Conventional Systemic Agents for Psoriasis. A Systematic Review

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ABSTRACT. Very few well designed studies have evaluated the conventional systemic agents for psoriasis. This is a systematic, evidence-based review of the literature evaluating both the efficacy and safety of the medications cyclosporine, methotrexate, acitretin, hydroxyurea, and 6-thioguanine. Treatment recommendations are made. (First Release May 15 2006; J Rheumatol 2006;33:1442–6)

Key Indexing Terms:
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6-THIOGUANINE FUMARIC ACID ESTERS ACITRETIN

INTRODUCTION

Psoriasis displays a range of disease severity: it may be limited to coin-size plaques affecting a small percentage of the body surface area (BSA) or may involve as much as 75% to 100% of the BSA in erythrodermic patients. Rarer forms of psoriasis may be postinfectious (guttate psoriasis), pustular, or intertriginous. Psoriasis commonly is incessantly pruritic, and cracked or fissured plaques are often painful[1].

Disease severity is described as either "mild" or "moderate to severe." Patients with mild disease have limited BSA involvement and control their disease with a myriad of topical formulations. Patients with moderate to severe disease usually have more BSA involvement and cannot maintain a satisfactory quality of life solely using topical agents, which are either ineffective or inconvenient. Disease severity cannot be defined solely by BSA involvement; the impact of psoriasis on a patient's physical and psychological well-being also must be considered.

For the treatment of patients with more severe disease, dermatologists turn to either phototherapy or systemic agents. Phototherapy involves the chronic exposure of psoriatic skin to ultraviolet light[2]. Systemic therapy uses a variety of either oral or injectable medications. The oral medications [i.e., methotrexate (MTX), cyclosporine, or acitretin] are commonly referred to as conventional systemics, while the injectable medications are deemed the biologics[3]. In the past, dermatologists were advised to rotate therapies from one to the next in an effort to reduce exposure, and thus toxicity related to any given drug. Currently, however, dermatologists commonly use longterm therapy without rotation, using whatever medication that is both safe and effective. Combination therapies with 2 conventional drugs, a conventional drug and a biologic, or a systemic drug plus phototherapy, are increasingly being employed for more treatment-refractory patients.

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Outcome Measures

Commonly, patients enrolled in clinical trials must demonstrate a minimum BSA of involvement and/or a minimum score on the Psoriasis Area and Severity Index (PASI), a metric that ranges from a value of 0 (clear) to 72 (the most severely involved). The BSA ignores the qualitative features of psoriasis that play a large role in patient satisfaction and has very large interobserver variability[4].

The most common primary endpoint in most clinical trials is the percentage of patients in a treatment group that achieves a 75% reduction in the PASI score (the PASI75) over a predetermined period of time. The PASI score considers not only the BSA of involvement, but also the degree of erythema, scale, and thickness of the plaques. However, the PASI score is a nonlinear metric that may be impractical for patients with milder psoriasis (scores < 10). The PASI ignores issues of quality of life, pruritus, pain, bleeding, and any other patient-reported measures of disease severity[4,5].

The static physician global assessment (PGA) is another commonly used metric, grading disease severity at a single timepoint. Problems with the PGA include its limited range of scores (usually 0–6) and its lack of ability to detect small changes in disease[4].

Search Strategy

Few prospective, randomized, double-blind, placebo-controlled studies of the conventional systemic agents exist. Controlled studies often suffer from small sample sizes, treatment groups with less than moderate-to-severe psoriasis, atypical and nonvalidated measurements of efficacy, nonfixed dosing regimens, and poor statistical analysis.

For this review, several articles were identified using the Medline database from 1965 to the present and searching for the words "therapy" or "psoriasis" and the following medications: cyclosporine, MTX, leflunomide, sulfasalazine (SSZ), acitretin, hydroxyurea, and 6-thioguanine. The following inclusion and exclusion criteria were then applied:

Inclusion criterion: Controlled studies (either placebo- or active-controlled) involving more than 30 adult patients with psoriasis.

Exception: Hydroxyurea and 6-thioguanine were exempted from this requirement as they historically have been used to treat moderate to severe psoriasis; only open-label studies of these agents are available.

Exclusion criterion: Drugs or articles existing only as anecdotal reports, poorly-controlled studies, and small case series. Fumaric acid esters (Fumaderm® and its successor, Panaclar®) have not been included because of their limited use (primarily in Europe). However, wider approval of Panaclar for treatment of plaque-type psoriasis is expected in early 2006.

RESULTS

See Table 1 for an overview of the data.

Cyclosporine. The only placebo-controlled analysis of cyclosporine enrolled 85 adult subjects with moderate to severe psoriasis into 3 dosing arms (3.0, 5.0, and 7.5 mg/kg daily); a fourth group received a placebo[6]. Efficacy was measured after 8 weeks and quantified the subjects becoming "clear or almost clear." The analysis by intention-to-treat (ITT) showed that cyclosporine improved psoriasis in a dose-dependent manner, with clear or almost clear results achieved by 36% in the cyclosporine 3.0 mg/kg daily group, 65% in the 5.0 mg/kg daily group, 80% in the 7.5 mg/kg daily group, and 0% in the placebo group. These results were statistically significant. The glomerular filtration rate (GFR) decreased by a median 16% in 34 subjects evaluated. Higher doses of cyclosporine had greater adverse effects on systolic blood pressure, GFR, and serum creatinine, uric acid, bilirubin, and cholesterol. No quality of life assessments were reported.

