

Medical therapy for clinically non-functioning pituitary adenomas

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Abstract

Surgery is the first-line treatment of patients with clinically non-functioning pituitary adenomas (NFAs). Because of lack of clinical syndrome these tumours are diagnosed with a variable delay, when patients suffer from compression symptoms (hypopituitarism, headache and visual field defects) due to the extension of the tumour outside the pituitary fossa. Surgery is followed by residual tumour tissue in most patients. In these cases, radiotherapy is generally used to prevent tumour regrowth. However, NFA cell membranes, in analogy with GH- and PRL-secreting adenomas, express somatostatin and dopamine receptors. Treatment with somatostatin analogues (SSA) and dopamine agonists (DA) induced some beneficial effects on visual field defects and was also followed by tumour shrinkage in a minority of cases. DA seem to be more effective on tumour shrinkage than SSA. More recently, a combination treatment with both SSA and DA have been tested in a few patients with interesting results. Lack of randomized, placebo-controlled trials prevents any conclusion on the efficacy of these drugs. By contrast, use of gonatotrophin-releasing hormone analogues has been abandoned.

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Introduction

Non-functioning pituitary adenomas (NFAs) represent a very heterogeneous group of tumours, accounting for 25% of all pituitary adenomas (Katznelson *et al.* 1993). They often present with macroadenomas that cause neurological symptoms due to mass effects, as hormonal inactivity led to delayed diagnosis when compared with functioning pituitary adenomas. In fact, as recently reported by the results of a large database (Ferrante *et al.* 2006), almost all tumours were macroadenomas (96.5%) and the main presenting symptoms are visual defects (67.8%) and headache (41.4%), and the most frequent pituitary deficit was hypogonadism (43.3%).

Neurosurgery is the treatment of choice of these tumours (Jaffe 2006). However, because of frequent supra- or parasellar extension, surgery is infrequently curative, leaving tumour remnants that regrow during long-term follow-up in a significant proportion of cases (Ebersold *et al.* 1986, Harris *et al.* 1989, Colao *et al.* 1998). The use of post-operative radiotherapy is still controversial. Despite the demonstrated efficacy of

radiotherapy in preventing tumour regrowth (Colao *et al.* 1998, Turner *et al.* 1999, Boelaert & Gittoes 2001), the selection of patients who will benefit by this therapy is made difficult by the absence of specific markers of tumour aggressiveness along with the potential side effects of this procedure that include hypopituitarism, neurocognitive dysfunction and cerebrovascular disease (Gittoes 2003, Greenman *et al.* 2003, Erfurth & Hagmar 2005). In addition, development of secondary intracranial tumour might rarely follow radiotherapy (Gittoes 2003, Greenman *et al.* 2003).

However, by immunocytochemistry, the large majority of these tumours are glycoprotein producing, and less commonly are non-functioning somatotroph, lactotroph or corticotroph adenomas (Jaffe 2006). In analogy with actively secreting adenomas, a proportion of NFA (up to 90%) is shown to secrete low amounts of FSH and LH and/or their α - and β -subunits either *in vitro* or *in vivo* (Katznelson *et al.* 1993, Jaffe 2006), and the vast majority of NFA also express on cell membranes different subtypes of somatostatin and dopamine receptors in a variable amount. Based on this feature, both dopamine agonists (DA) and somatostatin

analogues (SSA) have a rationale in the treatment of NFA. However, the results of DA and SSA so far have been rather disappointing (Colao et al. 2000a), except for some case reports.

The existence of a functional interaction between dopamine and somatostatin receptors (Rocheville et al. 2000) has opened a new perspective of medical treatment for such tumours.

This review focuses on the experimental background of pharmacotherapy in NFA and summarizes literature data reporting on (SSA (octreotide or lanreotide)), (DA (bromocriptine, quinagolide or cabergoline)), or a combination of both in NFA-bearing patients. Though abandoned from several years, the data on gonadotrophins suppression using gonadotrophin-releasing hormone (GnRH) analogues is also briefly revised.

Experimental background of medical therapy in NFA

Somatostatin and dopamine actions are mediated by five specific receptor subtypes respectively, sst₁–sst₅ and D₁–D₅ (Missale et al. 1998, Hofland & Lamberts 2004). Two different isoforms of sst₂ and D₂ have also been found and characterized (Missale et al. 1998, Hofland & Lamberts 2004). The different somatostatin and dopamine receptors have variable organ-, tissue- and cytospecific distribution and play different physiological roles.

