Pulse Dosing of Thioguanine in Recalcitrant Psoriasis

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Background: Patients with severe psoriasis may be unresponsive to or unable to tolerate the adverse effects of traditional therapy. Thioguanine has been used to treat psoriasis, but experience is limited. Most previous studies have used daily therapy and have demonstrated significant hematologic abnormalities.

Objective: To reduce the adverse effects of traditional thioguanine therapy, our study patients were treated with thioguanine with a pulse-dosing schedule of 2 to 3 times per week.

Observations: Marked improvement of recalcitrant psoriasis was noted in 10 (71%) of 14 patients receiving thioguanine therapy using a pulse-dosing schedule. Maintenance dosage ranged from 120 mg twice a week to 160 mg 3 times a week. Adverse effects were minimal.

Conclusions: Thioguanine therapy is an effective treatment for recalcitrant psoriasis. A dosing schedule of 2 or 3 times per week is recommended to minimize the potential adverse effects. Routine laboratory follow-up is suggested to screen for potential adverse effects, with special attention to bone marrow suppression.

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Thioguanine is a purine analog that has been used extensively in the treatment of leukemia.1-2 It has also been used in the treatment of certain autoimmune diseases3 and psoriasis,4-7 but experience has been limited. Other antimetabolites, such as methotrexate, have been beneficial in the treatment of psoriasis; therefore, a trial was initiated to document the effects of thioguanine in psoriasis. We report our clinical experience with patients with severe psoriasis treated with thioguanine.

RESULTS

Eleven of the 14 patients showed improvement during thioguanine therapy. One patient (7%) was unavailable for follow-up after her second visit, at which time a positive response had been noted. Long-term response was evaluated in the 10 remaining patients who were responders. Clearing of psoriasis by 75% or greater was attained in all 10 patients (Figure 1 and Figure 2). The duration of treatment to achieve this level of clearance ranged from 14 to 43 weeks, with a mean of 26 weeks. Three patients (21%) failed to respond to treatment (mean duration of treatment, 13 weeks; range, 8-22 weeks).

An initial response was seen in 6 (54%) of the 11 responders within the first 2 to 4 weeks of treatment (Figure 3). Initial response was defined as the time when improvement was first noted by the physician with regard to scaling, pruritus, thickness of plaques, or number of pustules. The mean time to an initial response was 7.4 weeks, the longest duration being 16 weeks. Five patients had an initial response at cumulative doses equal to or less than 0.8 g. The mean dose at initial response for the remainder of the patients was 1.9 g. Three (21%) of the 14 patients failed to respond to thioguanine therapy.

The cumulative dose in patients in whom treatment failed ranged from 2.0 to 3.06 g, with a mean of 2.63 g. The duration of their therapy ranged from 1.5 to 5 months. Concomitant therapy with topical corticosteroids was used in 5 patients (amicinonide in 3 patients and clobetasol and triamcinolone in 1 patient each). In 2 patients, low-dose etretinate therapy (25 mg/d) was added after 5 to 6 months of treatment with thioguanine. Photochemotherapy was continued in 1 patient after thioguanine therapy was initiated. Sufficient improvement occurred to discon-

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PATIENTS AND METHODS

From August 1994 through March 1996, 14 patients with severe recalcitrant psoriasis in whom previous therapy had failed or had not been tolerated were treated with thioguanine. There were 4 women and 10 men, whose age ranged from 43 to 71 years (mean age, 55 years). There was a minimum follow-up of 8 months. Before they began taking thioguanine, several of the patients had received multiple therapies, all of which had been discontinued because of unsatisfactory clinical response or because of intercurrent toxic effects. Eleven of the 14 patients had been previously treated with methotrexate. Three patients had received cyclosporine. Other previous treatments included photochemotherapy (7 patients), etretinate (6 patients), hydroxyurea (1 patient), and topical calcipotriene (1 patient).

The risks and benefits of oral thioguanine and other potential therapies for psoriasis were discussed with all patients before treatment was initiated. The patients were initially treated with 80 to 100 mg of thioguanine twice a week. The dosage was increased by 20 mg every 2 to 4 weeks, until an acceptable response was seen. The maintenance dosage ranged from 120 mg twice a week to 160 mg 3 times a week. The average weekly maintenance dose was 340 mg.

A determination was made as to when improvement was first noted with regard to scaling, pruritus, thickness of plaques, or number of pustules. This initial determination was defined as the initial response. Evidence of long-term improvement was determined and was defined as 75% or better over baseline.

The adverse effects were minimal. One patient had thrombocytopenia, with a platelet count of $105 \times 10^9/L$ at baseline, which progressed during thioguanine therapy to a low of $84 \times 10^9/L$, but it was not clinically significant. Another patient, with insulin-dependent diabetes mellitus, had an elevated level of glucose at baseline (8.7 mmol/L [156 mg/dL]), which increased over 9 months to 43.3 mmol/L (780 mg/dL). All remaining patients had normal laboratory test results throughout treatment, including hemoglobin level, white blood cell count, platelet count, and liver function tests.

