

THERAPEUTIC TRIALS WITH ORAL COLCHICINE IN PSORIASIS¹

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Abstract. Twenty-two psoriatic patients were treated orally with the antichemotactic agent, colchicine, at a dosage of 0.02 mg per kg per day for a duration of 2-4 months. Complete clearing or marked improvement were noted in 8 of the 9 patients, in whom thin papules and thin plaques were the predominant type of lesion. Much less favorable results were obtained in patients with chronic, stable, thick plaque-type disease, although decreased scaliness, erythema and infiltration and marked diminution of the pruritus were observed in almost all of the cases. A considerable improvement of the joint pains was noted in each of the 8 patients who suffered from arthralgias. Five additional patients with extensive, chronic, stable plaque-type psoriasis were given oral colchicine immediately after complete clearing of their skin lesions with Goeckerman's method or with methotrexate. Four of them continued to take colchicine for 8-9 months and during that time they remained free of significant skin disease. These findings lend support to the hypothesis that the migration of the activated psoriatic neutrophils into the skin could be an important factor in the initiation and possibly also in the perpetuation of the psoriatic lesions. Closely controlled, long-term studies conducted in large numbers of patients are warranted in order to determine the exact therapeutic role of oral colchicine in the long-term management of psoriasis.

One of the characteristic histologic features of the acute and subacute psoriatic lesion in the infiltration of the epidermis—and mainly of the parakeratotic stratum corneum—by numerous neutrophils (1). Furthermore, in a study on the very early psoriatic lesion, it has been shown that the migration of neutrophils into the upper dermis and epidermis is the earliest histologic change and that it precedes the usual signs of epidermal hyperproliferation (2).

Psoriatic scale contains leukotactic substances that appear to be products of complement activation (3). Psoriatic plaque epidermis contains greater amounts of a proteinase which induces the accumulation of neutrophils by activating complement—in contrast to uninvolved epidermis (4). On the other hand, circulating neutrophils from psoriatic patients have shown enhanced chemotactic responsiveness

and increased phagocytic activity when compared with neutrophils from healthy subjects (5, 6). Circulating polymorphonuclear leukocytes from patients with psoriasis are also more adherent to glass wool columns than those from normal or appropriate disease control patients (7). These findings and others have led certain investigators to believe that the migration of activated neutrophils into the skin could play an important role in the pathogenesis of the psoriatic lesion (8).

Colchicine, a microtubule disruptive agent which is effective in inhibiting the chemotactic migration of neutrophils both *in vitro* (9) and *in vivo* (10), has been extensively used in the prophylactic treatment of gouty arthritis (11) and of Familial Mediterranean fever (12, 13). At the low dosage in which it is used in the above-mentioned conditions, colchicine therapy is considered to be safe even when administered over long periods of time. It was therefore decided to try to treat psoriasis patients with low oral doses of colchicine.

PATIENTS AND METHODS

Twenty-two psoriatic outpatients were treated orally with colchicine at a dosage of 0.02 mg per kg per day divided into three equal doses for a period of 2-4 months. The study was conducted between November 1978 and March 1979. Each patient was interviewed with respect to the duration and severity of his disease seasonal variations, and the presence and severity of joint complaints and pruritus. Each patient underwent a dermatological examination and the percentage of body-surface involved, type of disease and predominant types of lesions were determined. The patients were instructed not to use any topical medication other than emollients.

Each patient was seen again at monthly intervals. Photographs were obtained before treatment and after 2, 3, or 4 months in most cases. Routine blood counts, urinalysis and blood chemistry (SMA-12) were performed before treatment and every month thereafter.

¹ Approved by the institutional Helsinki committee for human experimentation.

