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TREATMENT OF PSORIASIS WITH ORAL MYCOPHENOLIC ACID

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Mycophenolic acid (MPA), an inhibitor of purine synthesis, was evaluated for its therapeutic and adverse effects in 29 patients with psoriasis.

MPA was administered orally for at least 12 weeks, during which time the daily dose was increased from 1600 to 4800 mg depending on occurrence of adverse reactions.

Complete clearing occurred in 1 of the patients, almost complete clearing in 14, definite improvement in 13, slight or doubtful improvement in 1. The full effect of MPA required a median time of 8 weeks (range 5–14). After discontinuing MPA, relapses began at a median time of 4 weeks (range 3–8). The severity of psoriasis was scored on a 0 to 108 scale using a newly devised system. The mean severity and range before treatment was 47 (21–88); after 12 weeks, 15 (0–50).

Adjustment of dose on the basis of side effects resulted in a median daily dose of 3600 mg (range 2400–4800 mg; 30–96 mg/kg ideal weight). Characteristic dose-limiting side effects were soft or frequent bowel movements, diarrhea, nausea, and anorexia. One instance of reversible, dose-related leukopenia was identified.

Experience has shown that drugs which slow cellular replication may have a beneficial effect on psoriasis when administered systemically. In recent years, systemic administration of methotrexate [2–6], hydroxyurea [7,8], azaribine [9–12], or other antimetabolites [13,14] has achieved some degree of efficacy in suppressing the activity of psoriasis. Adverse reactions and other problems encountered with the drugs used to date indicate that the search should continue for a more satisfactory psoriasis suppressant. Drugs that are safer and more selective in their action, and thereby more practical to use, are the objects of this search.

Mycophenolic acid, a weak organic acid, is one of several phenolic fermentation products of *Penicillium stoloniferum* and was named by Alsberg and Black in 1913 [15]. A similar, if not identical, phenol had been isolated from the broth of a culture of *P. glaucum* in 1896 by Gozio [16]. The complete structure of mycophenolic acid was reported in 1952 by Birkinshaw et al [17] and is shown in Figure 1. Limited antibiotic and antifungal activity of the compound was detected [18,19] and it was noted to have in vitro antiviral activity [20], as well as the ability to inhibit virus-induced Rous sarcoma and Friend leukemia in vivo. Sweeney and co-workers were able to demonstrate that mycophenolic acid was active against several solid murine tumors, but was inactive against murine leukemias [21,22].

In vitro biochemical studies have demonstrated that mycophenolic acid interfers with the synthesis of guanosine monophosphate, a purine precursor of RNA and DNA. Adenosine monophosphate synthesis is not inhibited by the drug. Specifically, mycophenolic acid inhibits inosine monophosphate dehydrogenase which converts inosine monophosphate to xanthosine monophosphate, and guanosine monophosphate synthetase, which converts xanthosine monophosphate to guanosine monophosphate [23]. These sites of metabolic blockade are illustrated in Figure 2.

Free mycophenolic acid is lipid soluble and rapidly absorbed after oral administration. Only one-half of a 60 mg/kg orally administered dose of [^{14}C]mycophenolic acid was detected in the gastrointestinal tract of tumor-bearing C3H mice after 15 min, the time at which maximum blood levels were observed. Rats, mice, and marmosets were fed the labeled compound and placed in respirometer chambers; no $^{14}CO_2$ was detected in the expired air, indicating that mycophenolic acid is not metabolically degraded. Ninety percent of the administered radioactivity was found in the urine and feces within 24 hr [23]. Similar data were obtained utilizing parenterally administered water-soluble monosodium mycophenolate.

Preclinical toxicologic studies with this compound provide evidence of a wide margin of safety. The acute LD_{50} of orally administered myco-

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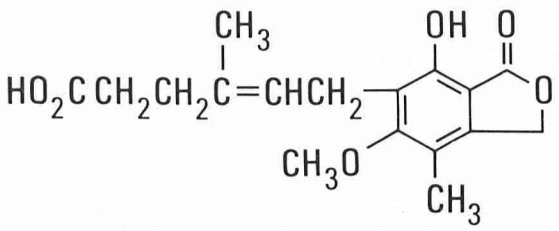

FIG. 1. Structure of mycophenolic acid.

phenolic acid in mice is 1917 mg/kg (SE ± 232), and in rats, 452 mg/kg (SE ± 36) [24]. In our laboratories no clinical, laboratory, or autopsy evidence of toxicity was found in rabbits that received 320 mg/kg/day for one year (GC Todd, unpublished data). Preliminary clinical trials in 37 patients with a variety of advanced malignant tumors, though failing to demonstrate significant antitumor effect, established that doses of up to 6400 mg daily were relatively free from toxic effects. There was no evidence in any patient of drug-induced leukopenia, thrombocytopenia, hemolysis, or liver damage [25]. In another series of 23 patients with neoplastic disease, gastrointestinal intolerance was noted at high doses, but no other clinical or laboratory abnormalities were identified [26].