Somatostatin receptors

Somatostatin receptors have been demonstrated to be highly expressed in all pituitary adenomas, with a predominance of sst₂ and sst₅ and infrequent expression of sst₄ (Greenman & Melmed 1994a,b, Hofland & Lamberts 2001). The expression of sst₂ predicts the response to octreotide and lanreotide, the two SSA most widely used in clinical practice, showing high affinity for sst₂ and sst₅ and low affinity for sst₃ (van der Hoek et al. 2007). In NFA, the receptor subtype expressed in a higher amount was found to be the sst₃ followed by the sst₂ (which is the most expressed receptor in GH-secreting adenomas) while sst₁, sst₄ and sst₅ transcripts were detected only in a few tumours (Taboada et al. 2007). Native somatostatin (binding all ssts) and selective analogues for sst₃ and sst₂ inhibited chromogranin-A (CgA) and α -subunit levels (Pawlikowski et al. 2007). CgA inhibition also correlated with sst₅ expression (Pawlikowski et al. 2007). The expression of sst₂ and sst₅ in NFA was also associated with reduced cell viability by 20–80% (in 8 of 13 tumours sst₂ positive) and 15–80%

(in 10 of 13 tumours, all but three sst₅ positive; Padova et al. 2008). Accordingly, pasireotide (SOM230), a somatostatin analogue binding sst_{1–3} and sst₅, completely abrogated the promoting effects of vascular endothelial growth factor on NFA cell viability (Zatelli et al. 2007).

Dopamine receptors

In the normal pituitary, the D₂ mediates the tonic inhibitory control of prolactin (PRL) secretion (Lamberts & MacLeod 1990) by dopamine, and in prolactinomas drugs acting on D₂ level are able to reduce the size of the tumour and control PRL excess (Duet et al. 1994). Ligand-binding studies and scintigraphic evaluations have shown the presence of dopamine-binding sites (most likely D₂) in NFA (Bevan & Burke 1986, Hedner & Valdemarsson 1989, Kwekkboom & Lamberts 1992, Ferone et al. 1998, Colao et al. 2000b, Pivonello et al. 2004). A heterogeneous expression of D₂ isoforms was observed in 16 out of 18 NFA, while in the remaining two no D₂ expression was found (Renner et al. 1998). In gonadotrophin-immunopositive adenomas, the D₂ was mainly localized in the LH- and FSH-immunopositive cells (Renner et al. 1998). Similarly, the D₂ was found to be expressed in 67% of NFA with a prevalence of D_{2long} (50%) when compared with the D_{2short} (17%), and with both D₂ isoforms expressed in 33% of cases (Pivonello et al. 2004). The D₂ receptor is not the only dopamine receptor expressed in the pituitary gland. Indeed, the D₄ receptor, in particular its D_{4.4} variant, is also expressed, though its role in the physiology of the pituitary gland is not known (Van Tol et al. 1992). The D₄ was found to be expressed in 17% of NFA (Pivonello et al. 2004). Based on these data, the effects of different DA were investigated in these tumours both *in vivo* and *in vitro* (Bevan et al. 1992). Cabergoline administration *in vitro* inhibited α -subunit concentration in 56% of cases and this result was associated with D₂ expression (Pivonello et al. 2004).

Interaction between somatostatin and dopamine receptors

As mentioned before, D₂ and sst₅ interact physically through hetero-oligomerization to create a novel receptor with enhanced functional activity (Rocheville et al. 2000). Based on this observation, several investigators investigated whether the combination treatment with selective ligands of these two individual receptors as well as new molecules binding both receptors simultaneously could be effective in

NFA cell cultures. Florio *et al.* (2008) recently reported on 38 fibroblast-deprived NFA characterized for GH, POMC, sst_{1–5} and D₂ and (in 15 of 38 cases) D₂ long and short isoforms mRNA expression, and for α -subunit, LH and FSH release. They demonstrated that BIM-23A760, a molecule with high affinity for D₂ and sst₂, significantly inhibited ³H-thymidine incorporation in 23 out of 38 (60%) NFA cultures (Florio *et al.* 2008). However, BIM-23A760 effects were similar to those induced by cabergoline (Florio *et al.* 2008).

