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Cinacalcet is effective in relapses of secondary hyperparathyroidism after parathyroidectomy

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Abstract

Background. Relapses of secondary hyperparathyroidism (SHPTH) after parathyroidectomy (PTx) in haemodialysis patients are relatively frequent. Calcimimetics (cinacalcet HCl) offer a new therapeutic opportunity for their treatment. However, no data about the treatment with cinacalcet of relapses of SHPTH after PTx are available in literature. The aim of this single-centre prospective study was to evaluate the therapeutic efficacy of cinacalcet in this high-risk category of patients.

Methods. Twelve haemodialysis patients of our Dialysis Unit had a relapse of SHPTH after PTx, defined as serum levels of immunoreactive intact parathyroid hormone (iPTH) >300 pg/ml. They were stratified into a treatment group (the six patients having the highest serum levels of iPTH) and a control group (the remaining six patients): the former were treated for 6 months with a dose of cinacalcet ranging from 30 mg every other day to 60 mg a day; the latter continued to be administered the conventional treatment. Serum levels of albumin, iPTH, calcium (Ca), phosphate (P) and alkaline phosphatase were determined monthly. The treatment group included four cases of nodular hyperplasia and two cases of carcinoma of parathyroid glands, whereas the control group included four cases of nodular hyperplasia and two cases of diffuse hyperplasia.

Results. At the start of the study, the six patients treated with cinacalcet showed a more severe picture of biochemical abnormalities when compared with the control patients. After 6 months of treatment, a statistically significant reduction in the serum levels of iPTH, Ca, P and Ca $\times$ P product was obtained only in the patients treated with cinacalcet. Symptomatic episodes of hypocalcaemia (serum Ca <7.0 mg/dl) were observed in three patients of this group. The six patients undergoing the conventional treatment showed at 6 months a not significant decrease in the mean serum levels of iPTH and a not significant increase in the mean serum levels of Ca, P and Ca $\times$ P product, when compared with the baseline values.

Conclusions. Our single-centre prospective study, even though small and of short duration, shows that cinacalcet is effective also in controlling relapses of SHPTH after PTx, thus representing a solid, and sometimes unique, therapeutic opportunity for this high-risk category of patients.

Keywords: cinacalcet; haemodialysis; hyperparathyroidism; parathyroidectomy

Introduction

At present, medical treatment and, when possible, prophylaxis of secondary hyperparathyroidism (SHPTH) are the first choice in the clinical approach of this serious complication of chronic uraemia. However, a large number of uraemic patients develop a refractory SHPTH [1]: the reasons for the failure of response of parathyroid glands to the wide therapeutic armamentarium available today must be looked for in several domains, such as intrinsic factors linked to the large volume of the glands themselves with nodular hyperplasia, a reduced density of vitamin D receptors (VDR) and calcium-sensing receptors (CaSR), and a persistent hyperphosphataemia, which represents one of the most important factors of resistance to calcitriol treatment and, then, one of the most important factors in the development of SHPTH [2].

Parathyroidectomy (PTx) is reserved for dialysis patients who have severe osteitis fibrosa, unresponsive to vitamin D therapy or in whom such a treatment is contraindicated. This is particularly true in the presence of uncontrolled hyperphosphataemia and progressive metastatic calcifications [1]. The mean annual incidence of first PTx is about 30 per 1000 patient years in those dialysis patients treated for more than 10 years [3]. Relapses of SHPTH after PTx (either subtotal or total with forearm autograft) are relatively

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frequent ranging from 10% after 3 years to 30% after 7 years [4]. Usually they are represented by severe cases, characterized by having the most aggressive histological pictures with monoclonal proliferation of parathyroid cells, reduced expression of VDR and CaSR and subsequent resistance to the conventional treatment [2]. The latter does not appear to be able to control these forms; furthermore, the risk of inducing hypercalcaemia and/or hyperphosphataemia with the conventional treatment determines an unavoidable therapeutic discontinuity, which represents a further limit to the efficacy of the conventional treatment.