Table 1. Clinical details and results of oral colchicine therapy in 22 psoriatic patients

- no complaints; + pain in one or more joints - sometimes; ++ severe and frequent joint pains in many joints necessitating the frequent administration of analgesics. Excellent: clearing of 75% or more; Good: clearing of 50% to 74%; Fair: clearing of 25% to 49%; Poor: clearing of less than 25% or worsening

No. /Sex/ Age, y.	Duration of disease, y.	Type of disease	Prodromant type of lesions	% of body sur- face involved	Arthritic com- plaints
1/F/31	11	Vulgaris	Flat papules, small plaques	20	+
2/M/54	5	Generalized, spreading	Chronic plaques, new guttate lesions	40	-
2/M/4	3/12	Generalized	Large thin plaques, guttate lesions	70	-
4/F/55	10	Vulgaris	Chronic plaques	18	++
5/M/46	10	Flexural	Flat plaques	8	-
6/F/25	5	Vulgaris	Thin papules, small plaques	6	+
7/M/50	2	Flexural	Flat plaques	14	-
8/F/47	10	Generalized	Flat papules	12	++
9/F/50	46	Vulgaris	Small flat plaques, guttate lesions	12	-
10/M/69	10	Generalized	Flat plaques, guttate lesions	30	-
11/F/26	4	Generalized	Flat papules, small plaques	9	-
12/M/19	18	Generalized, spreading	Pustular	25	-
13/M/45	22	Vulgaris	Chronic plaques	15	+
14/M/53	10	Generalized	Large, thick, hyperkeratotic plaques	25	-
15/M/48	14	Scalp, palms, soles.	Thick, chronic plaques	10	-
16/M/35	4	Generalized	Thick plaques	40	+
17/F/69	50	Generalized	Chronic thick plaques	8	-
18/M/32	10	Generalized	Small thick plaques	8	++
19/M/39	15	Generalized	Chronic hyperkeratotic plaques	25	-
20/M/37	10	Generalized	Chronic thick plaques	25	++
21/F/28	20	Vulgaris	Chronic thick plaques	3	-
22/M/57	15	Vulgaris	Large chronic thick plaques	20	-

Serum vitamin B₁₂ and carotene levels were determined every 2 months. Peripheral blood neutrophil-chemotaxis was assayed in 10 of the patients before and 2 months after the initiation of therapy using a modification of the Boyden chamber method as described elsewhere (6).

The clinical response of the patients was evaluated as follows: 'Excellent' = complete clearing of 75% or more of the initial lesions; 'good' = complete clearing of 50-

74% of the lesions initially found; 'fair' = complete clearing of 25-49% of the initial lesions and decreased scaling, erythema and infiltration of the remaining lesions; 'poor' = clearing of less than 25% of body surface involved, or worsening.

The clinical details of the patients are summarized in Table 1. Fourteen were males and 8 females. Their ages ranged between 4 and 69 years (mean 41.8 years). The

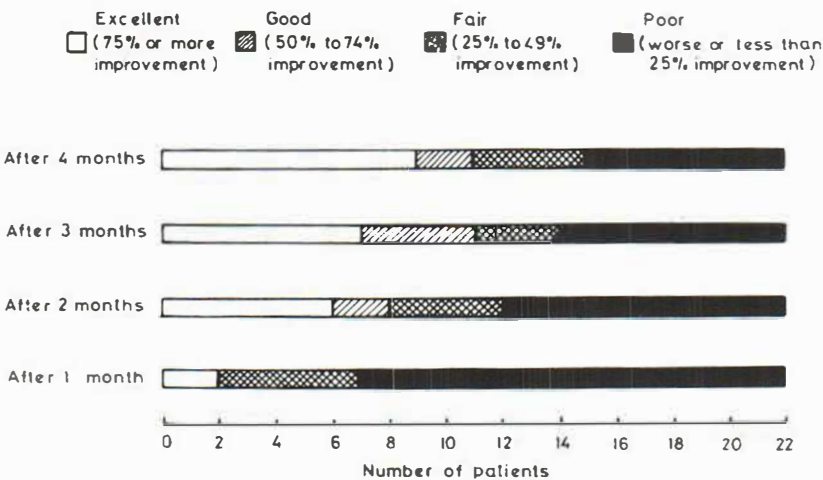


Fig. 1. Results of oral treatment of psoriasis patients with colchicine according to the duration of therapy.