Clinical trials will clarify whether the experimental results will be confirmed.

Results of treatment with SSA

During the past 20 years, different SSAs have been used. The first available SSA is the short-acting form of octreotide (OCT), an octapeptide with preferential binding to sst₂ and sst₅, for s.c. administration, then another analogue, the slow-release lanreotide (LAN), showing that a similar receptor affinity for sst of OCT was made available for i.m. injections every 7–14 days. More recently, OCT and LAN have been made available for injections either i.m. or s.c. every 28–56 days respectively. The former represents OCT incorporated in microspheres of a biodegradable polymer, poly (DL-lactide-co-glycolide glucose) thus allowing the i.m. injection every 28 days (LAR), while the latter is LAN in water with no additional excipients (autogel (ATG)). The only available data so far have been produced using OCT. LAN was only tested *in vitro* in 12 NFA specimens which was shown to

inhibit phorbol myristate acetate-induced cell proliferation (Florio *et al.* 1999), while no data are available for LAR and ATG.

A few clinical trials have been conducted to evaluate potential effects of OCT in patients with NFA (Warnet *et al.* 1989, 1997, Liuzzi *et al.* 1991, Turpin *et al.* 1991, De Bruin *et al.* 1992, Katznelson *et al.* 1992, Gasperi *et al.* 1993, Merola *et al.* 1993, Plockinger *et al.* 1994, Borson-Chazot *et al.* 1997, Colao *et al.* 1999), as summarized in Table 1. Tumour reduction was reported only in 12% of cases, while the vast majority of patients had stable remnant tumours (Table 1). Importantly, only in 5% of the patients the tumour was found to increase during treatment, but generally follow-up of patients was too short (6 months in average) to draw final conclusion on a potential effect of OCT in preventing tumour regrowth. There are controversial data on the potential use of scintigraphy depicting sst expression of ¹¹¹In-pentatreotide and treatment efficacy with OCT in NFA patients (Faglia *et al.* 1991, Duet *et al.* 1994, Plockinger *et al.* 1994, Warnet *et al.* 1997, Colao *et al.* 1999). Duet *et al.* (1994) demonstrated that of the five patients with NFA who had pituitary uptake of ¹¹¹In-DTPAD-phe¹-octreotide, only the patient with very high uptake (index of 15.1) had significant tumour shrinkage after OCT treatment. Similarly, we reported (Colao *et al.* 1999) significant tumour shrinkage ($\geq 30\%$ of baseline size) in two of six NFA during long-term OCT therapy. We also found a significant correlation between percentage of α -subunit suppression after 6–12 months of OCT therapy and tumour-to-background ratio in both early and late images. In fact, α -subunit levels

Table 1 Summary results of octreotide s.c. treatment in patients with clinically non-functioning pituitary adenomas^a

Authors (year of publication)	Visual field			Tumour volume			Octreotide	
	Improved	Unchanged	Worsened	Increased	Unchanged	Decreased	Dose (μ g/d)	Duration (months)
Warnet <i>et al.</i> (1989)	3/5	2/5	0/5	0/2	2/2	0/2	100–300	1–12
Turpin <i>et al.</i> (1991)				0/1	1/1	0/1	300–450	6
De Bruin <i>et al.</i> (1992)	3/4	1/4	0/4	0/4	4/4	0/4	1200	3–6
Katznelson <i>et al.</i> (1992)	1/3	2/3	0/3				200–750	2
Gasperi <i>et al.</i> (1993)	1/5	3/5	1/5	2/8	6/8	0/8	300	3–6
Merola <i>et al.</i> (1993)	1/9	8/9	0/9	0/19	18/19	1/19	150–300	1–12
Plockinger <i>et al.</i> (1994)				2/14	12/14	0/14	300–1500	3
Liuzzi <i>et al.</i> (1991)	1/20	19/20	0/20	3/20	14/20	3/20	300–500	3–12
Warnet <i>et al.</i> (1997)	9/22	9/22	4/22	3/7	3/7	1/7	300–600	2
Borson-Chazot <i>et al.</i> (1997)	8/16	6/16	2/16	0/16	16/16	0/16	300	1
Colao <i>et al.</i> (1999)				2/9	7/9	0/9	300–600	12
Summary	27/84	50/84	7/84	12/100	83/100	5/100		

^aPubMed search using as keywords 'octreotide, lanreotide and clinically non-functioning adenomas' or 'octreotide, lanreotide and functionless adenomas'. Last search on 31 July 2008.