Calcimimetics represent at the moment the most important therapeutic option for the treatment of SHPTH of the uraemic patient on maintenance haemodialysis. This new class of agents augments the sensitivity of CaSR of parathyroid glands to extracellular calcium (Ca) concentrations, by that way causing both the suppression of parathyroid hormone (PTH) secretion [5] and of cellular proliferation [6]. In contrast to vitamin D, which suppresses PTH at the cost of concomitant increases in serum Ca and phosphate (P) levels, cinacalcet generally results in significant [7] and sustained [8] decreases in levels of serum immunoreactive intact parathyroid hormone (iPTH), Ca, P and of the Ca × P product.

The efficacy of cinacalcet in reducing serum levels of PTH and in controlling serum levels of Ca and P with the subsequent achievement of the new targets recommended by the NKF/K-DOQI guidelines [7,9] has been demonstrated in several controlled clinical trials in uraemic patients on haemodialysis, even though cases of resistance to the drug have been reported [10–13]. No data about the treatment with cinacalcet of relapses of SHPTH after PTx are available in literature: actually, calcimimetics could offer a new therapeutic opportunity for the treatment of these forms of recurrent SHPTH, otherwise almost inevitably referred to the surgeon. The aim of this single-centre prospective study was to evaluate the therapeutic efficacy of cinacalcet in the metabolic control of relapses of SHPTH after PTx.

Methods

Study protocol

Fifty-six PTx were effected in 52 haemodialysis patients of our Dialysis Unit in the years 1986–2005 due to refractory SHPTH. Histological studies of the parathyroid glands with light microscopy were performed on seven serial sections of the glands. Diffuse hyperplasia was defined as increased numbers of parenchymal cells with normal lobular structures, and nodular hyperplasia as at least one well circumscribed, encapsulated and virtually fat cell-free accumulation of parenchymal cells [14]. Carcinoma of the parathyroid glands was defined according to the criteria of Schantz and Castleman [15]. Among the 52 patients undergoing PTx, five died owing to clinical causes not related to PTx, seven underwent renal transplantation. Among the remaining 40 patients, four underwent a second PTx because of either the persistence or the precocious relapse (in the first six months after the operation) of SHPTH. Summarizing, the cohort of haemodialysis patients with a previous PTx currently followed in our Dialysis Unit consists of SHPTH in 40 (36 with one PTx and 4 with 2 PTx) out of 131 subjects. Twelve of them (30%) had a relapse of SHPTH, defined as serum levels of iPTH >300 pg/ml in a mean follow-up period of 137.6 ± 55.4 SD months (range 64–240). These patients had mean serum iPTH levels of 996.2 ± 53.8 pg/ml (range 370.4–1800.2). Their therapy in the months preceding the study included calcitriol (either oral or i.v.) in all, Ca containing phosphate binders or Ca-free phosphate binders. These 12 haemodialysis patients (all of them more than 18 years old and clinically stable) were enrolled into the present study after written informed consent. They were stratified into a treatment group (the six patients affected by the most severe form of SHPTH according to the serum levels of iPTH) and a control group (the remaining six patients): the former were treated for six months with a dose of cinacalcet ranging from 30 mg every other day to 60 mg a day at supper time; in designing this study, we decided to stop calcitriol treatment four weeks before the start of the study and not to administer calcitriol in the treatment group (at least in the first three months, if possible), in order to avoid the confounding effect of calcitriol on serum iPTH levels in the calcitriol group. The control group continued to be administered the conventional treatment (only phosphate binders, phosphate binders plus calcitriol either i.v. or oral or paricalcitol i.v. at the end of the dialysis session).

Study procedures

Serum levels of albumin, iPTH, Ca, P and alkaline phosphatase (ALP) were determined monthly 12 h after the administration of cinacalcet. Serum concentrations of albumin, Ca, P and ALP were measured by routine automated methods. Serum concentrations of iPTH were measured by using chemiluminescence immunoassay (Nichols, San Juan Capistrano, CA, USA, normal range, 10–65 pg/ml). Measured serum Ca levels were adjusted by albumin levels as follows, when they were less than 4.0 g/dl: Calcium = measured calcium levels + [(4.0 − albumin levels) × 0.8] mg/dl [16].