Subjective complaints included pruritus in 2 patients, dry mouth in 1 patient, and possible initial worsening of psoriasis in 2 patients. No patients had gastrointestinal complaints or other adverse effects.

Antimetabolites have been used extensively in the treatment of psoriasis. Although there is a long history of methotrexate use, there has been limited experience with thioguanine. Marked improvement of psoriasis during pulse thioguanine therapy was noted in 10 (71%) of our patients with recalcitrant psoriasis. Earlier studies have reported a range of responses, from 89% in a series of patients described by Zackheim and Maibach7 to 61.5% in a series by Molin and Thomsen.6 In a more recent study by Zackheim et al.,7 49% of patients achieved “a degree of improvement judged by both the patient and physician as sufficient to warrant continuing treatment” for a median of 33 months. In these trials, initial dosing schedules of 40 to 80 mg/d were used.5,6 Molin and Thomsen state that “an effect upon the skin is only seen if bone marrow toxicity also occurs.” Zackheim and Maibach make a similar comment: “Very often, maximum clinical benefit is seen at the time of hematopoietic depression.” In Zackheim and colleagues’ more recent series, some of the patients were treated with an intermittent dosing schedule, with the remainder receiving daily dosing. Everyday dosing was used for those with extensive, rapidly progressive disease and in those who did not respond to intermittent-dose regimens. Two patients in Zackheim and colleagues’ study had life-threatening emergencies involving bone marrow suppression. One patient received therapy at a dosage of 80 mg/d. The other patient, who had been receiving a daily dosage of 80 mg/d, developed mild leukopenia and anemia, and the dosage was switched to 120 mg every other day. Pancytopenia necessitating hospitalization subsequently developed.

The patients in our series were treated on a schedule of 2 to 3 times per week. The percentage of responders (71%) was similar to that observed in previously reported series, but the risk of bone marrow suppression appeared to be greatly reduced using pulse dosing. Our study included 1 patient who was thrombocytopenic before the initiation of thioguanine therapy. Although this patient’s platelet count decreased further, no adverse clinical signs were noted. All other patients maintained normal hematologic parameters. Eleven (79%) of the 14 patients in our study had been previously treated with methotrexate; therefore, hepatotoxic effects were of concern. No patients in our series developed abnormal liver function test results while receiving pulse dosing. In contrast, Zackheim et al.7 noted that elevated liver enzyme levels developed in 30.3% of the patients who had previously been treated with methotrexate. It is unknown how many of their patients were on daily dosing schedules. The most commonly reported adverse effect of thioguanine therapy is myelosuppression, ranging from a reported frequency of 22% to 68% in patients with psoriasis. This range of frequency represents a number of different dose schedules and cumulative doses. Leukopenia was most frequent, followed by anemia and thrombocytopenia. No hematologic abnormalities were noted in our patients.

The second most commonly reported adverse effects are gastrointestinal complaints. In the largest group of patients previously described, nausea, gastritis, and/or diarrhea were found in up to 12% of the patients. Elevated liver enzyme levels (aspartate aminotransferase and alanine aminotransferase) occurred in 25% of patients.7 Acute hepatitis and acute cholestasis have rarely been reported.7 Thioguanine therapy has also been reported to cause hepatic veno-occlusive disease.6-10 Kao and Rosenblate6 reported a case of acute toxic hepatitis and hepatic veno-occlusive disease that developed at a dosage of

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Figure 1. Psoriasis in a patient before initiation of thioguanine therapy demonstrating thick plaques with heavy scale.

Figure 2. Same patient as in Figure 1 after 18 weeks of thioguanine therapy (160 mg 2 times per week), demonstrating complete flattening of psoriatic plaques and resolution of all scales, with only residual erythema.
Figure 3. Initial improvement of psoriasis with thioguanine therapy.

320 mg/d. Six months after the treatment was discontinued, the patient’s liver function test results were all within normal limits.

Drug eruptions during thioguanine therapy have been reported rarely.7 Zackheim and Maibach7 and Zackheim et al5 describe 4 patients who developed frequent nonmelanoma cutaneous malignancies after treatment with thioguanine. It was documented that 2 of the 4 patients had undergone previous psoriatic treatments known to increase cutaneous malignancies. Previous use of potentially carcinogenic therapy was not noted in the other 2 patients.

We did not have sufficient follow-up of our patients to determine the adverse effects that may occur after years of treatment with thioguanine. Seven patients have been followed up for 3.6 to 18 years by Zackheim et al5 with no evidence of irreversible adverse effects.7

Three patients in our series failed to respond to thioguanine therapy. They had received a mean cumulative dose of 2.63 g, which was in excess of the mean dose of 1.51 g at which the 11 responders had improved. Therefore subtherapeutic dosing does not appear to be a factor in those in whom there was no improvement.