Table 2 Summary results of dopamine agonists treatment in patients with clinically non-functioning pituitary adenomas^a

Authors (year of publication)	Visual field			Tumour volume			Treatment		
	Improved	Unchanged	Worsened	Increased	Unchanged	Decreased	Drug	Dose (µg/d)	Duration (months)
Johnston <i>et al.</i> (1981)				0/1	0/1	1/1	BRC	20	25
Wollesen <i>et al.</i> (1982)				0/11	2/11	9/11	BRC	15–60	2–33
Wass <i>et al.</i> (1982)				0/1	0/1	1/1	BRC	7.5	4
Barrow <i>et al.</i> (1984)				0/12	6/12	6/12 ^b	BRC	7.5	1.5
Grossman <i>et al.</i> (1985) ^c				0/15	15/15	0/15	DA		3–36
Pullan <i>et al.</i> (1985)	1/5	4/5	0/5	0/5	4/5	1/5	BRC	15–37.5	10
Verde <i>et al.</i> (1985)	1/20	15/20	4/20	0/20	19/20	1/20	BRC	7.5–20	1–32
Zarate <i>et al.</i> (1985)				0/7	7/7	0/7	BRC	15–22.5	0.5–12
Vance <i>et al.</i> (1985)	1/0	0/1	0/1	0/1	1/1	0/1	BRC		
D'Emden & Harrison (1986)	3/3	0/3	0/3				BRC	7.5	1–3
Bevan <i>et al.</i> (1987)				0/8	8/8	0/8	BRC	5–40	4–12
Klibanski <i>et al.</i> (1988)				0/4	2/4	2/4	BRC	2.5–10	1.5
Van Schaardenburg <i>et al.</i> (1989)	1/25	23/25	1/25	1/25	20/25	4/25	BRC	5–22.5	18
Hedner & Valdemarsson (1989)	1/1	0/1	0/1	0/1	0/1	1/1	CV	0.3	3
Ferone <i>et al.</i> (1998)				0/6	4/6	2/6	CV	0.6	6–12
Garcia-Luna <i>et al.</i> (1989)	1/1	0/1	0/1				LAR		
Abs <i>et al.</i> (1991)	1/1	0/1	0/1	0/1	0/1	1/1	LAR		
Kwekkeboom & Lamberts (1992)	2/5	3/5	0/5	0/5	4/5	1/5	CV	0.3	12
Nobels <i>et al.</i> (2000)	0/10	6/10	4/10	6/10	4/10	0/10	CV	0.3	36–93
Colao <i>et al.</i> (2000b) ^d	3/10	7/10	0/10	0/10	8/10	2/10	DA		
Giusti <i>et al.</i> (2000)				0/1	1/1	0/1	CAB ^e		
Lohmann <i>et al.</i> (2001)	2/13	11/13	0/13	0/13	6/13	7/13	CAB	1	12
Pivonello <i>et al.</i> (2004)	4/9	5/9	0/9	3/9	1/9	5/9	CAB	1–3	12
Greenman <i>et al.</i> (2005)				7/33	15/33	11/33	BRC	5–10	12
Summary	21/104	74/104	9/104	17/199	127/199	55/199			

DA, dopamine agonists; BRC, bromocriptine; CV, quinagolide; CAB, cabergoline; LA, bromocriptine long-acting injectable repeatable.

^aPubMed search using as keywords 'bromocriptine, quinagolide, cabergoline and clinically non-functioning adenomas' or 'bromocriptine, quinagolide, cabergoline and functionless adenomas'. Last search on 31 July 2008.

^bPositive PRL immunostaining.

^cTreatment was performed with BRC, mesulergine or pergolide.

^dTreatment was performed with quinagolide or cabergoline

^eThe dose of CAB is in mg/week.

were significantly reduced in the six patients with moderate to intense uptake of ^{111}In -DTPAd-phe¹-octreotide calculated on the pituitary background ratios (Colao *et al.* 1999). It should be stated, however, that ^{111}In -DTPAd-phe¹-octreotide scintigraphy is not anymore used in patients with pituitary adenomas.