Lintrup et al [27] have studied the metabolism of mycophenolic acid given orally and parenterally. Their data indicate that following a single intravenous dose of the sodium salt, concentrations of free mycophenolate fall rapidly, with a measured half-life of 4 min after a dose of 500 mg, and 12 min after a dose of 1000 mg. Oral doses of 1000 mg resulted in maximum serum concentrations at 1 hr which fell to negligible levels at 4 hr. In patients receiving the compound both parenterally and orally, excretion was rapid and essentially complete within 24 hr. All mycophenolic acid recovered in the urine was in the form of the glucuronide conjugate.

These studies underscore a unique and very desirable type of tissue selectivity which was suspected in early tissue culture screening experiments [28]. Free mycophenolic acid exerts a significant antiproliferative effect; mycophenolic acid glucuronide shows no such effect. When administered systemically, the free drug is rapidly converted by the liver to the inactive glucuronide which cannot penetrate cell membranes. Theoretically, in tissues such as human epidermis, which contain a high degree of activity of beta glucuronidase [29], the glucuronide is hydrolyzed to free and active mycophenolic acid which can exert a localized effect. Only those animal tumors that have very high levels of hypoxanthine–guanine phosphoriboxyltransferase and are able to bypass the mycophenolic acid block are drug resistant [23].

This communication reports the results of a pilot study which was undertaken over a period of 1½ years in a group of 29 patients with psoriasis. The objectives of the study were as follows: (1) to determine the maximum dose levels that could be tolerated by patients with psoriasis and the characteristic side effects produced by such doses; (2) to determine what dose levels, if any, might suppress psoriasis; (3) to obtain other information concerning the drug's characteristics, such as time needed for full effect and duration of remissions, that would be useful in designing further studies for proving the effectiveness and studying the safety of long-term use.

MATERIALS AND METHODS

Subjects. Only patients with psoriasis who were unable to achieve satisfactory results with conventional therapy other than methotrexate were admitted to the study. Informed written consent was obtained from each subject. All subtypes of psoriasis, including the plaque, guttate, inverse, pustular, palmar, nail, and arthritic types, were considered suitable for study. Dermatologists in the Indianapolis and Miami areas were invited to refer patients with severe psoriasis to the clinical investigators. The protocol excluded the following groups of patients from the study: (1) premenopausal women with childbearing potential; (2) children under 12 years of age; (3) patients receiving methotrexate, until the drug had been discontinued for at least 30 days; (4) patients with preexisting leukopenia.

The study population included 22 women and 7 men; 15 of the patients had received prior therapy with methotrexate. The patients ranged in age from 27 to 84 with a mean age of 52. Their mean weight was 162 pounds (range 100–232) which compared with an "ideal" weight (data from Metropolitan Life Insurance Co., New York) of 133 pounds (range 107–180). The mean extent of body area involved before treatment was 23% (range 3–67) and the mean severity score (see below) before treatment was 47 (range 21–88). Activity of disease was considered "severe" if greater than 10% involvement was evident; 3 patients with less than 10% involvement had disabling palmoplantar psoriasis.

Treatment. Application of bland emmolients such as petrolatum or hydrophylic ointment USP was permitted during the study period if needed for relief of itching and burning. The few patients who were allowed to continue the sparing use of topical corticosteroid creams or ointments in the study period were observed for a minimum pretreatment period of 1 month, and mycophenolic acid therapy was begun only after the severity had stabilized. Topical therapy was interdicted in those areas utilized in scoring severity of disease.

