Adverse events due to psoriasis treatment

F. Kokelj, C. Plozzer and G. Trevisan

SUMMARY

Any treatment can cause some undesired reactions that may be local, systemic, predictable or unpredictable. In the present study we describe our experience concerning the incidence of drug reactions caused by the most common psoriatic treatments. Both topical, vitamin D derivatives and topical retinoids, or systemic, etretinate and cyclosporin A, can cause a large spectrum of adverse reactions that must be known and considered by both doctors and patients in order to obtain the best clinical results. In this paper we summarize our experience with the more common and recent treatments for psoriasis.

KEY WORDS

psoriasis, therapy, adverse drug reactions

Introduction

A good knowledge of all the side effects of different drugs is of great importance for the choice of treatment. Unfortunately, the side effects are often underevaluated for various reasons: both patients and doctors seem to be more interested in the efficacy and possibilities of new drugs than in their side effects, while drug companies play an increasing role in supporting clinical studies, research and symposia. As an example, we remind the number of studies on side effects presented at the last European and International Symposia on Psoriasis (Table 1). It is clear that the increased number of presentations is not accompanied by an increase of reports on side effects.

Drug reactions may be classified as predictable, dose-dependent and related to drug actions, and unpredictable, dose-independent and unrelated to drug actions. The predictable reactions are hyperdosage, side effects, secondary effects, and pharmacological interactions, while intolerance, idiosyncrasy, allergy and pseudo-allergy belong to the unpredictable ones. The reactions to the treatment of psoriasis are usually predictable, while allergy, pseudo-allergy, intolerance and idiosyncrasy are extremely rare.

In this paper we summarize our experience on adverse drug reactions caused by the most common and recent treatments for psoriasis.

Calcipotriol

Vitamin D derivatives represent one of the most important new topical treatments for psoriasis developed in the last years. Calcipotriol is a structural analogue of the natural, biologically active 1,25 (OH)2-D3. It is as active as calcitriol in inducing keratinocyte differen-

tiation and in inhibiting keratynocyte proliferation (1). Calcipotriol has proven to be effective and well tolerated also in our experience. Side effects are relatively rare and consist of localized cutaneous reactions, observed in 4 % of our 192 patients (2). This incidence is lower than that described in literature - from 4 to 20 % - (3) and is probably due to the different criteria of enrolment. Allergic contact dermatitis to calcipotriol was described (4, 5) but we have never observed any case. On the contrary, in 1995 we described three cases of persistent pigmentation on the site of application of ointments after repeated sunbathing (6). This observation is confirmed by other authors and for this reason we invite patients to apply the medication after the light treatment to avoid this undesirable effect.

Tacalcitol

Tacalcitol 1,24 (OH)2-D3, another side-chain derivative of calcitriol, has demonstrated to be effective in treating moderate plaque psoriasis (7). It is applied once daily (calcipotriol must be applied twice) and may be used also for psoriasis of the face its irritant power lower than that of calcipotriol.

In the Italian multicenter study on tacalcitol (8), in which this cream was compared with betamethazone valerate ointment in 63 patients, we observed only two cases of itching on the site of application (3 %).

In the last year we observed two cases, one of mild and one of major skin irritation of the face in the area treated with tacalcitol. In both cases there was no particular situation to justify this unexpected reaction.

Tazarotene

Tazarotene is the first receptor selective topical retinoid (9); it is a potent synthetic analogue of the acetylenic class of retinoids. In vivo it is rapidly converted into its free acid metabolite, tazarotenic acid. Its most important side effect is the irritation on the site of application and around the treated plaque. The incidence of this side effect is variable (10).

In the first year of our experience with this gel we observed numerous cases of burning irritation usually on the site of application (45 % of the patients treated); in some cases it was sufficient to invite the patient to apply less gel on the plaque or to apply tazarotene every second or third day in order to continue the treatment, while in 23 % of the cases the patients had to interrupt the application due to a severe reaction. We underline that a more detailed explanation of the criteria of tazarotene application can decrease the incidence of this side effect.

Retinoids (etretinate)

Retinoids include a large number of synthetic and natural compounds derived from vitamin A and used for different dermatological problems (11). Etretinate remains a first choice drug for different forms of psoriasis: it is effective and well tolerated when used in usually prescribed doses (0,5-1 mg/kg/day), while its teratogenic effect remains its first and most important side effect. For this reason fertile women should not use it (12). In table 2 we summarize our experience on a group of 109 patients affected with extensive vulgar psoriasis treated with etretinate at a starting dose of 0,6 - 1 mg/kg/day. These data are in agreement with those of other authors (13, 14). We experienced a high percentage of side effects (92%). Nevertheless only few patients had to interrupt the treatment, 3 % of our patients, and all of them for an important increase in the serum lipid level; in all the other cases the reaction improved with the reduction of the dosage.

Cyclosporin A

Cyclosporin A is the more recent systemic drug proposed for the treatment of severe forms of psoriasis. This immunosuppressive drug presents different side effects in relation to the dosage used; consequently the spectrum of reactions observed during the treatment of

Table 1. Number of reports presented at European Symposia on Psoriasis.

	TOTAL REPORTS	REPORTS ON THERAPY	REPORTS ON DRUG REACTIONS
Trieste 1978	33	0	0
Trieste 1983	49	20	0
Trieste 1988	68	30	1 (1,5 %)
Trieste 1993	92	39	2 (2 %)
Milan 1998	184	71	1 (0,5 %)

Table 2. Incidence of the different adverse reactions caused by etretinate in a group of 109 patients.