A still unexplained finding was reported by Warnet *et al.* (1989) and confirmed by De Bruin *et al.* (1992): OCT treatment was followed by a rapid improvement in headache and visual disturbances, without any change in tumour volume. This effect was likely not owing to a direct effect on tumour size but more likely to a direct effect on the retina and the optic nerve (Lamberts *et al.* 1995). Borson-Chazot *et al.* (1997) reported a positive predictive value of 61% and a negative predictive value of 100% of ^{111}In -DTPAd-phe¹-octreotide scintigraphy in predicting the improvement of visual field after OCT treatment. Conversely, Plockinger *et al.* (1994) did not find any significant value of ^{111}In -DTPAd-phe¹-octreotide scintigraphy in predicting tumour shrinkage. However, approximately in one-third of the patients there was an improvement in visual field defects (Table 1).

Results of treatment with DA

DA are the main treatment in prolactinomas (Gillam *et al.* 2006). In NFA, as shown in Table 2, the cumulative evidence for tumour shrinkage after DA therapy is 27.6% (Johnston *et al.* 1981, Wass *et al.* 1982, Barrow *et al.* 1984, Grossman *et al.* 1985, Pullan *et al.* 1985, Verde *et al.* 1985, Zárate *et al.* 1985, D’Emden & Harrison 1986, Bevan *et al.* 1987, Klibanski *et al.* 1988, García-Luna *et al.* 1989, van Schaardenburg *et al.* 1989, Abs *et al.* 1991, Kwekkboom & Lamberts 1992,

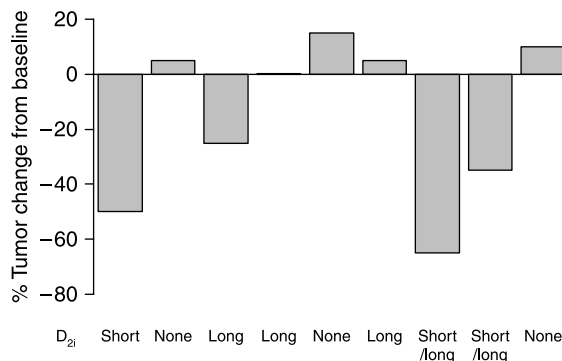


Figure 1 Individual tumour changes after 12 months of cabergoline treatment according to the expression of dopamine receptors on surgically removed tumour tissue. Data redrafted from ref Pivonello *et al.* (2004) D_{2i}, dopamine type 2 receptor isoforms.

Van Tol *et al.* 1992, Ferone *et al.* 1998, Colao *et al.* 2000b, Giusti *et al.* 2000, Nobels *et al.* 2000, Hoffland & Lamberts 2001, Lohmann *et al.* 2001, Pivonello *et al.* 2004, Greenman *et al.* 2005). When compared with that obtained with SSA (5%), the latter was significantly different (χ^2 test, $P < 0.0001$). Additionally, as also observed in patients treated with SSA, there was an improvement in visual field defects (20.2%), which was similar to that obtained with SSA (32.1%). To note, prevalence of improvement in visual field defects is even higher than that calculated in Tables 1 and 2, as we reported the data related to the entire population and not to the population of patients presenting with visual field defects before starting treatment, as this information was not available in every study. Interestingly, the rate of tumour regrowth was as low as in the SSA-treated cohort (8.5 vs 12%, $P = 0.46$). Short duration of follow-ups, both in patients treated with SSA and DA, is clearly