Daily dosage of colchicine, mg/day	Duration of treatment, months	Result of treatment
1.5	4	Excellent
1.5	3	Fair
0.75	2	Excellent
1.5	3	Excellent
1.5	2	Excellent
1.25	3	Good
1.5	4	Excellent
2.0	2	Excellent
1.5	3	Good
1.0-1.5	3	Excellent
2.0	2	Excellent
1.5	3	Good
1.5	4	Fair
1.5	3	Poor
1.5	3	Poor
1.5	3	Fair
1.5	3	Poor
1.5	3	Fair
1.5	3	Poor
1.5	3	Poor
1.5	3	Poor
1.5	3	Poor
1.5	3	Poor

duration of the disease varied between 4 months and 50 years (mean 14.1 years). Twelve of the patients had chronic, stable, thick plaque-type psoriasis; in 7 the lesions consisted mainly of thin papules and thin small plaques; 2 had flexural psoriasis and 1 generalized pustular psoriasis. Five additional patients with chronic, stable, extensive, thick plaque-type psoriasis were hospitalized and treated with one of the well-known modalities (Goeckerman or methotrexate). After complete clearing of their skin lesions the initial treatment was stopped and oral colchicine therapy was started at the same dosage as mentioned above. The patients continued to take the medication on an outpatient basis for periods ranging between 4 and 9 months (mean 7.4 months) and were followed-up monthly in our clinic. Each patient was thoroughly interviewed with respect to the duration and severity of his disease, seasonal variations, previous hospitalizations, previous treatments, their effectiveness and the length of the remissions obtained.

RESULTS

Therapeutic response

Eleven of 22 patients responded well to the treatment with colchicine (clearing of more than 50% of the initial body-surface involved and decreased

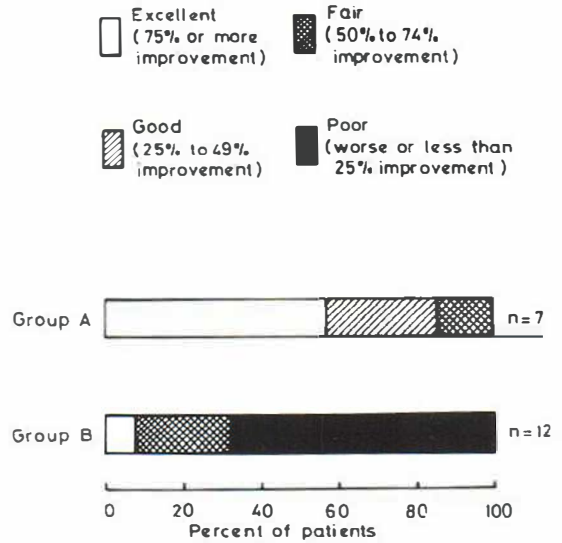


Fig. 2. Results of a 3-month course of oral colchicine in two subgroups of psoriatic patients: group A consists of patients with guttate or thin papular and small plaque lesions; group B includes patients with chronic thick and hyperkeratotic lesions.

scaling, erythema and infiltration of the remaining lesions). In 7 of these 11, the results after 3 months were considered to be excellent (clearing of more than 75%) (Table I, Fig. 1). In 3 patients, a moderate improvement was noted (25-49% clearing) and in the remaining 8, poor results were obtained (clearing of less than 25%).

Classification of the patients according to the chronicity and thickness of the lesions revealed that the results were much better in those patients in whom thin papules and thin plaques were the predominant types of lesions (Table I, Fig. 2). Marked improvement was noted in 6 out of 7 such patients. In 2 additional patients with flexural, thin plaque-type psoriasis the results were excellent. In contrast, a marked improvement was noted in only 1 out of 12 patients with chronic, stable, thick plaque-type psoriasis. Put in another way, in 8 out of 12 patients with chronic, thick plaque-type disease, poor results were obtained, whereas none of the 9 patients with the thin papular and thin plaque variety responded poorly to the treatment.

One of the patients had acute, spreading, generalized pustular psoriasis with fever and constitutional symptoms. Administration of colchicine stopped the spreading of the disease as well as the formation of new pustules and improved his general

