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ABSTRACT

Introduction: Prolactinomas represent the most common pituitary adenomas encountered in the clinic. While a majority of these tumors will be successfully treated by dopamine agonist (DA) such as cabergoline, their management becomes problematic since a resistance to DA can occur and/or if the tumor displays features of aggressiveness, two conditions that are closely related.

Areas covered: Epidemiology and medical treatment of prolactinomas; resistance to DA and molecular basis of DA-resistance; therapeutical alternatives in case of DA-resistant Prolactinomas and therapies in development; summarizing conclusions.

Expert opinion: The management of DA-resistant prolactinomas requires a multidisciplinary approach by an expert team. Along with discussions about surgery with or without gamma knife radiosurgery, genetic screening for multiple endocrine neoplasia type 1 (MEN1) syndrome is actively discussed in a case-by-case approach. In case of surgery, a careful analysis of the tumor sample can provide information about its aggressivity potential according to recent criteria. Ultimately, temozolomide can be indicated if the tumor is rapidly growing and/or threatening for the patient.

1. General considerations on prolactinomas

Prolactinomas represent the most common hormone-secreting pituitary tumor encountered in the clinic with a prevalence of 100 per million of the population [1,2]. It currently accounts for 30–40% of all pituitary adenomas (PA) and, depending on their maximal diameter, they are commonly classified into microprolactinomas (<10 mm) or macroprolactinomas (≥ 10 mm). Histopathological data previously learned us that prolactin (PRL) can be secreted by several types of PiTNETs deriving either from lactotrophs, somatotrophs or mammosomatotrophs cells. Likewise, sparsely or densely granulated lactotroph tumors, acidophil stem cell tumors, poorly differentiated Pit1-lineage tumors can also lead to hyperprolactinemia. Therefore, in the following sections we will exclusively refer to the most common type of PRL-secreting PiTNETs, namely the one arising from lactotroph cells and called as Prolactinomas thereafter. Prolactinomas are overwhelmingly diagnosed in women population with a sex ratio estimated to be 10:1 before the fifth decade [3]. After this age, the frequency of Prolactinomas is the same in both gender, although macroprolactinomas are generally diagnosed at a later age in men as compared to women (median age incidence of 51 years in men vs. 34 to 42 years in women). In children and adolescents, PA is a rare pathological condition (less than 2% of all intracranial tumors) and prolactinomas represent about half of the PA phenotypes encountered in this population [4].

Because of their remarkable response-to-treatment, their slow-growing behavior and their almost non-existent propensity to metastasize, Prolactinomas represent the archetype of benign tumors. In few cases however, they can present with stigmas of aggressivity represented by either invasion of perisellar structures (e.g. the cavernous sinus) and/or several relapse in spite of a well-conducted treatment. Accordingly, pathologists and clinicians adopted the terminology Pituitary Neuroendocrine Tumors (PiTNETs) instead of PA [5].

In exceptional cases, the primitive PRL-secreting tumor can be complicated by releasing of tumoral cells in the cerebrospinal fluid and/or distant metastasis in the central nervous system, two conditions that defined a PRL-secreting carcinoma [6].

The clinical symptoms and complains from patients diagnosed with microprolactinomas are usually the consequence of the hyperprolactinemia-induced gonadotroph deficiency, namely irregular menstruation or amenorrhea, decreased libido and erectile dysfunction. These symptoms reflect the inhibitory effect exerted by PRL on the reproductive axis by reducing both the secretion and pulsatility of gonadotropin-releasing hormone (GnRH) neurons from the hypothalamus [7,8]. The latter effect could be mediated through inhibition of Kisspeptin neurons, which express PRL receptors and are major regulators of GnRH neurons [9,10]. The involvement of Kisspeptin neurons have been also demonstrated in both sexual and emotional functions which could, at least partially, explain the decreased libido observed in patients with hyperprolactinemia [11]. Besides irregular menstruations, PRL-secreting PiTNETs can cause galactorrhea and be associated

with an increased risk of vertebral fractures in both men and women [12,13].

In macroprolactinomas, symptoms at the diagnosis include headaches, visual field impairment, symptoms related to anterior pituitary deficiencies and/or hyperprolactinemia [14].

Accordingly, the aim of the therapy in patients with macroprolactinomas is therefore twofold:

(1) to reduce and ideally normalize the serum PRL levels.
(2) to control the tumor volume, with recovery of the visual defect and/or pituitary functions when deficient.

The aim of this review is to summarize the current and recent therapeutical strategies to optimize the clinical management of difficult-to-treat macroprolactinomas.

2. The medical treatment of prolactinomas

In patients with Prolactinomas, we previously assumed that the aim of the therapy is to restore normal gonadal functions, fertility and to reduce tumor size [15]. DAs represent the cornerstone of the medical treatment and are always discussed as the first-line therapy in micro- as well in macroprolactinomas [16]. Their action is based on the property the lactotroph adenoma cells has to express high level of the dopamine receptor subtype 2 (D2DR) which, once binded by DA, led to the inhibition of both PRL secretion and cell proliferation [17]. Three DA are currently available, two that are ergot-derived compounds (i.e cabergoline and bromocriptine), and one, quinagolide, which is a non-ergot-derived DA [18]. All of these DA are orally administered and their efficacy in the treatment of macroprolactinomas or in case of primary resistance to DA is briefly resumed in Table 1.

2.1. Bromocriptine

Bromocriptine (BRC) is the first DA which were used for the treatment of Prolactinomas as its prescription started at the end of the 80's [19,20]. A posology ranging from 2.5 mg to 15 mg per day (median of 7.5 mg per day) is commonly used but higher doses until 20 to 30 mg per day can be required in almost a third of patients [21]. Results of a plethora of studies indicate that for microprolactinomas, BRC succeeds to normalize PRL levels, restores gonadal functions and decreases tumor mass in 80–90% of patients, while similar outcomes are found in 70% of patients with macroprolactinomas [21]. One of the major issues of BRC is the occurrence of adverse side effects, which can be observed in up to 10–12% of patients and mainly represented by digestive (nausea/vomiting, constipation, reflux, pain), neurological (headaches, dizziness, confusion, dyskinesia) and cardiovascular (postural hypotension, syncope) symptoms [22,23]. They generally occur after the initial dose and with dosage increases, but can be minimized by introducing the drug at a low dosage (0.625 or 1.25 mg/d) at bedtime, by taking it with food, and by very gradual dose escalation [1]. BRC has been largely superseded by other DA with longer lasting effects and improved side effect profiles. Even its historical preferential use over others DA during pregnancy is now null [24].

