Ophthalmic results in patients with macroprolactinomas treated with a new prolactin inhibitor CV 205–502

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Abstract
Macroprolactinomas are pituitary tumours which have been effectively treated medically since the introduction of bromocriptine. The visual function of 13 patients treated with a new prolactin (PRL) inhibitor CV 205–502 (Sandoz Basle), a potent and selective dopamine D2 receptor agonist, was evaluated. This is the first detailed ophthalmic report of the use of this drug in macroprolactinomas. Patients were enrolled from June 1988 to July 1990 (mean follow up 30 months). Visual function including visual acuity, ocular pressure, and visual fields was regularly controlled. Visual fields (VF) were tested with Goldmann and automatic static perimetry (Vision Monitor). Treatment was globally effective. No modifications of the visual function were observed in nine patients (six normal, three previous VF losses after surgery). In four other patients, visual function dramatically improved (regression of a III paresis, one case; disappearance of a chiasmatic syndrome, three cases). A pituitary necrosis was observed in one case and successfully cured. CV 205–502 seems to be an effective and well tolerated treatment of macroprolactinomas. (Br J Ophthalmol 1993; 77: 785–788)

For 10 years, dopamine agonists have been used in the treatment of macroprolactinomas, either as a preparation for surgical removal, or as a unique treatment. CV 205–502 (octahydrobenzo[g]quinoline) is a new non-ergot long acting prolactin inhibitor, a pure D2 agonist. For 2 years several clinical teams have reported the first results in the treatment of macroprolactinomas. It was shown that CV 205–502 was effective in the treatment of macroprolactinomas in cases in which bromocriptine was poorly tolerated or ineffective. CV 205–502 is well tolerated and its long action makes one dose a day possible. CV 205–502 can induce normalisation of prolactin (PRL) secretion and a noticeable reduction in tumour size. In the control of tumour volume, ophthalmic controls are essential. In this study we present the ophthalmic results in 13 patients treated with this new drug, with a mean follow up of 30 months. The early results in eight patients after 9 months of treatment have been published previously. To our knowledge, this is the first detailed ophthalmic report of the use of this drug in macroprolactinomas.

Material and methods
This open study was designed by Sandoz Ltd (Basle, Switzerland) and approved by our institutional ethics committee. Thirteen patients with...
Tumour remnants were visible on computed tomographic scan (CT) or magnetic resonance imaging (MRI).

**Figure 2** Evolution of normal bitemporal hemianopia. The bitemporal hemianopia was observed before treatment with CV 205–502 (upper); the visual field is normal after 1 month of treatment (lower).
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Figure 3 Visual field (VF) of patient 10; (upper) the defect is limited to an irregular left temporal scotoma after 13 months of treatment with CV 205–502. (Lower) corresponds to the beginning of pituitary necrosis after 16 months of medical treatment with visual failure (LE 6/18; RE 6/9), huge central scotoma on the RE, temporal hemianopia on the LE.

Figure 4 CT scan of patient 10 after 16 months of treatment with headache and visual failure. Coronal section showing the heterogeneous aspect of the tumour corresponding to pituitary necrosis.

compared with the map in the device; improved when a regression of more than 50% of the VF defect was observed qualitatively and quantitatively.

Results
The overall tolerance was good.

BASELINE NORMAL VISUAL FUNCTION (TABLE 1)
Six patients had an initial normal visual function: visual acuity and visual fields were normal in one de novo case (No 6) and five who had undergone surgery (Nos 2, 5, 7, 9, 13). No visual complication was observed under treatment with CV 205–502 with a range of observation from 30 to 43 months. A certain degree of variability in the visual fields was observed; variable and regressive relative scotomas were present without modifications of the prolactin levels, but there was no significant difference between the mean total deficit before and after treatment (t test).

BASELINE ABNORMAL VISUAL FUNCTION (TABLE 1)
Four of these patients had undergone previous pituitary surgery (Nos 1, 8, 11, 12), three were de novo cases (Nos 3, 4, 10).

In three patients (Nos 1, 8, 12) with alterations of visual field, sequelae of previous pituitary surgery, no amelioration was observed. Some variations of the VF were observed in case 8. In case 12, who had a left strabismic amblyopia, the left homonymous lateral hemianopia was associated with a III right palsy, sequelae of pituitary surgery performed 5 years before. In case 11, an isolated left III paresis was observed 8 years after the patient had undergone pituitary surgery. The regression of the ptosis and the diplopia was observed after only 6 weeks of medical treatment. An excellent and quick regression of visual field abnormalities was observed in the three de novo cases (Nos 3, 4, 10). A complete normalisation was observed in 1 month in case 3 (Fig 2). In the two other cases VF improved in 4 months and 1 month respectively.

We shall examine case No 10 in more detail. After 16 months of closely monitored treatment, the reduction of the volume of the tumour on CT scan was incomplete in spite of a good control of prolactinaemia and an improved VF. The patient suddenly complained of headache and his vision decreased bilaterally from normal to RE: 6/9, LE: 6/18 to (lower part of Fig 3) and to 'no light perception' in either eye associated with a right ptosis within 2 days. On the CT scan a heterogeneous aspect of the macroadenoma associated with an increase of size was compatible with the diagnosis of pituitary necrosis (Fig 4).
Surgical treatment with a trans-sphenoidal approach was quickly carried out. The visual acuity of the patient rapidly improved and reach 6/9 and 6/12 1 month after surgery. In spite of a good anatomical result the PRL level rose and the patient was again treated with dopamine agonist CV 205–502. The visual field undertaken 8 months later remained improved.

Discussion
In our study, CV 205–502 was effective in the treatment of macroprolactinomas. In our 13 cases, six patients had a normal baseline visual function and maintained it during a mean follow up of 30 months. Some variations of their visual fields were observed at different checks without statistically significant differences. However, no clear explanation for these modifications could be given, PRL levels remaining normal at the same time. A transient modification of the size of the tumour could not be excluded since repeated radiological investigations were impossible. The visual abnormalities we observed did not differ from those previously published. The evolution of visual signs under treatment is summarised in Table 2 using the authors’ own, sometimes imprecise, terminology. There is an important difference between an intractable visual field defect after surgery and a visual field hemianopia in de novo cases. In our three patients who had been submitted to previous surgery visual field losses remained unchanged as in a case of Vance.

In the three de novo cases, the positive and rapid effect in reduction of the visual field loss was obtained, as described previously, between 4 and 8 weeks. In patients with laterosellar extension of macroprolactinoma as in case 11, the use of a dopamine agonist is a good alternative to high risk surgery. Resolution of diplopia is effective (case 6 of Van Verlaat and in the second case of Vance). Despite the normalisation of plasma PRL levels, tumoral tissue may still be present in large amounts. There is a discrepancy between the antiserotonin and the antitumoral responses, which has been previously reported with bromocriptine.10 In our case 10, no complete shrinkage of the tumour was observed in spite of a normalisation of visual field and endocrine parameters. There were no signs predicting pituitary necrosis. CV 205–502 is an effective and well tolerated treatment of macroprolactinomas with few side effects. However, a visual risk of pituitary necrosis remains.11 A regular control of ophthalmic function is mandatory as with the other dopamine agonists.

References
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