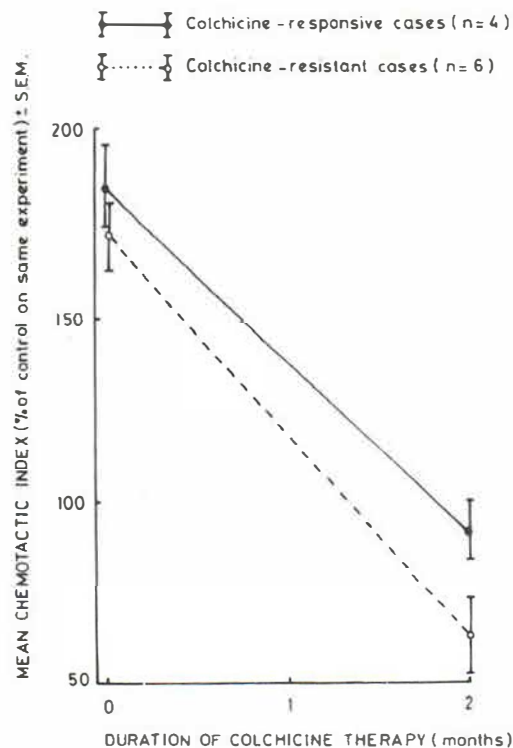


Fig. 3. Effect of colchicine therapy on the chemotactic responsiveness of neutrophils derived from the peripheral blood of 10 of the treated psoriatic patients.

condition markedly within one week. Continued administration of the drug for 3 months resulted in a gradual and slow resolution of 70% of his skin lesions.

Eight of the patients suffered from arthralgias. In 4 of the 8, the pain was frequent and severe and necessitated the frequent administration of analgesics. A considerable diminution of the joint pains was noted by each of these patients during the administration of colchicine regardless of the presence or lack of response of the skin lesions to the treatment.

Three of the patients suffered from pruritus. In 2 of them, the pruritus was severe and accompanied by numerous excoriations and hemorrhagic crusts; both of them had chronic stable thick plaque-type psoriasis. A marked improvement of the pruritus was noted by all 3 patients during the administration of the drug. In the last 2 patients the excoriations and the crusts disappeared; the scaliness, erythema and infiltration of the lesions decreased, though the percentage of the body-surface involved was not

reduced significantly and the overall results of the treatment were considered to be poor.

Prophylactic schedule

Five patients with chronic stable plaque-type psoriasis of long duration were given oral colchicine immediately after complete clearing of their skin lesions with Goeckerman's or methotrexate. In 4 out of the 5, colchicine was continued for 8-9 months. All these 4 patients remained completely free of skin lesions except for a few small papules on their elbows and back which were easily treated with topical steroid preparations. Two representative cases of these 4 are reported here in detail. The fifth patient developed a clinical relapse 4 months after the initiation of colchicine therapy; however, the proportion of the body-surface involved was about half of that initially involved.

Patient H. S.: A 42-year-old otherwise healthy male had begun to suffer from psoriasis at the age of 26. During the last 5 years his condition worsened and large areas of his skin became permanently covered with large thick psoriatic plaques. During the summer months some improvement occurred, but even then his skin disease was generalized and extensive. Six months before his present admission, he was hospitalized in our department and treated with Goeckerman's regimen. After 8 weeks, his skin cleared completely and he was discharged. Two months later, he relapsed and after a further 2 months he was rehospitalized. On admission 35-40% of his body surface was covered with large thick psoriatic plaques. He was again treated with Goeckerman's method, with good results. After complete clearing of his skin lesions, he was discharged and instructed to take 4 tablets of colchicine per day (0.5 mg per tablet). The patient was followed up monthly in our clinical for 9 months and except for a few papules and small flat plaques on his elbows and buttocks he remains free of lesions.

Patient B. D.: A 59-year-old, otherwise healthy male, began to suffer at the age of 49 from extensive, chronic, stable plaque-type psoriasis. Even during the summer months, he was never free of significant skin disease. During these last 10 years, he was hospitalized and treated many times in our department. However, his skin disease always recurred after 1-2 months. He was readmitted to our department in February 1979. On admission, many large chronic plaques were found on his limbs, back, chest and scalp. In addition many recent guttate lesions were also seen all over his body. He was successfully treated with Goeckerman's method and after 2 months he was discharged and instructed to take 1.5 mg of colchicine daily. The patient was seen monthly in our clinic for 9 months. After 4 months, the patients complained of diarrhea, which disappeared only after reducing the colchicine dosage to 1.25 mg per day. So far, the patient has remained free of skin lesions except for a few small papules on his elbows and back.

