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The Modern Approach: New Combined Treatments for Psoriasis

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The clever physician, especially if he is also an investigator, tries, whenever possible, to treat his patients with only one active drug, so that he can obtain exact information about the effectiveness of the drug and about any side effects that it may produce.

For psoriasis, a chronic, recurrent and often recalcitrant disease, attempts have been made to combine more than one drug in the hope of improving the effectiveness of the treatment. We have demonstrated that since psoriasis has precise self-maintaining mechanisms, recurrences are significantly more frequent when the disease has been only alleviated, instead of when the clinical symptomatology has completely disappeared (Table I).

There are many valid and non-valid reasons for which several treatments are often combined. Sometimes the drugs in the combination act at different sites, and therefore the combination may be more effective. Sometimes drugs with differing toxicity are combined to reduce the risk, or one can combine low doses of toxic drugs to reduce the toxicity. Sometimes high doses of toxic drugs are given in the hope of curing the disease within a short period of time. The ultimate and not really rational reason for combining several treatments is a very recalcitrant case which is treated 'shotgun', in the hope of finding an effective cure. Combining several drugs can result in cancellation of their individual effects (antagonism, which must absolutely be avoided) or else a simple summation of their effects, but ideally will have synergistic effects, which is to say that the effectiveness of each drug is greater than the same dose given alone. Summation may make it possible to shorten the period of treatment without increasing any side effects. Synergism, instead, increases the therapeutic effectiveness and decreases the side effects at the same time, which is the definition of the term 'better therapeutic ratio'. Drugs may interact directly (chemically or physically) or through reciprocal alterations of gastrointestinal absorption or of protein binding, or else of metabolism or renal excretion. Finally, they may interact at receptor sites. Receptor site interactions may be competitive or may be chemical alterations of the receptor or biological changes at different sites in the same system, or else work through different systems with similar biological effects.

Psoriasis can be treated locally or systemically and I will speak for the most part about systemic treatments. The currently available systemic treatments for psoriasis that have proved effective are photochemotherapy, retinoids, methotrexate and other cytostatic drugs such as hydroxyurea, cyclosporin and perhaps some fumaric acid esters, but the effectiveness of the latter has not been definitely demonstrated and we do not know the mechanism of their action.

I will now summarize rapidly the mechanisms of action of the drugs listed above, with the aim of deciding whether or not it might be possible to combine them.

Retinoids, especially etretinate, which is by far the most widely used drug of this class for psoriasis, act by regulating the differentiation of keratinocytes, inhibiting the chemotactic activity of neutrophilic granulocytes and reducing the adhesion of the cells and their anchorage-independent growth. Their major targets are the keratinocytes and the neutrophilic granulocytes.

Photochemotherapy acts by inhibiting the activities of the keratinocytes, the Langerhans cells, the T-lymphocytes and the neutrophilic granulocytes. The same cells are the targets for methotrexate.

Cyclosporin blocks the production of IL-1, IL-2, TNF, GM-CSF and gamma-IFN, decreases the activity of the Langerhans cells, inhibits phospholipase A2 and – only in vitro and at doses much higher than the therapeutic ones – decreases keratinocyte mitoses. The target cells for cyclosporin are, therefore, the T-lymphocytes, the monocytes and the Langerhans cells.

When designing a combined treatment, the first thing to keep in mind is to avoid summing of the same side effects of each drug. PUVA treatment, methotrexate and cyclosporin are all cancerogenic drugs and therefore must not be combined. The retinoids have been shown to have antineoplastic activity and might therefore be combined with each of the drugs listed – except methotrexate, which has hepatotoxic effects, as have the retinoids.

In Table II, I have summarized all the possible useful combinations of drugs for treatment of psoriasis, both systemically and topically, based on what I have listed theoretically above, on my personal experience and on the data in the literature. PUVA therapy can be combined locally with calcipotriol and systemically with retinoids. This combination (Re-PUVA) has been known for years and often reported in the literature to be one of the most effective treatments for psoriasis, with fewer side effects.

Table I. *Relapses of psoriasis after remission in 147 pts (median follow-up: 15 months)*

	Cleared 75–99%	Cleared 100%	
Relapses	68 (47%:	28 (27%)	χ^2: $p < 0.001$
No Relapses	76 (53%)	75 (73%)	

Table II. *Drug associations for psoriasis*

PUVA	MTX	CsA	RETINOIDS
Retinoids	Calcipotriol	Retinoids	PUVA
Calcipotriol	Dithranol	Calcipotriol	CsA
		Dithranol	Calcipotriol

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Methotrexate can be combined, essentially, only with such topical drugs as calcipotriol and dithranol, excluding the tars because of their potential oncogenic activity. Although the combination of methotrexate and retinoids should be effective theoretically, it should absolutely be avoided because of the high probability of hepatotoxicity, also reported in the literature.

Cyclosporin can be combined with non-oncogenic topical drugs such as calcipotriol and dithranol and, very likely, might be useful in alternating cycles with retinoids.

Finally, retinoids can be combined with PUVA therapy, calcipotriol and, apparently with cyclosporin.

The combination of cyclosporin with etretinate has different targets and thus should produce a truly synergistic therapeutic effect as well as reducing the possibility of side effects, especially the widely-feared oncogenic effects of cyclosporin. The long half-life of etretinate may also prolong the interval free of psoriasis after cure as I have seen in a large case list.

Recent studies by Weber and Back have also demonstrated that there is no metabolic interaction in the liver between cyclosporin and etretinate. Probably the two drugs are metabolized by different isoenzymes of cytochrome P-450 and, therefore, their use either in combination or alternatively does not increase their toxicity.