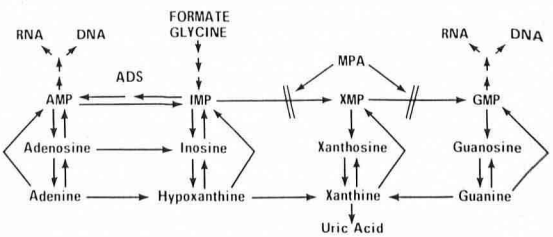

FIG. 2. Sites of metabolic blockade. Mycophenolic acid (*MPA*) blocks the interconversions of inosine-5'-phosphate (*IMP*) to xanthosine-5'-phosphate (*XMP*), and xanthosine-5'-phosphate to guanosine-5'-phosphate (*GMP*). *ADS* = adenylosuccinic acid; *AMP* = adenosine-5'-phosphate. (Figure partially reproduced from Wheeler GP, Alexander JA, Cancer Res. 21:390, 1961.)

Mycophenolic acid was supplied in 400-mg capsules. Previous experience with the drug indicated that a minimum starting dose of 1600 mg per day would be tolerated [26]. For hospitalized patients (3 of the 29) a maximum dose of 9600 mg per day was chosen because of the likelihood of gastrointestinal adverse reactions at or above this dose. For outpatients (26), the arbitrary maximum dose was 4800 mg per day. Daily divided doses were prescribed at 6-, 8-, or 12-hr intervals. Dosage was increased stepwise, depending upon response, not less than every 2 days, but generally once each week. For those patients unable to tolerate 4800 mg per day, the dosage was adjusted downward to the maximum dose that could be tolerated without adverse reactions. The maximum continuous treatment period was limited to 12 weeks. A 4-week rest period elapsed before a second course was started. Ten patients who used the drug at 6- or 8-hr intervals were given a second 12-week course using 12-hr dose intervals, to compare the relative effectiveness and tolerance of the two regimens.

Measurement of disease severity. Before, during, and after treatment, the severity of psoriasis was scored using a standardized system. Each of 6 selected representative skin sites was graded quantitatively for the degree of erythema, scaling, and thickening on a scale of 0 to 6 (0 = absent, 1 = trace, 2 = mild, 3 = mild to moderate, 4 = moderate, 5 = moderate to severe, 6 = severe). Representative sites were usually selected from areas of predilection in 6 zones, viz, the occipital scalp, the extensor surface of an arm or an elbow, the lumbar area, the knee, and 2 other sites, including a nail fold, and a palmoplantar surface, if involved. The total "severity score" at each observation was recorded as the sum of the 18 individual scores and was expressed on a 0 to 108 scale. The percent of body area involved with erythema and scaling was estimated at the beginning and at the conclusion of the treatment. Pruritus and pain, when present, were also recorded on a scale of 0 to 6, but were not included in the severity score; patients were observed and scored at least weekly during the first 8 weeks, then every 2 weeks. Post-treatment observations were made at intervals of 2 to 4 weeks to document the duration of remissions.

Adverse reactions. Using a check list, patients were questioned at each visit concerning adverse reactions, particularly those related to the gastrointestinal tract, the urinary tract, and the central nervous system. Laboratory examinations were made at least once weekly during the first 8 weeks and included complete blood counts, BUN, serum uric acid, total bilirubin, total protein, albumin, alkaline phosphatase, SGOT, LDH, glucose, cholesterol, calcium, phosphorus, urinalysis, and stool examinations for occult blood. As the study progressed, the stool examinations were discontinued because of predominately negative results. After 8 weeks, these laboratory observations were made every other week both while the patient received mycophenolic acid and during the post-treatment period.

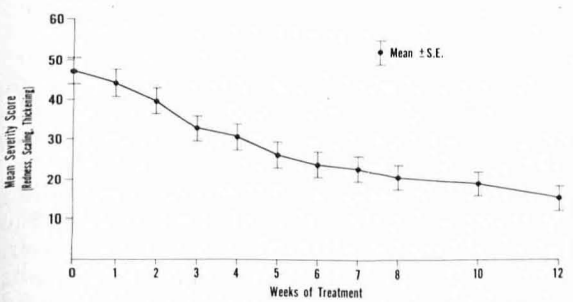

FIG. 3. Decline in mean psoriasis severity score during treatment with mycophenolic acid.

TABLE I. *Degree of improvement during treatment with mycophenolic acid*

Description	Mean severity score after 12 weeks	Number of patients
Complete clearing	0	1
Almost complete clearing	9	14
Definite improvement	23	13
Slight or doubtful improvement	27	1
No improvement		0
Worse		0

RESULTS

Most patients first noted improvement in psoriasis during the third or fourth week of treatment. Achievement of a maximum response to the drug required a median time of 8 weeks (range 5–14). The mean severity score of the 29 patients diminished from 47 to 15 over the initial 12-week treatment period. The rate of decline in mean severity score is shown in Figure 3.

