulate prolactin secretion. In such cases, the supplementation of a selective aromatase inhibitor like anastrozole was recommended. In such cases it is necessary to avoid all other prolactin stimulating drugs.

For prolactinomas resistant to dopaminergic treatment a new class of drugs is emerging: novel somatostatin / dopaminergic chimeric ligands were developed which contain structural elements of both, somatostatin and dopamine agonist in a single molecule. After binding of a ligand, both receptors were shown to hetero-oligomerize and thereby enhance their functional activity in decreasing prolactin levels in prolactinomas as well as growth hormone in acromegaly. Such compound which binds to dopamine D2 (DAR2) receptor and somatostatin 2 (SSTR2) receptor was called BIM-23A387. Another compound under development binds to SSTR2, SSTR5 and DAR2 and may have still more profound effects. A selective somatostatin analogue for SSTR1 receptor – BIM-23926 – is claimed to be effective in prolactinomas as well.

The indication for surgery in the treatment of prolactinomas is usually given in following situations: Extensive bleeding to prolactinoma, liquorhea, resistant prolactinomas to DA, especially with compressive syndromes, and intolerance of DA. The surgery is a domain for treatment of pseudoprolactinomas, i.e., non-prolactin secreting adenomas that restrain the access of hypothalamic dopamine to lactotrop cells of surrounding pituitary. The differentiation of a pseudoprolactinoma may be difficult. Diagnosis of prolactinoma is definite with serum prolactin levels higher than 8000 mIU/l and very likely with more than 4000 mIU/l. It may be uncertain with lower levels. In such cases a therapeutic trial is necessary. In case of damage to visual fields the therapy with DA is instituted and continued for three weeks. In non-resistant prolactinomas subjective improvement is present during the first week and perimeter improves in 2-3 weeks. If there is no improvement, such a patient should be sent for neurosurgery. In case there is no damage to visual fields, we check MRI of pituitary in 6 months. Rarely, a prolactinoma first responds to DA but later on
demonstrates new growth of the tumour. In such a case, there is a suspicion of a pituitary carcinoma with prolactin secretion.

In pregnancy we use to interrupt the treatment in patients with microprolactinomas because of only a small risk of clinically significant tumour enlargement (about 1%). In macroprolactinomas, where the possibility of the tumour growth under the stimulation of high levels of estrogens is high (about 20-25%), we continue with DA throughout the pregnancy. There is no evidence of any harmful effect of DA on pregnancies.

In some cases, after normalisation of prolactin levels women do not ovulate. In such cases the combination of DA with ovulation stimulators like clomifene is advisable. In men hyper-prolactinaemia causes decrease in testosterone secretion. The restoration of normal testosterone levels may be delayed and if the prolactinoma is not resistant to dopaminergic agonists (see above), the replacement by testosterone analogues should be instituted. Even with normalisation of serum testosterone levels, sexual dysfunction may persist in some patients.

The conventional fractioned radiotherapy is not used with much effect in the treatment of prolactinomas. We have experiences with radiosurgery by Leksell gamma knife (LGK). The irradiation by LGK normalised prolactin levels in 50% of patients with prolactinomas resistant or intolerant to DA and substantially decreased prolactin levels in others. In our clinic the supplementation of DA to irradiated patients normalised prolactin in most of them.

2. Acromegaly

At present time there is a worldwide discussion on the first-line treatment in patients with acromegaly: surgery or medical treatment.12,15

The main reason for preference of surgery is to avoid the necessity of the life-long treatment with expensive medicaments. Surgery achieves immediate endocrine normalisation in 70% microadenomas and 40% of macroadenomas and practically always the debulking of the mass effect, which is important especially if there is the compression of the optic nerve and chiasm.14,15 The skill and experience of the neurosurgeon is an important determinant of the favourable surgical outcome.16 It is advised that a "pituitary neurosurgeon" should operate at least 50 patients with pituitary tumours a year. The shrinkage of acromegalic adenoma with somatostatin analogues is usually not so frequent, rapid and spectacular as in prolactinomas. Pegvisomant does not decrease the size of acromegalic adenoma but its growth may continue during the treatment. On the other hand some pituitary adenomas are not easily removable by surgery (i.e., when extended to cavernous sinus) and in some cases the surgery may be contraindicated because of poor state of the patient status. In these cases other forms of treatment like medical treatment and radiosurgery may replace or may be complementary to surgery. According to most authors, the treatment should be individually tailored for each patient.17

The medical treatment of acromegaly is possible with dopaminergic agonists, long-acting somatostatin analogues, combination of somatostatin analogues and dopamine agonists and GH receptor antagonists.