2.2. Cabergoline

Cabergoline (CAB) is a selective D2DR agonist which currently represents the most efficient DA as compared to BRC and quinagolide [25,26]. In a retrospective study assessing 455 cases of hyperprolactinemia, amongst who 41% and 42% were due to PRL-secreting micro- and macroadenomas, respectively, the PRL excess had been normalized in a total of 86% of cases under cabergoline treatment [27]. More specifically, the normalization of PRL level was obtained in 77% of patients with macroprolactinomas [27]. Similar results were observed in successive studies, which, in parallel, demonstrated that CAB restored menses in 82% of women with amenorrhea [25], improved fertility by normalizing the sperm quality and sexual function in male [28] and eventually led to a significant tumor shrinkage in around 90% of patients with Prolactinomas [29]. Male gender, invasive growth and giant tumors (i.e. diameter >4 cm) are associated with a lower response to cabergoline [30–32]. A starting posology of 0.5 mg/week is common, including in cases of macroprolactinomas, as the antitumor effect observed with this compound can be both massive and rapid, as exemplified by the occurrence of chiasmal herniation (and visual field impairment) that have been described with low posologies of CAB [33]. Similarly, cases of cerebrospinal fluid rhinorrhea were described in the weeks following the initiation of CAB when the macroprolactinoma invaded the sphenoidal sinus [34]. If low doses of CAB do not normalize hyperprolactinemia and if the patient tolerance is good, it is worthwhile to progressively increase the dose of the drug. As such, around 60% of patients with macroprolactinomas will achieve a normalization of their hyperprolactinemia under CAB in an average delay of less than two years [35]. In a monocentric study, 44 patients (19.6%) received CAB doses >2 mg/week with an average interval of 8 months between each dose increment, and a definitive CAB resistance diagnosed in half of the patients (21 had a partial response to CAB with decrease but no normalization of PRL level and 1 was unresponsive at all) [35]. Thus, increasing the dose of CAB with periodical monitoring of both PRL levels and tumor volume seems reasonable over a period of 24 months, before stating that the tumor is resistant. Whether increasing the posology of CAB can expose the patient to develop cardiac valvulopathy was still source of uncertainty. However, a recent study showed that for the posologies generally used in the treatment of

Table 1. **Overview of the main studies summarizing the efficacy of dopamine agonist in patients with macroprolactinoma and/or primary resistance to bromocriptine**. BRC, bromocriptine; QNA, quinagolide.

Dopamine agonist (DA)	Population of the study	Inhibition of prolactin secretion in % of patients (N: normalization; D: decrease)	Tumor volume decrease (TVD) and disappearance (TD)	Major side effects	Ref.
CABERGOLINE (CAB) (dose/week)					
0.25 to 2 mg	*N* = 23 prolactinomas 3 operated before CAB treatment 8 previously treated with BRC	N: 82% at 12–24 months.	TVD ≥ 80% in 61% patients at 24 months. TD in 6 patients at 12 months	None	[132]
0.25 to 10.5 mg	*N* = 85 macroprolactinomas 18.8% resistant to BRC 37.6% intolerant to other DAs	N: 61.2% at 15 months D ≥ 75% in 28% at 15 months	TVD ≥ 25% in 53% patients at 15 months TD in 12.9% patients at 15 months	4.7% stopped the treatment	[133]
1.5 to 10.5 mg	*N* = 10 prolactinomas 4/10 operated before CAB therapy, without modifying the prolactin levels or the tumor size.	N: 50% at 12 months	TVD ≥ 25% in 90% patients at 12 months	None	[80]
0.5 to 7 mg	*N* = 41 macroprolactinomas Only men	N: 75.6% at 24 months. *10 patients classified as resistant (non- normalization with CAB>2 mg per week), dose increased to 7 mg per week without significant decrease.*	TVD: 100% at 24 months (reducing in diameter up to 73.7%) TD: 30% at 24 months.	None	[28]
0.5 to 12 mg	*N* = 57 macroprolactinomas	N: 98.2% at 12 months	NR	None	[46]
1 to 8 mg	*N* = 18 giant PRL-secreting adenomas (max size >60 mm) *NB: 1 patient treated with BRC 15 mg/day*	N: 11/18 patients (median: 20 months) D: 6/18 patients	TVD >90% in 8 patients 33% < –90% 7/18 reduction >33% at 7,8 years	3/18 CSF leak	[78]
1 to 5 mg	*N* = 47 giant prolactinomas	N: 68% at 3,5 years D: 19% decreased <100 ng/mL	TVD >50% in 87% patients TD: in 11% of patients	One case of CSF leak after initiation of therapy that resolved upon dose reduction.	[134]
0.5 to 8 mg	*N* = 260 macroadenomas 220/265 were treated with CAB 116/220 had only CAB	N: 60.8% of the 220 patients N: 71.6% of the 116 patients	NR	CSF leak occured in 8 patients	[35]
OTHER DOPAMINE AGONISTS					
BRC (dose 17.5 to 105 mg/week) CAB (dose 0.25 to 6/week)	*N* = 100 macroprolactinomas 65 patients have been treated by DAsalone	N: 60% at 7.3 years	NR	None	[135]
BRC (15/34 patients, dose: 5 to 30 mg/day) CAB (18/34 patients, dose from 0.5 to 7 mg/week) One patient with pergolide	*N* = 34 giant prolactinomas in women Follow-up 3 to 198 months	N: 7/15 (47%) under BRC N: 10/18 (55%) under CAB N: 1/1 (100%) under Pergolide	TVD: 79% under CAB >30% reduction	4 CSF leak (11,76%)	[31]
BRC (24/25 patients, dose from 2.5 to 15 mg per day) CAB (in 1/25 patient, dose 2 mg/week)	*N* = 25 giant prolactinomas	N: 76% patients (at 135 months).	TVD: 100% at 135 months (mean 98% decrease) TD: 76% had almost completely disappeared tumor.	One CSF leak who underwent surgery	[136]
QNA (dose from 0.075 to 0.4 mg per day)	*N* = 12 macroprolactinomas	N: 67% at 31.6 months	TVD: 75% a 31.6 months	2 patients present severe psychiatric disorders (severe depression and one suicidal ideas	[41]

(*Continued*)

Table 1. (Continued).