The degree of improvement observed with mycophenolic acid is categorized in Table I. Examples of the clinical improvement are shown in the before and after photographs in Figure 4.

After mycophenolic acid therapy was discontinued, patients gradually relapsed to their former state of involvement. The relapse was generally complete by a median time of 4 weeks (range 3–8).

As the dose was progressively increased, most patients encountered adverse reactions principally involving the gastrointestinal tract. Adjustment of dose on the basis of side effects resulted in a median daily dose of 3600 mg (range 2400–4800 mg). The median tolerated dose in the test group was 65 mg/kg ideal weight (range 30–96). Obesity did not appear to increase the patients' ability to tolerate high doses.

Several types of adverse reactions were characteristic of high doses; they are listed in Table II in the order of frequency of occurrence. These reactions subsided quickly upon temporary interruption of the medication or reduction of dosage. During the early weeks of treatment, mild to moderate nausea frequently was observed. Later, loose or frequent bowel movements were the most common patient complaints. Several women developed dysuria and were found to have significant bacteriuria. These patients were treated with appropriate antibacterial therapy and subsequently were able to tolerate the medication without development of symptoms referable to the urinary tract. Such symptoms did not occur among the male patients.

One patient developed leukopenia (WBC =

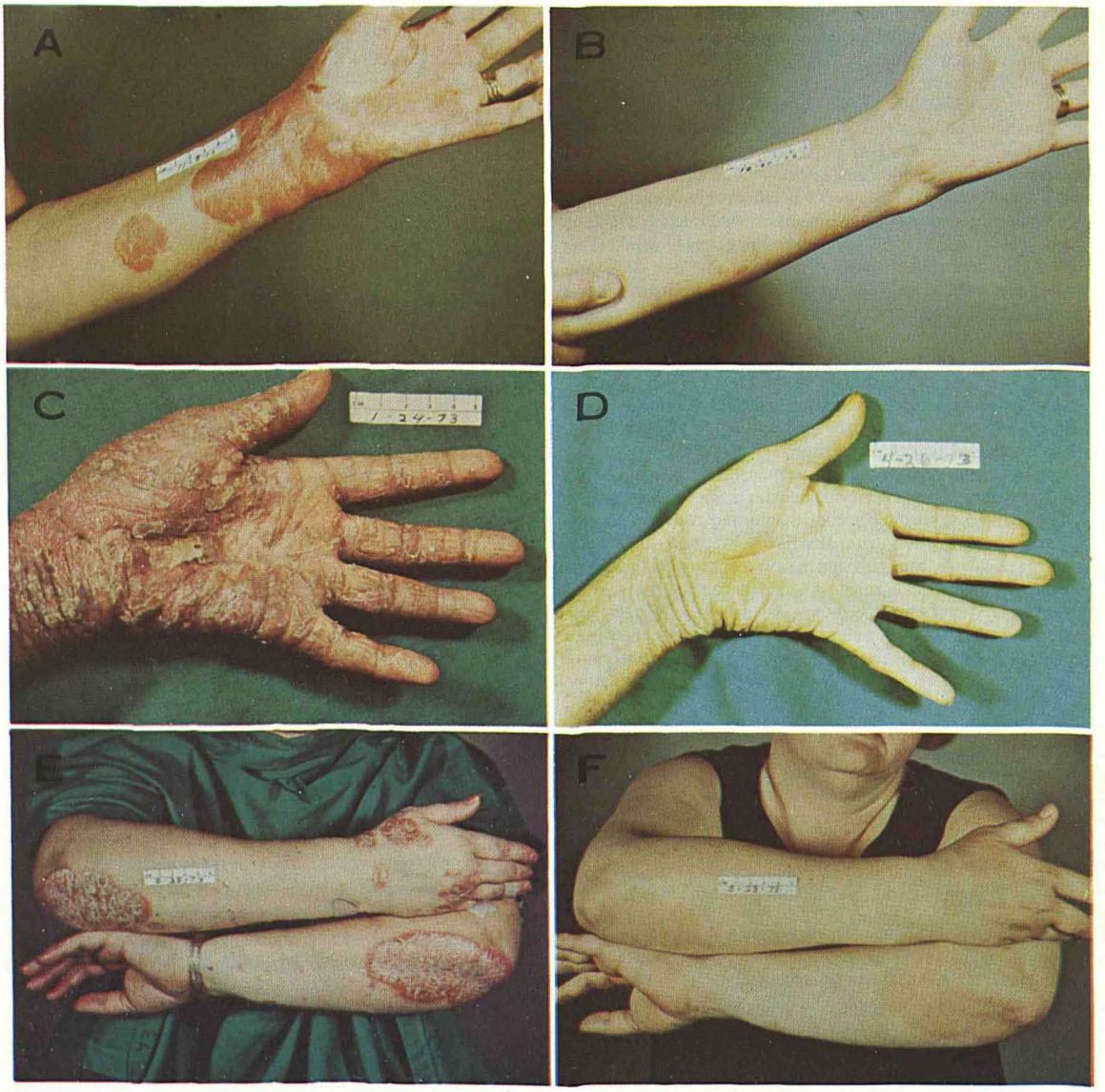

FIG. 4. Clinical photographs taken before and after 6 to 12 weeks of treatment with mycophenolic acid. Patients shown achieved almost complete clearing.

1200) within the first 7 weeks of treatment at a dose of 800 mg every 6 hr; mycophenolic acid was discontinued and the white blood cell count promptly rose to the normal range. Later, the patient resumed therapy at a lower dose, 1200 mg every 12 hr, and his white blood cell count fell to 3900. Thrombocytopenia of 66,000 and 90,000 platelets/mm^3 was noted in 2 patients. Their platelet counts increased promptly following discontinuation of the medicine; both of the patients subsequently were able to tolerate the drug without further thrombocytopenia.