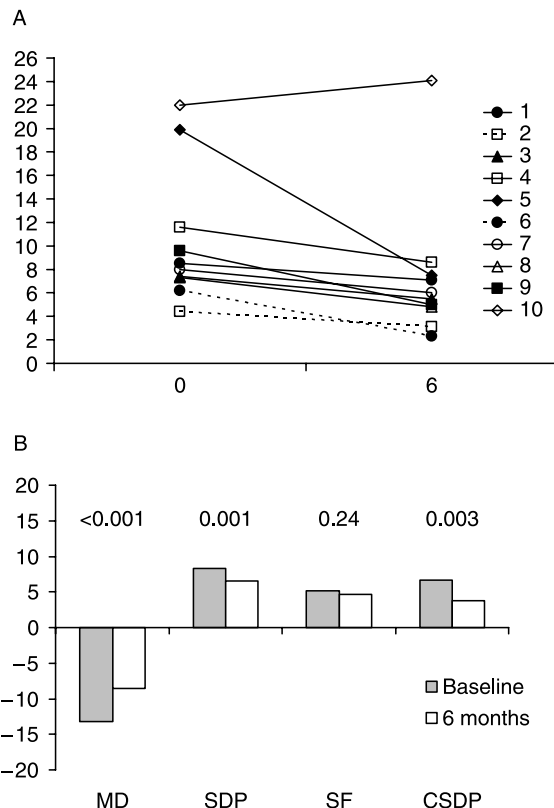


Figure 2 Treatment with a combination of lanreotide slow release (60 mg every 14 days) plus cabergoline (0.5 mg every alternate day) for 6 months in ten patients with post-surgery remnant NFA. (A) Changes in tumour volume before and 6 months after treatment as documented on MRI; (B) changes of visual perimetry before and 6 months after treatment. Data drawn from ref Colao *et al.* (2003) MD, mean defect; SDP, standard deviation pattern; SF, short-term fluctuation; CSDP, corrected standard deviation pattern.

Table 3 Summary results of gonadotrophin-releasing hormone analogues treatment in patients with clinically non-functioning pituitary adenomas^a

Authors (year of publication)	Effect on Gn			Effect on α -SU			Treatment	
	Decreased	Unchanged	Increased	Decreased	Unchanged	Increased	Dose (μ g/d)	Duration (months)
Roman <i>et al.</i> (1984)	0/1	0/1	1/1	0/1	0/1	1/1	200	1
Chapman <i>et al.</i> (1984)	0/1	1/1	0/1	0/1	1/1	0/1	600	3
Zarate <i>et al.</i> (1986)	1/1	0/1	0/1	1/1	0/1	0/1	100	5
Klibanski <i>et al.</i> (1987)	0/1	0/1	1/1	0/1	0/1	1/1	560	1
Sassolas <i>et al.</i> (1988)	0/2	0/2	2/2	0/2	0/2	2/2	100–200	2
Klibanski <i>et al.</i> (1989)	1/5	0/5	4/5	5/5	0/5	0/5	560–2540	2
Daneshdoost <i>et al.</i> (1990)	4/5	1/5	0/5	3/5	2/5	0/5	500–1000	1.5
Colombo <i>et al.</i> (1994)	4/8	1/8	3/8	0/5	4/5	1/5	1200	12
Summary	10/24	3/24	11/24	9/21	7/21	5/21		

^aPubMed search using as key words 'gonadotrophins and clinically non-functioning adenomas' or 'gonadotrophins and functionless adenomas'. Last search on 31 July 2008.

a limitation in investigating the prevalence of tumour growth. As already mentioned for ¹¹¹In-DTPAd-phe¹-octreotide scintigraphy in predicting tumour shrinkage, scintigraphy with radiolabelled dopamine analogue ¹²³I-methoxybenzamide was used to predict hormone inhibition and tumour shrinkage in NFA-bearing patients. In two different patients' series, intense uptake of ¹²³I-methoxybenzamide was associated with tumour shrinkage after CV or cabergoline (CAB) (Faglia *et al.* 1991, Florio *et al.* 2008). More recently, in 18 patients with NFA treated either with CAB or CV, *in vivo* imaging of D₂ using ¹²³I-epidepride was not associated with tumour shrinkage (de Herder *et al.* 2006). However, since medical treatment is applicable only after surgery at present, more interesting is the possibility to analyse D₂ expression on tumour specimens after surgical removal to correlate with subsequent response to DA treatment. Pivonello *et al.* (2004) demonstrated that 1 year of CAB treatment at the dose of 3 mg/week induced a more than 25% tumour shrinkage in 56% of patients with histologically proven NFA. Tumour shrinkage after CAB treatment was significantly correlated with D₂ expression (Fig. 1). Since this is only a single experience, more data have to be accumulated before a definitive conclusion can be drawn. However, the reported finding of tumour enlargement after stopping BRC treatment in NFA experiencing tumour shrinkage (Clark *et al.* 1985) support the use of DA in such patients. According with Greenman (2007), the routine use of DA can be suggested in patients with NFA for prevention of post-operative tumour remnant regrowth based on the available data and the associated sequelae to pituitary radiotherapy.