Dopamine agonist (DA)	Population of the study	Inhibition of prolactin secretion in % of patients (N: normalization; D: decrease)	Tumor volume decrease (TVD) and disappearance (TD)	Major side effects	Ref.
QNA (dose from 0.075 to 0.75 mg per day)	*N* = 107 patients previously treated with BRC and considered as BRC-resistant. 80 patients had a macroadenoma	N: 44% at 9.8 months	TVD: 100% in all patients (mean 31%) TVD >50% in 19.5% of patients TVD: 20/58 patients in the subgroup of macroadenomas without radiotherapy TVD >50%: 11/20 patients	11 (10.2%) patients had to discontinue treatment because of adverse reactions.	[137]
QNA (dose from 0.075 to 0.6 mg/day) CAB (dose from 0.5 to 3 mg/week)	*N* = 16 macroprolactinomas 12 months QNA next to 12 months CAB with a washout period. *Note all patient reincreased their PRL levels in the wash-out period.*	N: 14/16 for QNA At 12 months N: 14/16 for CAB at 12 months	At 6 months TVD >80% in 4/16 patients with TD in 2 patients in the QNA group TVD >80% in 5/14 patients with TD in 2 patients in the CAB group	None.	[42]

Prolactinomas, the use of CAB was safe and did not overexpose the patient to the risk of valvulopathy [36].

In conclusion, CAB is usually the first-line DA to be proposed with a side effects profile similar to those reported for the other DAs, but generally less frequent, less severe, and of shorter duration [37]. The only serious shortcoming currently under active investigation is the occurrence of a compulsive behavior in 5% of cases, such as excessive gambling and hypersexuality [38].

2.3. Quinagolide

Quinagolide (QNA) is a non-ergot-derived D2DR selective agonist which led, when administrated once-daily in patients with macroprolactinomas, to a significant reduction of tumor size and PRL levels in around 90% of patients and a further normalization of PRL level in 50% of them [39–42]. It is usually administered at the average dose of 150 to 300 µg per day. As compared to treatment with BRC, a greater reduction in nausea, vomiting, dizziness, and drowsiness during QNA administration is generally observed.

2.4. Other dopamine agonists

Pergolide is an ergot-derivated DA with long-acting D1 and D2 agonist properties, 100 times more potent than BRC allowing effective control of hyperprolactinemia with once-daily dose. However, it has been withdrawn from the market in 2007 because of cardiac valves adverse effects [43,44]

Lisuride is another ergot-derivated DA which was assessed for its ability to inhibit PRL secretion [21]. However, it never reaches the development to be used as a medical treatment in PRL-secreting adenomas. Finally, terguride, an analog of lisuride, can normalize PRL levels and reduce tumor size in a few number of patients with microprolactinomas, however it is currently not commercialized [20].

3. Prolactinomas resistant to dopamine agonists

The resistance-to-DA therapy represents the most challenging condition of difficult-to-treat macroprolactinomas. It systematically requires a multidisciplinary approach to optimize the care of the patient.

3.1. Definition of the resistance

The definition of resistance-to-DA still constitutes a source of uncertainty, and multiple definitions have been proposed in the literature. One, which is recurrent, defines the resistance as failure to achieve normal serum PRL levels under DA (commonly admitted CAB ≥ 2 mg/week) or failure to reduce tumor size by at least 50% from the initial volume [45] (Figure 1). The cut-off of 2 mg/week chosen on purpose for CAB resistance actually makes sense. Indeed, in the group of patients treated with more than ≥ 2 mg/week of CAB, only a third of them will normalize their PRL level under 3 mg/week [46]. Therefore, the concept of resistance-to-DA does not mean per se that it is impossible to normalize PRL secretion but rather refers to a state in which the usual posologies of DAs do not achieve

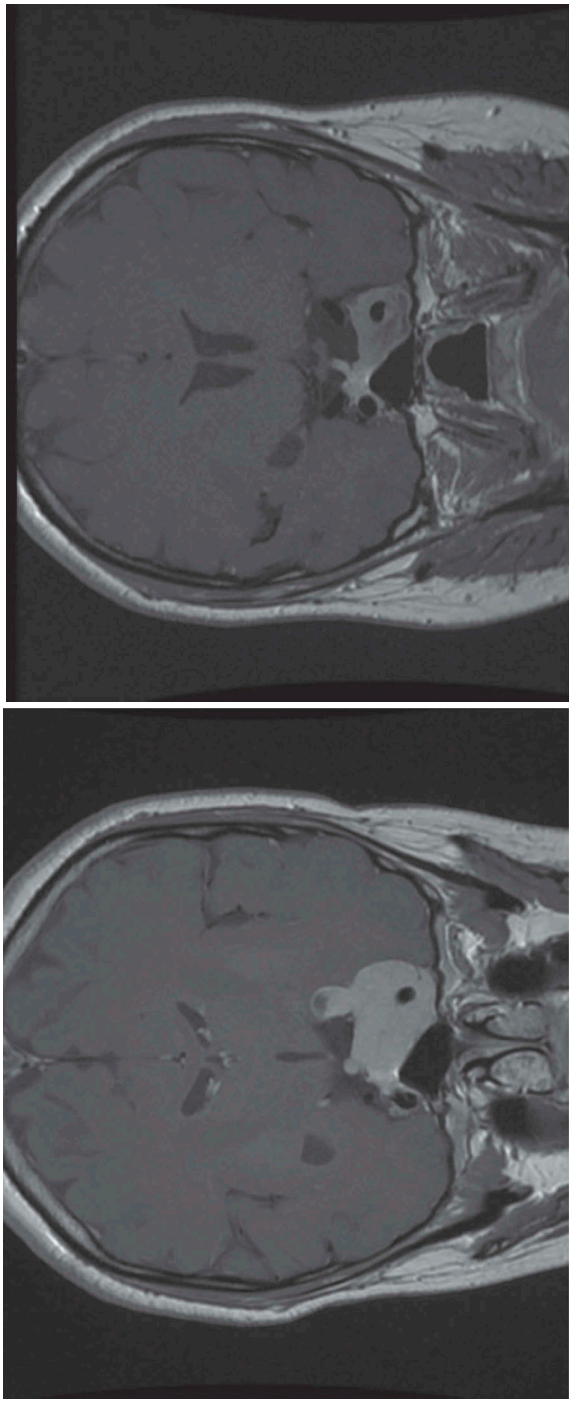

Figure 1. **MRI aspect of a DA-resistant macroprolactinoma in a 33-year-old patient**. [A] Before cabergoline (CAB) introduction, the patient was diagnosed with left diplopia and erectile dysfunction. Hormonal analysis revealed a prolactin (PRL) level up to 4800 ng/mL. [B] MRI after 12 months of CAB therapy. Posology increased gradually from 0.5 to 3 mg/week at the last follow-up. PRL decreased to 1200 ng/mL, but never reached the normal range and tumor volume shrinkage was considered to be less than 50% from the initial tumor volume. Interestingly, diplopia spontaneously resolved 3 weeks after the initiation of CAB therapy.

normalization of PRL levels or significant decrease of the tumor volume. According to these criteria, the prevalence of DA-resistance in patients with Prolactinomas is 10 to 15% [47] .