The laboratory values in a group of 20 study patients were tabulated and examined for shift in the mean values. The most striking change was the decline in blood uric acid, as illustrated in Figure 5. The eventual decline from the initial mean value was approximately 30%.

DISCUSSION

The method used in this study for quantitating psoriasis severity gave satisfactory consistancy between different scorers and from week to week with the same observer.

Although formal proof that mycophenolic acid is an effective psoriasis suppressant will require double-blind, placebo-controlled studies, our experience in this pilot study has been encouraging. Clearly, this is a drug that requires careful individualization of dose; the doses required to control psoriatic lesions are close to those at which many

TABLE II. *Adverse reactions associated with high doses of mycophenolic acid in 29 patients with psoriasis*

Number of patients	Adverse reaction
20	Nausea
12	Weakness
11	Diarrhea
11	Soft bowel movements
10	Decreased appetite
8	Abdominal cramps
7	Frequent bowel movements
6	Vomiting
5	Urgent or frequent urination
4	Vaginal itching or burning
4	Dysuria
3	Trouble sleeping
2	Anal tenderness
2	Abdominal distention
2	Mouth sores
2	Thrombocytopenia
1	Leukopenia

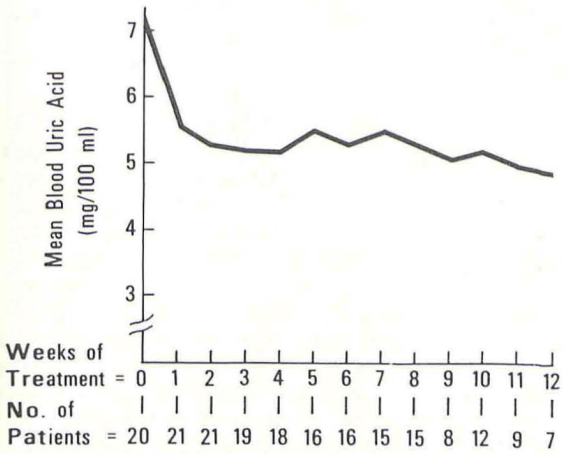

FIG. 5. Decline in mean blood uric acid concentration during treatment with oral mycophenolic acid.

patients experience adverse effects. We are confident that with further clinical studies of methods for optimizing the dosage and regimen, the therapeutic index of mycophenolic acid can be increased.

Patients with active psoriasis have been shown to have higher mean blood uric acid levels than the normal population [30]. The decline in uric acid levels observed during this study is compatible with the improvement in psoriasis and the action of the drug in inhibiting purine synthesis.

Ongoing animal toxicity studies indicate a high level of safety; in particular, no long-term hematologic or hepatic toxicity has been noted to date. Long-term clinical safety studies in a larger group of patients are in progress and are being conducted in parallel with double-blind, placebo-controlled efficacy studies.

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