Results of treatment with a combination treatment with SSA plus DA

Several data are available on the combination treatment with SSA plus DA in patients with GH-secreting tumours (Colao *et al.* 2007). This approach has been still poorly investigated in NFA. Andersen *et al.* (2001) reported that 6 months of a combination therapy with OCT and CAB at dosages of 200 μ g thrice daily and 0.5 mg/day was reported to induce a greater than 10% tumour shrinkage in 60% of ten patients with NFA. Following these results, we attempted a combined treatment of LAN (60 mg every 14 day) plus CAB (0.5 mg every alternate day) for 6 months in a small series of ten patients with NFA undergoing pharmacotherapy after unsuccessful surgery (Colao *et al.* 2003). We found a significant decrease of residual volume (from 9.8 ± 2.1 to 6.7 ± 2.1 cm³; $P=0.04$; Fig. 2) associated with improved mean defect at visual perimetry (from -14.5 ± 0.6 to -9.5 ± 1.2 on right eye; $P=0.0006$, and from -11.9 ± 2.4 to -7.7 ± 1.8 on left eye; $P=0.02$). These patients are still undergoing active follow-up to establish whether a combination treatment might have a role in NFA patients.

Results of treatment with GnRH analogues

Based on the evidence that NFAs produce intact gonadotrophins or, more often, α -subunit, attempts were made to inhibit gonadotrophin secretion by using GnRH analogues. As shown in Table 3, only a few cases have been reported (Chapman *et al.* 1984, Roman *et al.* 1984, Zárate *et al.* 1986, Klibanski *et al.* 1987, 1989, Sassolas *et al.* 1988, Daneshdoost *et al.* 1990,

Colombo *et al.* 1994). The prevalence of patients achieving decreased gonadotrophin or α -subunit levels was similar to that of obtaining increased levels after treatment with various analogues at different dosages and treatment periods. No data are available for tumour shrinkage or visual field defects. This treatment is not anymore used worldwide in patients with NFA.

Other medical approaches

Type I interferons (IFNs) are routinely used in the treatment of chronic hepatitis B and C, multiple sclerosis and few tumours (Vitale *et al.* 2008). During the past 15 years, evidence has emerged that IFNs may play a regulatory role in hypothalamic–pituitary axis. Hofland *et al.* (1999) reported that incubation with IFN- α resulted in inhibition of the secretion of gonadotrophins and/or α -subunit in all four NFA cases (27–62%). However, in healthy volunteers, or in patients treated long term because of hepatitis or multiple sclerosis, changes of testosterone or gonadotrophin levels were found only during short-term administration (Vitale *et al.* 2008).

Conclusions

First-line therapy of patients with NFA is surgery. However, since these tumours are generally large at diagnosis, most patients present remnant tumours after surgery. In fact, of the 295 patients included into a database (Ferrante *et al.* 2006), 290 (98%) underwent surgery and on the basis of radiological findings, only 105 patients (35.5%) were considered cured (i.e. they had total tumour debulking) after surgery. Therefore, there is a need for an additional treatment in the vast majority of NFA-bearing patients. Conventional radiotherapy is reported to delay tumour regrowth (Turner *et al.* 1999, Ferrante *et al.* 2006) but causes hypopituitarism in virtually all patients after 10 years (Colao *et al.* 1998), and is associated with early cerebrovascular mortality in patients with acromegaly (Ayuk *et al.* 2004, Kauppinen-Makelin *et al.* 2005) but also in patients with NFA (Erfurth & Hagmar 2005). There is, thus, need for efficacious medical treatments for patients bearing remnant tumours after surgery. Both SSA and DA were found to be of some efficacy in selected patients with NFA, with the latter drugs being significantly more effective in reducing tumour volumes. However, no placebo-controlled long-term studies are available to suggest the use of SSA or DA or a combination of them. Therefore, on a practical point of view, the use of these compounds in patients with NFA is not evidence based.

Interestingly, Dekkers *et al.* (2007) recently reported that in 28 non-operated patients with NFA, tumour growth occurred in 14 patients (50%) after 118 ± 24 months, but spontaneous reduction of tumour volume also occurred in eight patients (29%). They thus suggested that even observation alone might be considered as a safe alternative to surgery in selected NFA patients, provided that no risk of irreversibly compromising visual function occurs. These latter findings indicate that a more conservative approach can also be attempted since NFAs are proven to grow very slowly so that surgery can be used only in patients with tumour compressive symptoms such as visual field defects, headache or hypopituitarism.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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