3.2. Molecular mechanisms underlying the resistance to DA

3.2.1. Alterations in the dopamine receptor subtype 2 (D2DR)

Most of the studies that focused on the resistance-to-DA in Prolactinomas investigated the pattern of D2DR expression both at the mRNA and at the protein levels (Figure 2). Our group showed a significant decrease of the D2DR mRNA transcription and identified alterations in the D2DR-related signaling pathways of BRC-resistant human Prolactinomas, as compared to sensitive tumors [48–51]. More recently, the differential expression of D2DR isoforms was proposed as a putative molecular mechanism which leads to different response to DA. In the study conducted by Shimazu et al., patients with surgically resected Prolactinomas were divided, based on their response to DA, in responders (n = 5), resistants (n = 5) and secondary resistants to DA (n = 2). The authors found a significant decrease of the D2DR long isoform mRNA expression in resistant and secondary resistant tumors as compared to the sensitive ones [52]. In a similar approach, the correlation between the D2DR gene polymorphisms and the response to CAB was studied in a series of 148 patients with Prolactinomas (among whom 29 males and 75 macroadenomas), however without significant results [53]. A trend for similar results was found in the study of Filopanti et al. where the allele frequencies (i.e. the *Taq*I-A, *Taq*I-B, *Hph*I and *Nco*I alleles) of the four *D2DR* polymorphisms was compared between sensitive- and resistant-to-DA Prolactinomas, without any significant correlation eventually observed [54]. Nonetheless, in that study, a higher frequency of the *Nco*I-T allele was observed in resistant as compared to sensitive patients, which could suggest that this variant may lead to reduction of the expression and instability of the D2DR [54]. Recently, the whole-exome sequencing analysis of 12 human Prolactinomas (Six considered as responsive and six as resistant under a dose of 15 mg/day of BRC, 11/12 patients with macroprolactinomas) revealed a differential expression of the *PRDM2 (PR domain zinc finger protein 2*) gene, about five-fold lower in resistant tumors as compared to the responsive ones [55]. The *PRDM2* gene encodes a protein whose major role is to stabilize chromosomal structures, mediates gene expression and ultimately plays a role of tumor suppressor gene [56]. In resistant-to-DA Prolactinomas, the expression level of the PRDM2 protein was also significantly decreased as compared to sensitive cases and its overexpression in the MMQ cells, a rat PRL-secreting pituitary tumor cell line, led to the upregulation of D2DR expression and potentiated the inhibitory effect of BRC over PRL secretion [55].

3.2.2. The TGF beta pathway

Amongst its multifunctional known roles as a cytokine, TGF beta (TGF-β) can also regulates the proliferation of lactotroph cells as well as their PRL secretion [57]. The TGF-β signaling cascade is initiated by the binding of TGF-β1, TGF-β2, and TGF-β3 ligands to the type II TGF-β receptor (TGF-β RII), followed by recruitment

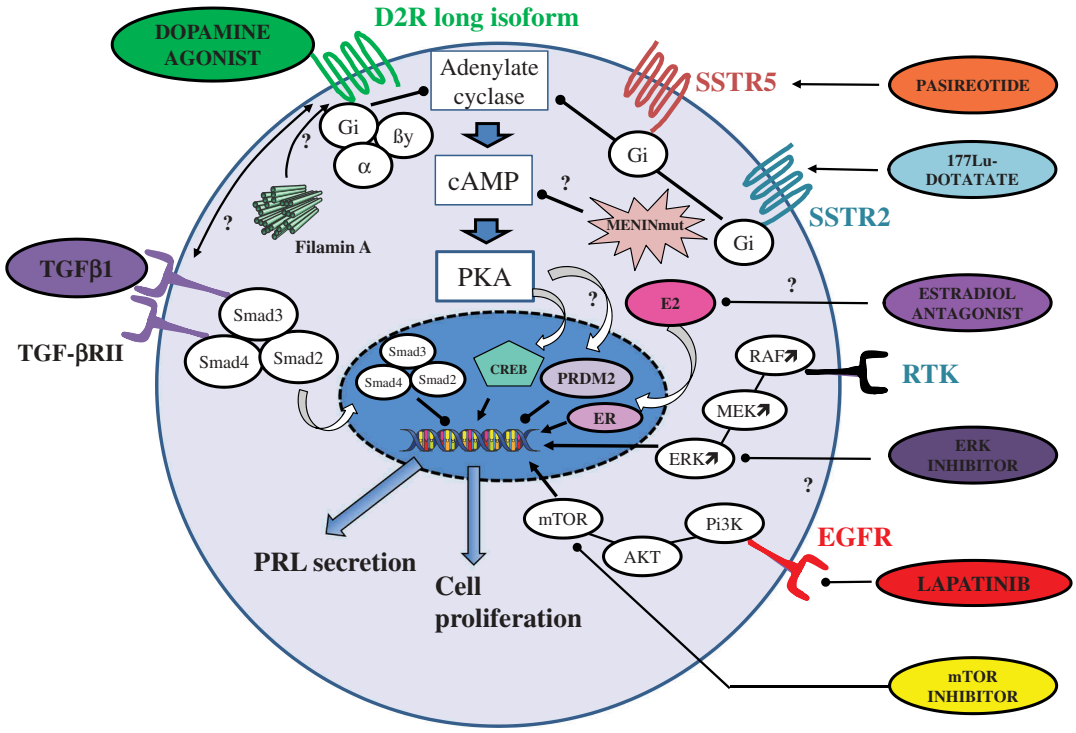

Figure 2. **Schematic illustration of the main signaling pathways involved in the response to dopamine agonist therapy in pituitary lactotrophs**. In the sake of clarity, major signaling pathways are simplified and readers can refer to the review for more details. On the right side of the cell, optional therapies and the ones that are in development are represented. The question mark means a possible effect supported by *in vitro* experiments.

and phosphorylation of the type I TGF-β receptor (TGF-β RI) to form a complex [58]. Once activated, TGF-β RI triggers the formation of a heteromeric complex between Smad2, Smad3 and Smad4, which ultimately translocates into the nucleus to regulate expression of various transcription factors [59]. Sarkar et al. was the first to show that TGF-β1 inhibits, in a similar manner than dopamine, both PRL secretion and proliferation of lactotrophs [60]. More recently, it was shown that, knocking out the D2DR expression or using a D2DR antagonist (sulpiride) resulted in the decrease of both TGF-β1 secretion and TGF-β RII expression by the lactotroph cells. These observations could suggest that the inhibiting effects of dopamine could be due, at least partially, to the TGF-β system [61]. Interestingly, in a series of 12 patients who underwent surgery because of resistance to BRC (failure of PRL normalization after at least 3 months of BRC ≥ 15 mg/day), a significant down-regulation of the TGF-β/Smad signaling cascade assessed by high-content screening techniques (qRT-PCR, western blot, immunofluorescence and ELISA) was observed as compared to normal human anterior pituitaries [62]. However, a comparison with DA-sensitive tumors was unfortunately lacking in this work.