Incidence of the different adverse reactions	
Labial xerosis	81 %
Paronychia	33 %
Increased lipid serum level	26 %
Palmar and plantar thinning and scaling	24 %
Defluvium	11 %
Visual disturbance	2 %
No side effects	13 %

Table 3. Incidence of minor side effects observed in a group of 63 patients treated with cyclosporin A.

Incidence of minor side effects	
Asthenia	58 %
Cramps and muscle weakness	44 %
Headache	40 %
Hypertrichosis	22 %
Gastro-intestinal disturbance	13 %
Gingival hyperplasia	11 %
No side effects	28 %

psoriasis is different from those observed in transplanted patients, when the dosage of cyclosporin is much higher. The most important problems (major adverse events) are the nephrotoxicity of cyclosporin, its immunosuppressive action and the risk of cancer induction (15, 16).

We observed 2 cases of acute renal failure and 1 case of hypertension in a group of 63 patients: all these cases improved with the interruption of the treatment and results of the tests returned to normal values.

In table 3 we report our data on the incidence of minor side effects in the same group of 63 patients. The use of the new microemulsion formulation (Neoral) allowed a reduction of the incidence of side effects (15). These data show the high frequency of side effects, present in more than 70 % of the cases. Usually the reduction of the dosage is sufficient to obtain the regression of this effect and only a few patients had to interrupt the treatment.

Conclusions

Any treatment, both topical or systemic, presents the possibility of some adverse reactions; in particular, systemic drugs cause more important predictable and unpredictable reactions in comparison with topical treatment and our data confirm the high incidence: *only 13 % of the patients treated with etretinate and 28 % of those treated with cyclosporin do not really present any side effect*, that sometimes are mild but sometimes influence their life quality. On the contrary, topical treatment is better tolerated even if minor side effects are possible. All these problems may influence the compliance and for this reason it is important that both doctors and patients consider and know the different adverse reactions as well as the risk/benefit ratio of the different treatments in order to obtain the expected results.

REFERENCES

1. Binderup L, Bramm E. Effects of a novel vitamin D analogue MC 903 on cell proliferation and differentiation in vitro and on calcium metabolism in vivo. Biochem Pharmacol 1988; 37: 889-95

2. Lavaroni G, Plozzer C, Torsello P, Kokelj F. Effetti collaterali del trattamento con calcipotriolo topico (MC 903): nostra esperienza di tre anni. Chronica Dermatologica, 1986, VI, 37-41

3. Barth Jones J. Comparison of Calcipotriol ointment with betamethasone valerate ointment and dithrenol and Investigation of the long term safety and efficacy of Calcipotriol. Acta Derm Vener 1994, Suppl. 186: 46

4. Yip J, Goodfield M. Contact dermatitis from MC903, a topical vitamin D3 analogue. Contact Dermatitis 1991; 25: 139-40

5. Bruynzeel DP, Hol CW, Nieboer C. Allergic contact dermatitis to calcipotriol. Br J Dermatol, 1992; 126: 66

6. Kokelj F, Lavaroni G, Perkan V, Plozzer C. Hyperpigmentation due to Calcipotriol (MC 903) plus Heliotherapy in Psoriatic Patients. Three Case Reports. Acta Der Venereol (Stockh), 1995; 75: 307-9

7. Matsunaga T, Yamamoto M, Mimura H. 1,24 (R)-dihydroxivitamin D3, a novel active form of vitamin D3 with high activity for inducing epidermal differentiation but decreased hypercalcemic activity. J Dermatol 1990; 17: 135-42

8. Gruppo Italiano di studio sul Tacalcitolo. Tacalcitolo ointment is an efficacious and well tolerated treatment for psoriasis. J Europ Ac Vener, 1996; 6: 142-6

9. Chandraratna R.A.S. Tazarotene: the first receptor-selective topical retinoid for the treatment of psoriasis. J Am Acad Dermatol, 1997; 37(2) Suppl. 12-17

10. Marks R. Clinical safety of tazarotene in the treatment of plaque psoriasis. J Am Acad Dermatol, 1997; 37(2): Suppl. 25-33

11. Bollag W. The development of retinoids in experimental and clinical oncology and dermatology. J Am Acad Dermatol 1983; 9: 797-805

12. Geiger JM, Baudin M and Saurat JK. Teratogenic risk with Etretinate and Acitretin treatment. Dermatology, 1994; 139: 109-16

13. Michaelsson G, Berquist A, Vahlquist A et al. The influence of "Tigason" (Ro 10-9359) on the serum lipoproteins in man. Br J Dermatol 1981; 105: 201-5

14. Windhorst DB, Nigra T. General clinical toxicology of oral retinoids. J Am Acad Dermatol 1982; 6: 675-82

15. von Graffenried B, Friend D, Shand N et al.. Cyclosporin A (Sandimmun) in autoimmune disorders. In: Thompson AN ed. Cyclosporin: mode of action and clinical applications. Kluver Academic Pub. 1989; 213-5

16. Mason J. Renal side-effects of Cyclosporin A. Br J Dermatol 1990; 122(36): 71-77

17. Kokelj F, Plozzer C, Trevisan G. Conversione dalla Ciclosporina in formulazione tradizionale a quella in microemulsione (Neoral); valutazione dell'efficacia e tollerabilità clinica in 63 pazienti psoriasici. G Ital Dermatol Venereol 1999; 134: 147-51

AUTHORS' ADDRESSES

Franco Kokelj, MD, Institute of Dermatology, University of Trieste, Ospedale di Cattinara, 34149 Trieste, Italy
Carmela Plozzer, MD, same address
Giusto Trevisan, MD, professor and chairman, same address