Adverse reactions. Nine out of the 27 treated patients (33%) complained of mild gastrointestinal symptoms which could be attributed to the medication. These included nausea, heartburn, abdominal discomfort, flatulence and diarrhea. These symptoms usually lasted several days and subsided spontaneously. Only in 2 patients was a slight reduction of the colchicine dosage necessary. None of the patients noted spontaneous weight loss during treatment. Repeated blood cell counts, urinalyses and blood chemistry tests remained normal throughout the trial, nor were any abnormalities detected in the serum levels of vitamin B₁₂ and carotene.

Neutrophil-chemotaxis. The chemotactic responses of neutrophils derived from the peripheral blood of 10 of the patients were assayed both before and 2 months after the initiation of the therapy. In each one of the patients, neutrophil chemotaxis decreased markedly during administration of colchicine. No differences in this respect could be detected between patients who responded well to the treatment and patients who did not respond (Fig. 3).

COMMENT

Although the number of the patients studied is too small to allow of any definite conclusions, it is our clinical impression that low oral doses of colchicine are therapeutically active in psoriasis. The therapeutic effect is usually very gradual and slow. This effect is much more prominent in those patients in whom thin papules and thin plaques dominate the clinical picture. The therapeutic response of patients with chronic thick plaque-type disease was usually much poorer, but even in these patients decreased scaling, erythema and infiltration were often noted. The intense pruritus from which 2 of these patients suffered stopped almost completely during the administration of colchicine. On the other hand, in 4 out of 5 patients with longstanding, chronic, stable, plaque type psoriasis, treatment with colchicine for a period of 8–9 months succeeded in preventing any significant recurrence of the disease. Another beneficial effect of colchicine therapy is the marked diminution of joint pains when such are present. Neutrophil chemotaxis decreased markedly during the administration of the drug, regardless of the clinical response of the skin. This most probably rules out the possibility that the

lack of therapeutic effect on the skin disease in some of the patients could be attributed to such factors as decreased gastrointestinal absorption or lack of effect on peripheral blood neutrophils. Lazarus et al. have found that psoriatic plaque epidermis contains markedly increased amounts of a complement-dependent chemotactic factor that is inhibited by serine proteinase inhibitors (4). It is possible that the quantity of this chemotactic factor in the hyperplastic epidermis of the chronic and thick plaques of psoriasis is so great that it can still induce the accumulation of neutrophils even after their chemotactic responsiveness is reduced by colchicine. On the other hand, such large quantities of serine proteinase could directly accelerate the rate of epidermal cell division (8), thus perpetuating the skin lesions even in the presence of reduced neutrophil accumulation into the lesions. The results of the present study, in our opinion, provide further support for the hypothesis that the migration of activated neutrophils into the skin could play an important role in the initiation and possibly also in the perpetuation of the psoriatic lesion.

Psoriatic lesions were found to disappear spontaneously under haemodialysis (14–15) or continuous peritoneal dialysis (16–17) without any additional topical medication and/or systemic treatment with cytostatic drugs. Glinski et al. (17) treated 10 patients with extensive psoriasis with continuous peritoneal dialysis for 11–28 consecutive days. Three of the 10 patients healed completely and a marked clinical improvement was noted in the remaining seven. The absolute number of PMNL depleted in each portion of the dialysate as well as the total PMNL loss during the whole treatment were significantly higher in psoriatics than in control patients with renal failure. Furthermore, the complete remission in the 3 psoriatic patients seemed to be related to extremely high numbers of PMNL depleted in a short period of time. These findings too lend support to the above-mentioned hypothesis.

Finally, the results of the present study seem to be sufficiently encouraging to warrant well-controlled, long-term studies on large numbers of patients in order to evaluate the feasibility and effectiveness of and to determine the exact therapeutic role of oral colchicine in the long-term management of psoriasis. Oral low-dosage colchicine may prove to be an effective, safe and highly acceptable method for the maintenance of remission in patients with extensive, chronic, stable

psoriasis, thus preventing relapses and avoiding the need for repeated treatments with potentially harmful (PUVA, methotrexate) or bothersome modalities (Goeckerman's). Oral colchicine may also prove to be especially suitable for the treatment of generalized pustular psoriasis because of its rapid beneficial effect on the general condition and on the pustular elements of the disease.

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