A standard bicarbonate, thrice-weekly haemodialysis treatment lasting 4 h was administered: a low-flux non-cellulosic membrane with a surface area ranging from 1.5 to 2.0 m^2 was utilized; dialysate and blood flows were respectively 500 and 300 ml/min. Ca concentration in the dialysate was 7.0 mg/dl in the treatment group and 6.0 mg/dl in the control group. We use to treat all PTx patients, who represent a very selected category, with a Ca concentration in the dialysate of 6.0 mg/dl at variance with Ca concentration of 5.0 mg/dl recommended by the NKF/K-DOQI guidelines [9]. Furthermore, in designing this study, we decided to adopt a Ca concentration in the dialysate of 7.0 mg/dl in the treatment group. The aim was to limit hypocalcaemia induced by cinacalcet by maximizing the transfer of Ca ions from the dialysate to the blood, as recommended also by the NKF/K-DOQI guidelines [9]. The other haemodialysis treatment modalities were kept constant during the study.

Statistical analyses

The distribution of the data was studied by means of the Kolmogorov–Smirnov test: all of them were non-normally distributed. The comparisons between unpaired data were made by means of the Mann–Whitney test; the comparisons between paired data were made by means of the Wilcoxon test. All statistical inferences were performed using the SPSS software package, version 10 (SPSS Inc., Chicago, IL, USA). Data are expressed as means ± SD or percentage of total, and values $P < 0.05$ were assumed as statistically significant.

Results

The clinical and demographic characteristics of the two groups are shown in Table 1. As far as the surgical procedures are concerned, subtotal PTx (7/8) was performed in seven patients (four of the treatment group and three of the control group); total PTx was performed in four patients (two of the treatment group and two of the control group); total PTx with forearm implantation was performed in one patient of the control group. As far as the histology of parathyroid glands is concerned, the treatment group included four cases of nodular hyperplasia and two cases of carcinoma, whereas the control group included four cases of nodular hyperplasia and two cases of diffuse hyperplasia.

At the start of the study, the six patients treated with cinacalcet showed a more severe picture of biochemical abnormalities when compared with the control patients (Table 2): in fact, they had higher mean serum levels of iPTH (1388.3 ± 461.7 *vs* 604.1 ± 161.2 pg/ml; $P < 0.007$), Ca (9.6 ± 0.6 *vs* 8.58 ± 0.3 mg/dl; $P < 0.017$), Ca × P product (52.7 ± 10 *vs* 40.0 ± 6.9 mg^2/dl^2; $P < 0.032$) and P, even though the latter were not significantly different (Table 2). After six months of treatment, a statistically significant reduction in the mean serum levels of iPTH (from 1388.3 ± 461.7 to 435.0 ± 139.9 pg/ml; $P < 0.01$), Ca (from 9.6 ± 0.6 to 8.3 ± 0.6 mg/dl; $P < 0.01$), P (from 5.5 ± 1.2 to 3.8 ± 1.0 mg/dl; $P < 0.01$) and Ca × P product (from 52.7 ± 10 to 31.3 ± 7.3 mg^2/dl^2; $P < 0.01$) was obtained only in the patients treated with cinacalcet (Table 2). Notably, as far as serum Ca and P are concerned, their levels decreased under the lower limits advised by the NKF/K-DOQI guidelines in two (P) and four (Ca) cases (serum P levels

Table 2. Biochemical characteristics of the two groups of patients

	Treatment group (No 6)	Control group (No 6)	P[a]
iPTH (pg/ml): Baseline	1388.3 ± 461.7	604.1 ± 161.2	0.007
After 6 months	435.0 ± 139.9*	526.6 ± 127.1	NS
%Variation	-68.7 ± 13.7	-13.3 ± 12.5	0.01
Ca (mg/dl): Baseline	9.6 ± 0.6	8.58 ± 0.3	0.017
After 6 months	8.3 ± 0.6*	9.1 ± 0.8	0.08
%Variation	-13.6 ± 7.9	6.11 ± 8.4	0.01
P (mg/dl): Baseline	5.5 ± 1.2	4.7 ± 0.9	NS
After 6 months	3.8 ± 1.0*	5.2 ± 0.7	0.021
%Variation	-30.3 ± 19.2	15.7 ± 25.4	0.01
Ca × P (mg^2/dl^2): Baseline	52.7 ± 10	40 ± 6.9	0.032
After 6 months	31.3 ± 7.3*	47.7 ± 9.2	0.007
%Variation	-37.9 ± 15.8	11.4 ± 30.2	0.01
ALP (U/l): Baseline	297.5 ± 211.2	155.3 ± 77.6	NS
After 6 months	285.5 ± 185.6**	164.2 ± 40.7	NS
% Variation	-4.0 ± 0.2	5.8 ± 0.6	NS

Both Wilcoxon test for paired data (*$P = 0.01$; **P = NS) and [a]Mann–Withney test for unpaired data were used. The data were expressed as mean ± SD and as percentage.
NS, not significant.