Because estradiol is known to increase PRL secretion and sustained lactotroph proliferation, a combined treatment with TGF-β1 and fulvestrant, a selective estrogen receptor degrader, was tested in the rat GH3 somatolactotroph cell line. Of interest, a significant cytotoxicity in a dose- and time-dependent manner was observed with a simultaneous activation of Smad3 [62].

Overall, decreased TGF-β1 activity and decreased expression of different components of the TGF-β1 system have been described in animal models of Prolactinomas as well as in human Prolactinomas [57]. Taking into account that TGFβ1 inhibits lactotroph proliferation and PRL synthesis and secretion, recovering local TGF-β1 activity may be one avenue worth exploring in case of DA-resistant Prolactinomas (Figure 2).

3.2.3. *Resistance-to-DA in the setting of genetic syndromes*

A condition that seems to be associated with a higher risk of resistance-to-DA is when the PRLoma developed in the setting of a multiple endocrine neoplasia type 1 (MEN1) syndrome. The latter is a genetic disease that predisposes carriers to development of various endocrine tumors including PiTNETs in 30–50% of patients [63]. Prolactinomas are the most frequent PiTNETs phenotype seen in MEN1 with 60% of cases. Moreover, MEN1-mutated (MEN1mut) patients seem to be less responder to DA as compared to their non-mutated counterparts [32,64]. We are still lacking molecular explanations to decipher why and how MEN1 mutations lead to a lower sensitivity to DA; however, it is noteworthy to mention that histologically, MEN1mut Prolactinomas are more frequently invasive as compared to non-mutated Prolactinomas [64,65]. Evolution of Prolactinomas in MEN1mut patients are characterized by a younger age at onset, a more aggressive behavior as reflected by a higher

propensity to invade surrounding structure and, in the scope of this review, a lower sensitivity to DA [66,67].

Besides MEN1, Prolactinomas can also be developed in the setting of a Familial Isolated Pituitary Adenomas (FIPA) syndrome where they represent 10% of all tumor phenotypes and even 25% when the Arylhydrocarbon Interacting Protein (AIP) gene is mutated [68]. In AIP-mutated Prolactinomas, 77% of patients were male with larger tumors, less sensitive to DA as compared to non-mutated patients [68].

3.2.4. Other molecular pathways involved in DA-resistance

Several other molecular pathways have been incriminated in the occurrence of DA-resistance in Prolactinomas. For instance, the expression of Filamin-A, a cytoskeleton protein with scaffolding properties, is downregulated in parallel to the one of D2DR in human DA-resistant Prolactinomas [69]. Moreover, silencing the Filamin-A expression in human DA-sensitive Prolactinomas resulted in a significant decrease of D2DR membranous expression and abrogation of the DA-induced inhibition of PRL release and antiproliferative signals. In a reciprocal way, a restoration of the D2DR expression and PRL responsiveness to DA occurred when Filamin-A was overexpressed in DA-resistant Prolactinomas [69]. Besides Filamin-A, a recent study showed that low levels of *PRB3* mRNA were observed in case of DA-resistant Prolactinomas and exposed the patients to a higher risk of tumor recurrence [70]. However, the exact role of the PRB3 protein in Prolactinomas remains, to date, elusive.

4. Therapeutical management of resistant-to-DA prolactinomas

In the case of resistant-to-DA Prolactinomas, several options can be discussed; all of them being either proposed alone, combined and/or in a sequential approach. It includes switch to another DA, surgery, external radiotherapy, other-than-DA medical therapies or a watch-and-wait attitude.

4.1. Switching to another dopamine agonist

Since its commercialization, CAB is usually preferred to BRC for the treatment of patients with Prolactinomas because of overall greater efficacy and tolerability. However, in certain regions of the world, BRC is still used as a first choice because of costs and/or stock availabilities. Over the past years, CAB showed a greater efficacy as compared to BRC for the control of PRL oversecretion and has been successfully tested in patients considered as being resistant to BRC [25,71–73]. Low posology of CAB could, likewise, significantly overcome the resistance to QNA in Prolactinomas [74], a drug which is already effective in case of BRC resistance. However, this result could be overestimated because of better compliance and tolerance to CAB as compared to QNA, which actually induces a bias in the statistical analysis. In resistant-to-CAB patient, the most common medical approach is therefore to increase the dose of CAB, as long as a reduction in PRL levels can be demonstrated with each stepwise increase [35,75]. Although it is unlikely that patient resistant to CAB will demonstrate sensitivity to BRC, there is an existing clinical report of two patients resistant-to-CAB with micro- and macroprolactinoma, respectively, who unexpectedly showed response to BRC [76].

4.2. Surgical treatment of prolactinomas

Before the development of DA, surgery was historically the treatment of choice for the cure of a PRLoma [1]. Currently, indications are mainly represented by cases of pituitary apoplexy, resistance-to-DA or by personal choice of the patient [77]. Even in cases of visual defect due to a macroprolactinoma, the standard of care favors the use of DAs as compared to surgery. The visual defect generally improves in the short term under DAs in a majority of patients, including those with giant (i.e. maximal diameter ≥ 4 cm) Prolactinomas and in spite of a partial antitumoral effect [31,78–80]. However, it should be noted that there is no dedicated studies which compared the outcome of the visual field defect in patients with macroprolactinoma when treated by DA as compared to patient treated in first-line by transphenoidal surgery. In highly trained hands, selective adenomectomy results in normalization of PRL levels in 75–90% of microprolactinomas. The multi-invasive nature of macroprolactinomas obviously affects the rate of cure obtained by purely surgical in such tumors which is achieved in around 40% of cases with recurrence rates of 20% over 10 years [81–83]. Surgery will provide the tumor histological characteristics, especially its pathological markers of aggressivity (Ki67 and P53 immunostaining, mitotic count). A recent retrospective study analyzed the surgical outcome of 184 men with surgically treated Prolactinomas. Among them, 178 patients had a macroprolactinoma (152 had a maximal size below 4 cm and 26 with a maximal size >4 cm) and 61/152 (33.1%) of cases were invasive [84]. A post-surgical initial remission of PRL levels was observed in only 10% of invasive cases (i.e. suprasellar and/or parasellar and/or sphenoidal invasion) [84]. In case of resistance to DA, surgery is a valuable therapeutic option which results in normalization of PRL in half of patients [85]. In expert pituitary center, surgery for macroprolactinomas can be complicated by a diabetes insipidus in around 5% of cases, cerebro-spinal-fluid leak in 2–10% and anterior pituitary deficiencies in 1–15%, respectively [82,86].