There appears to be 2 distinct groups of patients who responded to thioguanine therapy. Six (55%) of the responders had an initial response within 2 to 4 weeks (Figure 3), with the remainder averaging almost 3 times that long, ie, 12 weeks, before improvement was noted. At initial response, the early responders had taken a mean cumulative dose of 0.8 g; the late responders had taken more than double that dose (1.9 g). We could not identify factors that were predictive of which patients would be early responders. None of the patients had a sufficient response at a dosage of 80 mg twice a week. We therefore began starting therapy at 100 mg twice a week and increasing the dosage by 20 mg every 2 to 4 weeks.

The mechanism by which thioguanine improves psoriasis is speculative. It is a purine analog that interferes with DNA synthesis. It must be metabolized in the liver for therapeutic activity; thioguanine is converted to thioguanine-ribose monophosphate,2,11,12 which is diphosphated and triphosphated prior to incorporation into DNA and RNA. Because the drug interferes with DNA synthesis, it is possible that decreased keratinocyte proliferation is the major effect that produces clinical resolution.

Thioguanine may also affect the inflammatory aspect of psoriasis. Psoriasis has an immunologic pathogenesis with increased activated T lymphocytes (specifically T-helper type 1) and increased cytokines (interleukin 2, interferon gamma, and tumor necrosis factor α).13,14 Also, psoriatic plaques strongly express endothelial cell lymphocyte adhesion molecule 1, vascular cell adhesion molecule 1, and intercellular adhesion molecule 1.14 These adhesion molecules influence the movement of specific lymphocytes into the area of inflammation. Thioguanine may act by affecting the trafficking of inflammatory cells, resulting in decreased movement into psoriatic lesions.6

It may be possible to increase the efficacy of thioguanine in the treatment of psoriasis by cycling it with methotrexate. Synergistic effects of medications when given in a specific cycling order have been previously noted in cancer chemotherapy. There is, for example, increased efficacy of fluorouracil when the patient is pretreated with methotrexate.15,16 The mechanism appears to be the accumulation of an enzyme caused by the administration of the first drug. This enzyme is essential for the cytotoxic effect of the second drug. With an increased enzyme pool, the efficacy of the second drug is enhanced.

Increased cytotoxic effects of thioguanine were noted in cell cultures of L1210 leukemia cells when pretreatment with methotrexate occurred.2 Methotrexate interferes with purine synthesis. This interference leads to an accumulation of the enzyme phosphoribosyl-pyrophosphate. It is the cofactor in the metabolic step that converts thioguanine from its inactive form to the nucleotide thioguanine-ribose monophosphate, which is therapeutically effective.2,15 Because of the enlarged enzyme pool, thioguanine is more efficiently activated, resulting in significantly increased cytotoxicity to the leukemia cells.

In a clinical trial, children with relapsed lymphoma responded with extended remission to thioguanine therapy when they received pretreatment with a methotrexate infusion.17 This group did not have increased hematopoietic suppression.

It is interesting to speculate whether pretreatment with methotrexate would increase the efficacy of thioguanine in recalcitrant psoriasis. We were unable to correlate the recent use of methotrexate in our patients with more rapid response to thioguanine. This is an area that warrants further research to ascertain if cycling methotrexate and thioguanine results in significant improvement in patients with psoriasis without causing an increase in adverse effects.

The data in this study are limited by the retrospective review format. Patients were not consistently seen in follow-up at the same intervals, and treatment decisions were decided by individual situations rather than by strict protocol criteria. The small number of patients also limits the significance of both the response and the lack of adverse effects.

Thioguanine therapy appears to be an effective treatment for recalcitrant psoriasis. An intermittent dosing schedule is recommended, starting at a dosage of 100 to 120 mg twice weekly and increasing the dosage by 20 mg every 2 to 4 weeks until an acceptable response is achieved. Routine laboratory follow-up is recommended to screen for potential adverse effects, with attention to potential bone marrow suppression.
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REFERENCES


News and Notes

National Registry for Ichthyosis and Related Disorders. The National Institutes of Health, through the National Institute for Arthritis, Musculoskeletal and Skin Diseases, is sponsoring a National Registry for Ichthyosis and Related Disorders. The goals of the Registry are to promote the search for basic defects, improve methods of diagnosis, and develop effective methods of treatment and/or prevention of these disorders. Diagnosis of affected individuals will be based on specific, listed clinical and histological criteria and will be confirmed by determination of steroid sulfatase activity where indicated. Investigators and practitioners caring for individuals afflicted with these disorders or desiring access to the Registry database are encouraged to contact the National Registry for Ichthyosis and Related Disorders, Department of Dermatology, University of Washington, Box 356524, Seattle, WA 98195-6524; telephone: (800) 595-1263.