Table 1. Demographic and clinical characteristics of the two groups of patients at the baseline

	Gender (M/F)	Age (years)	Dialysis duration (months)	Time elapsed since PTx (months)	Relapse after PTx (months)
Treated					
1	M	57	289	156	56
2	F	59	432	240	118
3	F	49	283	126	76
4	F	58	204	65	28
5	M	33	106	86	47
6	M	63	218	126	78
		56.2 ± 10.9	255.3 ± 109.0	133.2 ± 61.5	67.2 ± 31.3
Controls					
7	M	24	86	64	21
8	F	64	320	126	64
9	F	51	249	120	48
10	M	47	264	189	132
11	M	48	286	136	24
12	M	45	348	210	72
		48.2 ± 13.8*	258.8 ± 92.1*	140.8 ± 53.3*	60.2 ± 40.7

Data were expressed as mean ± SD; the statistical analysis was performed utilizing the Mann–Whitney test for unpaired data; *P = not significant.

<3.5 mg/dl and serum Ca levels <8.4 mg/dl) [9]. Serum levels of iPTH decreased by 68.7% as a mean and the target (<300 pg/ml) was achieved in two cases. Two other patients treated with cinacalcet (one affected by carcinoma of the parathyroid glands and the other by nodular hyperplasia) maintained serum levels of iPTH of 600 pg/ml. In contrast, the six patients undergoing the conventional treatment showed at six months a not significant decrease in the mean serum levels of iPTH and a not significant increase in the mean serum levels of Ca, P and Ca × P product, when compared with the baseline values [9]. However, the differences did not reach any statistical significance (Tables 2 and 3).

Symptomatic episodes of hypocalcaemia (serum Ca <7.0 mg/dl), characterized prevalently by muscle cramps, were observed in three patients treated with 30 mg a day of cinacalcet. Their nadir serum Ca level ranged from 6.5 to 6.8 mg/dl; we could not observe any significant relationship of serum Ca levels with either the severity of SHPTH, or with the reduction in serum iPTH levels or with the pre-treatment serum Ca levels (data not shown). These episodes were treated immediately with infusions of Ca gluconate and thereafter by increasing the oral doses of Ca carbonate and/or by adding oral calcitriol to the treatment. Three episodes of vomiting (two of them in two patients experiencing also symptomatic hypocalcaemia) are to be reported as side effects of cinacalcet treatment. Finally, Table 3 shows individual results as far as biochemistry (serum Ca, P and iPTH) is concerned at three time-points (at the baseline, at three and six months). Furthermore, individual treatments (calcitriol, paricalcitol, Ca salts and sevelamer) at the same time-points are also reported in Table 3. The reason to restart calcitriol treatment in three out of the six patients of the treatment group at 3 months, and in 4 patients at 6 months was uniquely due to the necessity of counteracting the low serum Ca levels induced by cinacalcet, as shown by patients 2, 3 and 4 at the 3-month time-point and by patients 1, 2, 3 and 4 at the 6-month time-point. As far as the control group is concerned, calcitriol was not given to patient 10 because of peaks of hyperphosphataemia before the start of the study, to patient 11 because a serum iPTH level of 370 pg/ml and a serum Ca level of 8.4 mg/dl at the start of the study induced us to treat him with Ca carbonate salts only, or to patient 12 because of recurrent peaks of hyperphosphataemia after the 3-month time-point; sevelamer was introduced at that time.