4.3. External radiotherapy

External radiotherapy is usually discusses in patients who have clinically significant and symptomatic elevation of serum PRL in spite of DA therapy and/or transsphenoidal surgery (which means a third-line therapy in majority of cases). It can be proposed either as external beam radiation therapy (conformal radiotherapy) or stereotactic radiosurgery (SRS). Nowadays, the latter is preferably employed as its three dimensional approach is associated with a more rapid correction of hormone oversecretion and a lower risk of radiation-induced neoplasms and carotid stenosis [87]. Amongst SRS, gamma knife radiosurgery (GKRS) provides a highly conformal and selective therapeutic intervention in a single procedure performed with image guidance and using a multiheaded cobalt unit or a linear particle accelerator. On the opposite, the conformal radiotherapy is characterized by several fractions over the time (with generally daily administration). In Prolactinomas, previous studies, including one from our group, reported a mean rate of PRL normalization ranging from 26 to 43% with a time to remission comprised between 24 and 96 months [88–90]. In cases of resistance/intolerance-to-DA or invasive macroprolactinomas, a normalization of PRL level was obtained

in half of 38 patients with a mean and median prescribed doses which were 21.3 and 25 Gy to the 50% isodose line, respectively. These doses are the most common used for GKRS in Prolactinomas [91]. Even if comparative studies with a significant number of patients are lacking, there are several lines of evidence which showed that withdrawal of DA therapy during SRS could be associated with better outcomes in terms of endocrine remission [89,92]. It is noteworthy to mention that cavernous sinus invasion was shown to be a significant negative prognosticator of endocrine remission [92]. Finally, after 40 months, radiotherapy-induced hypopituitarism occurred in 30% of cases.

Besides stereotactic radiotherapy, a conformal external radiotherapy can be discussed with the risk of adverse effects which is proportional to maximal dose and to fractionated dose per day. As compared to GKRS, conformal radiotherapy has two main drawbacks: the first one is the time to remission, equals to 5–10 years which is longer than that observed with the GKRS and therefore requires an effective medical treatment during this period of therapeutic latency. The second drawback of conformal radiotherapy is the risk of side effects, including hypopituitarism (in more than 80% of cases), optic neuritis, radiation-induced cerebral tumors, cerebral infraction and/or cognitive dysfunctions. These latter side effects occurred after a mean time of 10–20 years, and were not (at least not yet) described with the use of GKRS.

The antitumor efficacy (which means stabilization and/or decrease of the tumor residue) of radiotherapy in the setting of Prolactinomas is high, observed in 70 to 100% of cases over a delay ranging from 12 to 36 months [89,93]. This suggests that GKRS could be a valid alternative treatment in cases of intolerance or resistance-to-DA. Of note, median time to remission was usually 20 to 40 months, which means that gonadal steroid hormones administration can be necessary during this period [94].

4.4. Medical treatment of DA-resistant prolactinomas

4.4.1. Temozolomide

In the setting of Prolactinomas, temozolomide (TMZ) never represents a first line treatment, however its indication can be actively discussed when the tumor is not controlled by the usual therapeutic regimen (DA, surgery, radiotherapy). Its efficacy was first demonstrated in glioblastomas before its successful use in advanced melanomas and neuroendocrine tumors [95]. TMZ is an alkylating chemotherapy, derivative of dacarbazine, with lipophilic properties allowing it to cross the blood–brain barrier and acts by inserting a methyl group to DNA bases (mainly guanine). By this way, it inhibits the gene transcription and cellular replication [96]. O(6)-methylguanine methyltransferase (MGMT) is an endogenous DNA repair enzyme that can remove this methyl group and thereby potentially counteracts the cytotoxic effect of TMZ. An inverse correlation has been shown between the degree of MGMT expression, due to silencing of the MGMT gene by methylation of its promoter, and the response to TMZ treatment in glioblastomas [97]. With 100% oral bioavailability, the standard regimen for administering TMZ consists in an oral daily dose of 150–200 mg/m2 body surface area for 5 days every 28 days. TMZ was proposed as a salvage therapy for the first time in 2006 to treat a PRL-secreting pituitary carcinoma [98] and subsequently tested in aggressive Prolactinomas [99]. In the latter and in PRL-secreting carcinomas, an overall control of tumor growth and PRL secretion under TMZ was observed in 66 and 73% of cases, respectively [100]. Moreover, patients carrying aggressive Prolactinomas who were responders to TMZ showed to have an improved overall survival as compared to their non-responders counterparts [101]. In our own experience, we previously reported a remarkable efficacy of the TMZ regimen in a patient with a MEN-1 pituitary carcinoma (Figure 3) [102] .

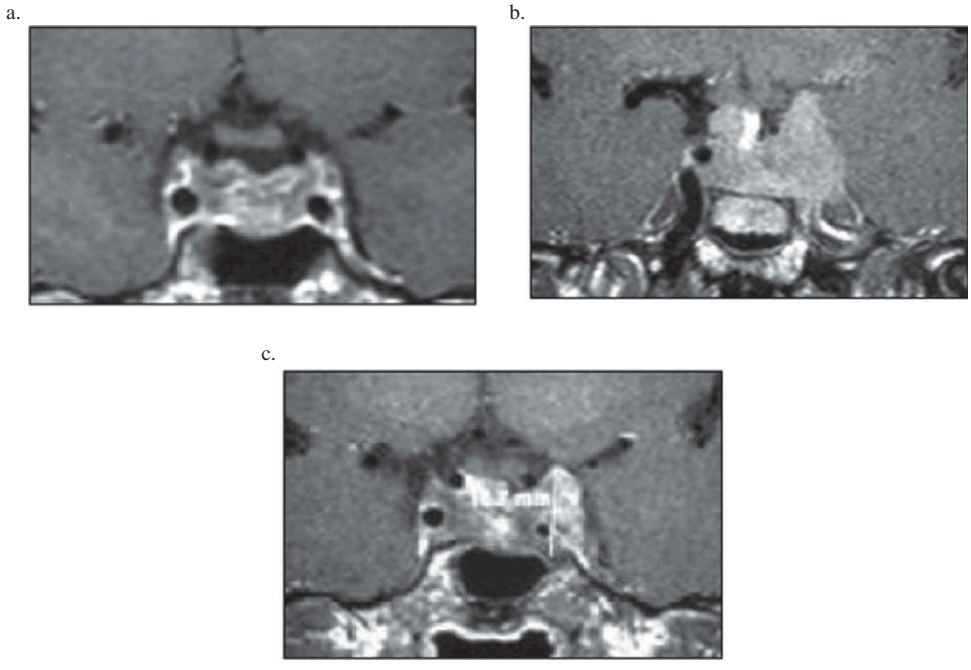

Figure 3. **Coronal T1-weighted pituitary MRI in patient with a DA-resistant prolactinoma treated with temozolomide**. [A] In 1995, after pituitary surgery, showing postoperative sequellae without any large visible residual adenomatous tissue. [B] In 2006, showing a relapse of the tumor with a large adenomatous residue in the left cavernous sinus. [C] In 2011, after 24 sessions of temozolomide (given between 2006 and 2008) with prolactin decreasing from 6950 to 98 ng/mL and the tumor volume from 62%, at the last follow-up.