Dopaminergic agonists (DA): DA such as bromocriptine, lisuride or terguride bring the endocrine (growth hormone plus IGF-1) normalisation in only about 10% of patients. Cabergoline is more successful with 30% endocrine normalisation and 50% reduction of the size of adenoma. Like with other medical treatments, the effect of DA depends on the activity of the adenoma. In less active adenomas, with IGF-1 levels less than 750 mg/l, the effect of cabergoline may bring normalisation in 50% of treated patients. Dopaminergic agonists may be especially useful in mixed GH/prolactin secreting adenomas.18

Somatostatin-analogues: There are two long-acting (slow release) somatostatin analogues: octreotide and lanreotide. For treatment of acromegaly the long acting (slow release) forms with 28 days duration are preferable. Octreotide, Sandostatin LAR® Novartis, is available in injections 20 mg to start with, 10 mg to reduce the dose when 20 mg is fully effective and 30 mg to increase the dose when 20 mg has not sufficient effect.19 The i.m. injections are given once in 4 weeks. Subcutaneous forms which should be injected 3 times daily are good for testing the effectiveness of octreotide. Lanreotide, Somatuline autogel® Ipsen, is produced as injections of 60, 90 and 120 mg.20 They are also injected once every 4 weeks. Success of both somatostatin analogues is comparable: using strict criteria about 50-60% of treated patients normalise their GH and IGF-1 levels.21 Moreover they may have an additional benefit: induction of IGF binding protein 1 (IGF BP1), which makes less free IGF-1 available for action. The shrinkage of adenomas is seen in about 50% of patients. In 25% of them the decrease in their volume is more than 50%. The development of new somatostatin analogues is promising. Octreotide and lanreotide bind with high affinity only to somatostatin receptor 2 (SSTR 2). However, some acromegalic adenomas express predominatly somatostatin receptor 5 (SSTR5). New somatostatin
analogues SOM203 of Novartis and BIM-23244 of Ipsen bind not only to SSTR2 but also to SSTR5 with high affinity. Novel somatostatin/dopaminergic chimeric ligands have been already mentioned.

If clinically indicated, the treatment with somatostatin analogues should be administered before surgery to lower risk of surgical and/or anesthetic complications. Such situations may be sleep apnea, congestive heart failure, arrhythmias, poorly controlled diabetes mellitus, or laryngeal abnormalities caused by soft tissue swelling. Up to now, it is not clear, if the pre-treatment with somatostatin analogues may improve the general surgical outcome. In some cases, decrease in the adenoma size by somatostain analogues may help the neurosurgeon to better remove the tumour.

Combination of somatostatin analogues and dopamine agonists makes the graduation of effect possible but it is relatively rare.

GH receptor antagonist – pegvisomant (Somavert® Pfizer) is a molecule of GH with nine mutations, eight of the mutations increase the affinity of pegvisomant to GH receptor and one mutation blocks the function of GH receptor by preventing its dimerisation. When given 10 – 20 mg by s.c. injection daily it normalises IGF-1 levels in 97% patients (GH remains to be high). The treatment starts with a loading dose of 80 mg. Pegvisomant is generally well tolerated and has shown a favourable safety profile in clinical trials to date except in two patients with elevated liver enzymes (transferrases). The only concern is the possible stimulation of the growth of pituitary adenomas by the negative IGF 1 – GH feedback. Up to now only two such patients have been referred, but the number may increase in future. The prevention of this re-growth may be done by the combination of pegvisomant with somatostatin analogues. In treated patients, fasting serum insulin and glucose concentrations significantly decreased as a marker of increased insulin sensitivity. IGF-1 levels must be thoroughly monitored especially at the beginning of the treatment to avoid the over-treatment with subnormal IGF-1 levels. Pegvisomant seems to be useful especially for the treatment of patients with refractory acromegaly. It is not advised as the first choice drug because additional studies are warranted to show its long-term safety.

The radiation therapy is performed either by conventional fractionated radiotherapy or by radiosurgery. Conventional radiotherapy achieved limited results only after a long latency of more than 10 years and considerable postradiation morbidity (hypopituitarism, cerebrovascular disease, psychical impairment because of postirradiation cerebral necrosis and presumably higher incidence of secondary malignant neoplasms). Much better and safe results has been achieved by radiosurgery either by Leksell gamma knife or linear accelerator. The radiosurgery enables to irradiate the tumour with high radiation doses without damage of surrounding structures. The latency to the hormonal normalisation is shorter than with fractionated radiotherapy but even so it takes in average from 3.0 to 5.5 years according to the criteria used.

In some patients the combination of all treatment modalities is necessary. In our clinic, the neurosurgery is the treatment of first choice in most cases. If not successful, the remnant is irradiated by Leksell gamma knife and treated by dopaminergic agonist or somatostatin analogue up to the hormonal effect of radiation.

3. Cushing’s disease

Selective transsphenoidal surgery remains to be the first line treatment. Medical treatment in Cushing’s disease is only adjunctive. In some advanced cases of Cushing’s disease it is advisable to decrease the activity of the disease before the surgery. Another role of the medical treatment is administration after incomplete surgery before the effect of final treatment (radiosurgery, reoperation, bilateral adrenalectomy). We use most often ketoconazol and metyrapon or their combination. Mitotan is a very effective drug, but in higher doses causes irreversible necrosis of suprarenal cortex.

Bilateral adrenalectomy is reserved only to patients where other treatments cannot normalize the hormonal activity.

Radiosurgery may be very useful to treat the tumorous remnants after incomplete surgery. In patients where surgery is not possible, radiosurgery may replace the operation as a primary treatment. The latency from irradiation to the effect is much shorter than in acromegaly and comprises one year in our patients.

4. TSH secreting adenoma

TSH secreting adenoma is a rare tumour but one of the most agressive and the combination of surgery, radiation and medical treatment must be used in combination. Somatostatin analogues represent the most effective medical treatment. They can decrease the TSH secretion in 80% of adenomas and cause the tumour shrinkage in 50% of them.
REFERENCES