Discussion

The efficacy of cinacalcet compared with placebo in decreasing PTH concentrations in haemodialysis patients with SHPTH was shown in several published studies [10–13], thus increasing the percentage of subjects who are able to achieve the NKF/K-DOQI targets [7,9]. Furthermore, a recent combined analysis of four trials showed that cinacalcet, compared with placebo in patients with end-stage renal disease and uncontrolled SHPTH, decreased the risk for PTx by 93% [17]. Calcimimetics have also shown good therapeutic efficacy in counteracting hypercalcaemia in persistent SHPTH after successful kidney transplantation, with a reported variable outcome of renal function [18–20]. Finally, a very recent case report has shown that cinacalcet was effective in one case of parathyromatosis (hyperfunctioning parathyroid tissue scattered throughout the neck), which is the most severe type of recurrent SHPTH after PTx [21]. The ability of cinacalcet to attenuate parathyroid cell proliferation in animal models [22] and the direct *in vitro* evidence of the suppressive effect of cinacalcet on PTH secretion in human parathyroid cells with pathologically reduced CaSR levels [23] offers encouraging support for efficient management of patients with parathyroid hyperplasia, often refractory to current medical treatment [2]. No data about the treatment with cinacalcet of relapses of SHPTH after PTx are available in literature. Some questions and concerns could be raised about the fact that the introduction in the treatment group of calcitriol at a given time-point and of a higher dialysate Ca concentration from the baseline time-point could have an impact not only on serum iPTH levels, but also on the efficacy of cinacalcet treatment. These questions and concerns can have many exhaustive answers: first, the concept of relapse is intrinsically linked to the concept of resistance to a given treatment; furthermore, the causes of the resistance to a given treatment must be looked for in the underlying histological picture: now the six patients, affected by nodular hyperplasia (4) and carcinoma (2) of the parathyroid glands, which, notoriously, are not responsive to the conventional treatment, all the same had been administered long-term calcitriol treatments before the study, unsuccessfully. Thus, the successful response of our patients to cinacalcet is the *in vivo* mirror of the *in vitro* evidence of the suppressive effect of cinacalcet on parathyroid cells with pathologically reduced CaSR levels [23]. Secondly, if it is well known that, on the one hand, a higher dialysate Ca concentration and calcitriol are able to suppress SHPTH via the induction of hypercalcaemia, it is also well known, on the other hand, that hypocalcaemia constitutes the most powerful stimulus for PTH secretion [2]. Now, when looking at Tables 2 and 3, it is clear that all the six patients of the treatment group underwent a significant decrease in serum Ca levels (from 9.6 ± 0.6 to 8.3 ± 0.6 mg/dl, $P = 0.01$) induced by cinacalcet, the introduction of calcitriol at a given time-point and of a higher dialysate Ca concentration from the baseline time-point notwithstanding. Notably, calcitriol was introduced in patients 1, 2, 3 and 4 because these patients had previously, and continued to have, serum Ca levels below the lower limits advised by the NKF/K-DOQI guidelines [9]. Thirdly, the final strong point about the fundamental role of cinacalcet in reducing serum iPTH levels is that the latter were more than halved at the 3-month time-point (from 1388.3 ± 461.7 to 573.7 ± 128.7 pg/ml, $P = 0.01$,

Table 3. Individual results and individual treatments at three time-points are shown