In summary, TMZ is currently a suitable therapy that can be used as a first-line chemotherapy in case of aggressive and DA-resistant macroprolactinomas or pituitary carcinoma with tumor growth [103].

4.4.2. Alternative medical therapies

Other medical therapies can be discussed in a personalized approach when the PRL-secreting PiTNET displays signs of resistance to DAs. Somastostatinergic analogs (octreotide and lanreotide) which bind the somatostatin receptor subtype 2 (SSTR2) are generally inefficient to inhibit PRL secretion and/or decrease the tumor volume [104]. Nonetheless, there are few clinical reports of DA-resistant Prolactinomas which showed that combination of octreotide plus CAB could further inhibit both PRL secretion and tumor volume [105,106]. We previously hypothesized that a chimeric compound made of SSTR2 and D2DR moieties, called dopastatin, could further inhibit PRL secretion in SST2-overexpressing DA-resistant Prolactinomas. Unfortunately, the inhibitory effect observed with dopastatin was similar to the one obtained with CAB [107]. Pasireotide (SOM230) is another somatostatin analog with high affinity for SSTR1, 2, 3 and 5. It is currently proposed in clinic for the treatment of acromegaly and Cushing's disease [18,108]. *In vitro*, SOM230 inhibits PRL secretion from primary culture of human PRL-secreting PiTNETs [109,110] and was successfully tested in a patient with DA-resistant PRLoma [111]. In the latter, the tumor expressed high level of SSTR5, a condition which remains exceptional in DA-resistant Prolactinomas and explains why SOM230 is most of the time ineffective in such cases [104]. Finally, peptide receptor radionuclide therapy (PRRT) with 111In-DTPA-octreotide has shown interesting result in a man with uncontrolled giant PRLoma resistant to conventional therapy [112] and could, in the era of the recent provision of 177Lu-DOTATATE (LUTHATERA®) [113], represent an interesting treatment to discuss in specialized center.

Two recent cases of patients with BRC-resistant Prolactinomas suggest that metformine, an oral treatment commonly used in type 2 diabetes, can lead to normalization of PRL level when it is used in combination with BRC, and also to a subsequent decrease of the tumor volume after 24 months of treatment [114]. These results are supported *in vitro* by a synergistic inhibitory effect of metformine and BRC in combination over tumor growth and PRL secretion of xenograft models of lactotroph tumors [115].

4.5. New therapeutical perspectives for DA-resistant prolactinomas

4.5.1. The EGF/EGFR system as a potential therapeutic target

The epidermal growth factor (EGF) system comprises several transmembrane tyrosine kinase receptors known as EGFR (ErbB1, HER1), ErbB2 (HER2), ErbB3 (HER3) and ErbB4 (HER4) which, once binded by EGF, form either homo- and/or heterodimers, and activation of the intrinsic kinase domain and intracellular signaling [116]. EGFR is expressed in human Prolactinomas even though the pattern of EGFR expression in Prolactinomas seems to be heterogeneous and unconstant from one tumor to another [117–119]. In experimental models, gefitinib, an EGFR antagonist, decreased i/the cell proliferation of the rat somatolactotrope GH3 cell line ii/the PRL mRNA expression, iii/the PRL-secreting xenograft volume in rodents and the PRL secretion *in vivo* [120]. In humans, two patients with DA-resistant Prolactinomas were treated with lapatinib (1,250 mg daily for 6 months), a tyrosine kinase inhibitor of ErbB-1 and −2. One of them showed a significant improvement of his PRL level (from 311 to 67 ng/ml) together with a regression of the central portion of the tumor mass, albeit incomplete. In the second patient, lapatinib was moderately effective with a decrease of PRL level from 447 to 259 ng/mL (at the last follow-up) however without any shrinkage of the tumor mass [118].

4.5.2. The RAF/MEK/ERK and PI3K/AKT/mTOR signaling pathways in prolactinomas

The RAF/MEK/ERK and PI3K/AKT/mTOR signaling pathways are crucial to many aspects of cell growth and survival, in physiological as well as in pathological conditions [121]. Previously, no differences were found between PA and normal pituitary samples in the expression of phosphorylated/total mTOR, TSC2 or p70S6K known to be the downstream effectors of the PI3K/AKT signaling pathway [122]. As such, the PI3K/AKT/mTOR signaling pathway does not seem to represent a canonical pathway involved in the pathogenesis of PA, especially Prolactinomas. On the opposite, the expression of the phosphorylated forms of MEK1/2 and ERK1/2, the downstream effectors of the MAPK signaling pathway, was significantly higher in Prolactinomas as compared to normal pituitaries [122]. Interestingly, a recent study suggests an intricate cross-talk between the ERK and PI3K signaling pathways in a rat somatolactotrope cell line GH4T2, in which PI3K appears as a counterregulatory mediator of the ERK-induced PRL transcription [123]. In the same cell line, the inhibition effect obtained with CAB over PRL secretion and cell proliferation was mediated through the phosphorylation of S6K, a target of mTOR which therefore seems to be closely involved in the response to DA in Prolactinomas. Besides the response to DA, the mTOR signaling pathway was recently identified as a promotor of pituitary tumor development, more specifically in Prolactinomas [124] and *in vitro* data suggest that rapamycin, a mTOR inhibitor, could be effective in the treatment of lactotroph tumoral cells [125]. Recently, a patient with DA-resistant PRLoma was successfully with everolimus, a mTOR inhibitor, with a significant decrease of both PRL levels and tumor volume after 5 months [126]. The tumor immunohistochemical analysis of this patient revealed high level of p-AKT, p4EBP1 and p70S6K [126]. In conclusion, pharmacological inhibitors of the ERK or PI3K pathways could constitute an interesting therapeutic approach in DA-resistant Prolactinomas.

5. Summarizing conclusions

In conclusion, Prolactinomas represent the most common hormone-secreting pituitary tumor with an overrepresentation of microadenomas in the population of young women. Difficult-to-treat Prolactinomas are represented by

Prolactinomas that are resistant to DA therapy a condition which is correlated to the occurrence of a macroadenoma in more than 80% of cases [47]. Because these tumors can be roughly assimilated to aggressive tumors, a multidisciplinary team meeting is obviously required to guide the best therapeutical approach to propose [103].

The above manuscript gives an overview of the valuable treatments to discuss when the patient does not respond (enough) to DA. In clinical practice, two situations can be distinguished. First presentation (which is the more frequent): the patient keeps a significant oversecretion of PRL after surgery, as it occurs in 60% of macroadenomas [85,127] but the tumor does not display features of aggressivity on the pathological analysis and does not exert a tumor mass effect on surrounding structures. The concern is mainly related to the effect of hyperprolactinemia, especially hypogonadism. A step-by-step therapeutic approach is generally adopted with increasing the dose of CAB, and potentially a subsequent radiotherapy. In the meanwhile, an hormonal substitution can be necessary with periodical follow up by pituitary MRI. It is important to underline that the risk of cardiac valvulopathy while increasing the dose of CAB is rare. In our daily practice, we recommend, as others do, to perform one echocardiography at baseline, which, if normal, will require a subsequent control in the future if the patient has an audible murmur, if he is treated for more than 5 years at a dose of more than 3 mg per week, or for those who maintain CAB treatment after the age of 50 years [128]. When the tumor is aggressive according to Trouillas criteria [129], the concern is rather related to its (uncontrolled) invasive behavior and requires urgent therapeutic management. Repeated surgery, MGMT immunostaining and ultimately TMZ can be proposed with a close monitoring. Once PRL is normalized, and as long as it remains normal or stable overtime, the likelihood of a significant tumor growth remains low, and we therefore assume that repeated pituitary MRI in the follow up are unnecessary [130].

In summary, different therapeutic modalities are discussed during the care of a patient with a DA-resistant macroprolactinoma. Selected therapeutic perspectives have been discussed and detailed in this review, but many others are in the pipeline and could be of interest in PRL-secreting PiTNETs. This is the case for the immunotherapy whose pharmalogical action rather targets the microenvironment than the tumor niche itself. A spectacular antitumoral effect of the combination of ipilimumab (anti-CTLA4) and nivolumab (Anti-PD1), was observed in a case of ACTH-secreting pituitary carcinoma [131]. The impact of the immune components in the pathogenesis, behavior and response-to-treatment of Prolactinomas remains largely unknown. Therefore, a better understanding of the molecular and cellular factors underlying the resistance to DA in Prolactinomas could allow in the future to personnalize the treatment for a patient and optimize his medical care.

6. Expert opinion

Dopamine agonist (DA) treatment represents the first-line therapy for Prolactinomas either micro- or macroadenomas and as such, their overall efficacy is one of the most remarkable observed in the field of medicine. Even when a single weekly dose of CAB is unsufficient, it is worth a try to increase the posology given the fact that a certain proportion of macroprolactinomas will respond at higher than conventional dose. Based on our experience, some clinical indicators are, from the moment of the diagnosis, are already highly predictive of resistance to DA: a (really) young age (i.e. <18 years old) at diagnosis, the existence of a *MEN1* or less frequently *AIP* germline mutation, and a giant adenoma (which means maximal diameter exceeding 4 cm). In the latter situation, a tumor mass effect usually occurs on the optic chiasm, likely responsible of visual field defect. The authors want to underline that CAB therapy, even when a state of resistance is observed with no reduction of the tumor volume, a dramatic improvement of the visual field can be observed, suggesting that the treatment with CAB can modify the consistency of the tumor making it more soft. This hypothesis is also supported by the possible occurrence of intratumoral hemorrhage during the treatment with CAB.

We usually recommend a careful assessment of the DA efficacy on both PRL secretion and tumor volume reduction by MRI, 4 months after initiation of the therapy and then 6 to 8 months later.

As such, we recommend to wait for 12 months of treatment under CAB before considering the tumor is resistant to DA.

The different works that have been published so far to decipher the molecular abnormalities involved in the resistance to DA in Prolactinomas have sparked many interest for the pharmacological research however without concrete clinical applications yet. Indeed, in the case of treating DA-resistant tumor (debulking) surgery is the prior therapeutic option more or less followed by stereotactic radiotherapy on the tumor residue. This therapeutical strategy at least offers to the clinician the access to the tumor histopathology and especially to its aggressive behavior. This last point is important in case of multiple relapse and uncontrolled growth of the tumor which therefore could indicate treatment with TMZ. The results obtained on tumoral residue with gamma knife radiosurgery (GKRS) are encouraging in a majority of patients when performed in an expert center, with few side effects and a prolonged control of the tumor volume and hormonal secretion. The current alternative therapies to dopamine agonist are almost nonexistent and only few ones have shown an interesting effect in case reports. This is the case with somatostatin analogs including pasireotide, whose use could be attempted when the tumor expressed high levels of somatostatin receptor subtype 5. Similarly, the use of Lapatinib could be of interest but its efficacy has been demonstrated in very few cases of resistant Prolactinomas. Overall therapies directed toward membrane receptors do not appear to us as the preferential targets to develop in case of DA-resistant or only in a cotargeting therapeutical approach. On the opposite, promising approach are represented by inhibitors of canonical signaling pathways situated downstream the transmembrane receptors (e.g. MAPK) as well as the development of epigenetic drugs that could lead to the re-expression of D2DR when this one is down-regulated.

A subgroup of patient will present with a tumor residue of their DA-resistant Prolactinomas however without significant

progression. As long as the tumor does not lead to tumoral and/or hormonal symptoms, a regular follow-up can be sufficient in the management of such patients. In all the remaining cases (i.e. when a significant progression is observed over the time) a multidisciplinary approach is of upmost importance to discuss which therapeutical strategy presents the best risk/benefit balance for the patient in regards to his/her clinical profile.

We, and others, assume that the therapeutical management of difficult to-treat macroprolactinomas will benefit, instead of increasing the posology of DA, from identification of new therapeutical targets in case of DA-resistance. As such, the recent works conducted by the group of Melmed investigated drugs directed against the Erb receptor as a reliable treatment to consider. Likewise, it is worth trying to assess the efficacy of pasireotide in tumors expressing significant level of somatostatin receptor subtype 5. Finally the coming years will probably also marked by new stereotactic radiosurgery procedures that will undoubtedly optimize the treatment of PRLoma residues.

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