	Baseline			Month 3			Month 6		
	iPTH (pg/ml)	Ca (mg/dl)	P (mg/dl)	iPTH (pg/ml)	Ca (mg/dl)	P (mg/dl)	iPTH (pg/ml)	Ca (mg/dl)	P (mg/dl)
Treated									
1.	1800	10.7	4.2	490	9.4	4.2	400	8.2	3.0
Rx		C 30 + S 2.4			C 60 + S 2.4			C 30 + CTR 0.25 + CC 1	
2.	1100	8.5	5.7	417	7.6	3.8	430	7.7	4.5
Rx		C 30 + CC 2			C 30 + CTR 0.25 + CC 2			C 30 + CTR 0.25 + CC 2	
3.	1780	9.9	4.8	574	8.0	5.0	600	7.5	5.2
Rx		C 30 + CC 1			C 30 + CTR 0.25 + CC 2			C 30 + CTR 0.25 + CC 2	
4.	1800	9.2	5.2	800	8.0	4.7	300	8.3	2.4
Rx		C30 + CC 2			C 30 + CTR 0.25 + CC 2			C 30 + CTR 0.25 + CC 1	
5.	750	9.5	7.7	581	8.3	6.8	280	9.0	4.0
Rx		C 30 + S 3.2			C 30 * + S 3.2 + CC 1			C 30 * + S 2.4 + CC 1	
6.	1100	9.9	5.5	580	9.5	4.5	600	8.9	3.8
		C 30 + S 2.4			C 60 + S 2.4			C 60 + S 2.4	
Control									
7.	610	8.4	5.2	600	8.6	6.1	680	9.7	6.4
Rx		CTRv 1 + CC 2			CTRv 1 + CC 2			CTR 1 + CC 1 + S 1.8	
8.	800	9.2	4.0	680	10.0	5.9	700	8.9	5.5
Rx		CTRv 3 + CC 2			CTRv 3 + S 3.2			PC 15 + S 3.2	
9.	750	8.6	5.0	720	8.7	4.6	480	9.0	4.8
Rx		CTR 3 + CC 2			CTR 3 + CC 2			CTRv 3 + CC 2	
10.	614	8.3	6.1	620	9.2	5.0	510	8.4	4.4
Rx		CC 2.5 + S 1.8			CC 2.5 + S 2.4			CC 2.5 + S 2.4	
11.	370	8.4	4.0	350	9.0	3.8	340	8.2	5.0
Rx		CC 2			CC 2			CC 2	
12.	480	8.6	3.8	380	8.2	4.8	450	10.4	5.2
		CTR 0.25 + CC 2			CTR 0.25 + CC 2			CC 2 + S 2.4	

Each number in the rows marked as Rx indicates the dose of the drug. C, cinacalcet (mg/day); CTR, calcitriol per os (μg/day); CTRv, calcitriol i.v. (μg/week); PC, paricalcitol i.v. (μg/week); CC, Ca carbonate (g/day); S, sevelamer (g/day); C 30 *, cinacalcet (30 mg every other day).

Table 3), thus, well before the introduction of calcitriol in the treatment. Thus, we can conclude that our single-centre prospective study, even though small and of short duration, shows that cinacalcet represents a solid, and sometimes unique, therapeutic opportunity for patients affected by relapses of SHPTH after PTx. This evidence is particularly important for this category of patients who are exposed to a higher risk because of the presence of comorbidities and/or for the technical difficulties linked to a neck re-operation.

The patients treated with calcimimetics, who had at the beginning a more severe histological picture of parathyroid glands and a more severe metabolic picture (higher serum iPTH levels could be due to a larger mass of parathyroid tissue), obtained a better biochemical control after 6 months. An important point is that, however, two out of these patients were non-responders: we hypothesize that this might be due to the loss of CaSR in parathyroid carcinoma and in part of parathyroid nodular hyperplasia. Furthermore, we have to state that to maintain normal levels of serum Ca in these patients was a difficult task: actually, we looked for an equilibrium between acceptable serum levels of Ca (i.e. no symptoms of hypocalcaemia) and the necessity of not administering more than 2 g of elementary calcium per os a day to each patient.

Cinacalcet was well tolerated; however, three patients (50%) showed at least a symptomatic episode of hypocalcaemia. These side effects advised us to be more prudent in increasing the doses of cinacalcet. These episodes indicate a greater difficulty in metabolic compensation in patients after PTx, whose causes remain to be elucidated.

Finally, parathyroid carcinoma is an indolent, albeit tenacious, tumour with rather low malignant potential; it has been described in several patients with end-stage renal disease. A case report reviewed 12 patients with parathyroid carcinoma who were receiving maintenance haemodialysis [24]. All demonstrated hyperplasia of other parathyroid glands. The diagnosis was made on an average of 6 years after the start of haemodialysis. In all cases, parathyroid carcinoma was diagnosed after PTx on the basis of local invasion (No = 5), tumour pathology (No = 4) or distant metastases (No = 2). The authors of the case report concluded that no pre-operative features distinguished these patients from those with parathyroid hyperplasia and that their clinical course may be more benign than patients having normal renal function because of the tendency for renal insufficiency to lower serum Ca levels [24].

In conclusion, our single-centre prospective study, even though small and of short duration, shows that cinacalcet is effective also in controlling relapses of SHPTH after PTx, thus representing a solid, and sometimes unique, therapeutic opportunity for this high-risk category of patients.

Conflict of interest statement. None declared.

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