A multicenter, randomized, double-blind, controlled study evaluated the efficacy of sirolimus versus cyclosporine[7]. In this study, 150 adult subjects with a minimum PASI score of 12 were randomized to one of 7 treatment arms. Two of these groups received either cyclosporine 1.25 mg/kg (19 subjects) or 5.0 mg/kg (15 subjects) daily. Using an ITT analysis, after 16 weeks of daily therapy the mean decrease in PASI from baseline was 70.5% in the cyclosporine 5.0 mg/kg treatment group, and 33.4% in the 1.25 mg/kg group. Side effects reported were headache (12%), abdominal pain (12%), nausea (12%), hyperlipidemia (9%), and serum creatinine increase (9%). No quality of life assessments were reported.

A prospective, randomized, assessor-blind analysis evaluated both cyclosporine and MTX "head to head"[8]. Eighty-eight adult subjects with a minimum PASI score of 8 were assigned randomly to MTX (15 mg/wk) or cyclosporine (3 mg/kg per day). After 4 weeks of treatment, the study allowed a dose escalation of up to 22.5 mg/wk for MTX and 5 mg/kg per day for cyclosporine in subjects in whom the reduction from baseline in their PASI score was less than 25%. After 16 weeks, the relative reduction in the baseline PASI score was 64% in the MTX-treated group and 72% in the cyclosporine-treated group (p = 0.14). Quality of life assessments were performed using the Medical Outcome Study Short Form 36 (SF-36). No significant differences between the 2 groups were found after 16 weeks in any of the subscales of the SF-36. Side effects for cyclosporine were headaches, muscle aches, elevated bilirubin, and distal paresthesias.

Methotrexate. No prospective, randomized, placebo-controlled trials evaluating MTX in psoriasis have been published. As described above, one active-controlled study has been published comparing MTX with cyclosporine[8]. In that study, MTX had a relatively poor tolerability (nearly 50% of the subjects reported nausea and about 25% of subjects discontinued therapy due to liver enzyme elevations), possibly because folate supplementation was not provided to the MTX-treated group (V. Heydendael, personal communication), an aspect of MTX therapy shown to reduce toxicity and improve tolerability of the drug[9].

Leflunomide. One published prospective, multicenter, randomized, double-blind, placebo-controlled study showed mild efficacy for the treatment of psoriasis[10]. In this study, 182 adult subjects with psoriasis and psoriatic arthritis were randomized to either a placebo or leflunomide given as 20 mg daily for 6 consecutive months. Subjects had a baseline BSA of involvement of 3% and were allowed low-dose systemic corticosteroids (about 15% of the leflunomide-treated group). The mean baseline PASI was about 9 for both the placebo and leflunomide groups. After 24 weeks of treatment, 17% of the leflunomide-treated subjects achieved a PASI75 versus 8% receiving a placebo (p = 0.048). The Dermatology Life Quality Index (DLQI) was significantly improved in subjects receiving leflunomide relative to placebo.

Sulfasalazine. In one study large enough to evaluate the efficacy of SSZ, a prospective, randomized, double-blind, placebo-controlled investigation enrolled 50 adult subjects with moderate to severe psoriasis, 50% of whom received SSZ for 8 weeks[11]. Dosing was escalated (as tolerated) over time, ranging from 1.5 g to 4.0 g of daily SSZ in the treatment group. An ill-defined metric of psoriasis severity was utilized (marked improvement = 60–89% change; moderate improvement = 30–59% change). After 8 weeks, about 26% of the SSZ-treated group discontinued (due to "rash" or nausea). Of the remaining 17 subjects, 7 had marked improvement and 7 had moderate improvement. The placebo arm had only one subject who showed moderate improvement, with the rest of the group "worsening." The statistical analysis was "per protocol" (subjects were required to have tolerated SSZ 2 g daily for 6 weeks) and not ITT. No quality of life assessments were reported.

Acitretin. A randomized, controlled trial compared the efficacy of acitretin versus etretinate, an older oral prodrug of acitretin[12]. The investigators enrolled 168 subjects with "long-standing, severe psoriasis" into a double-blind, 12-week

Table 1. Summary of clinical trials of psoriasis: conventional systemic agents.

Study	Disease Type	Agent	No. of Patients	Study Type	Outcome Measure	Results	p	Effect Size	Comments
Ellis[6]	Ps	CsA	85	DB, RPC	PGA: Clear or almost clear	At 8 weeks: CsA 3.0 mg/kg: 36% CsA 5.0 mg/kg: 65% CsA 7.5 mg/kg: 80% Pbo: 0%	< 0.0001	Cannot be calculated for PGA	
					Global Severity Score (7-point scale) reduction	At 8 weeks: CsA 3.0 mg/kg: 39% CsA 5.0 mg/kg: 58% CsA 7.5 mg/kg: 71% Pbo: 3%	< 0.0001	1.55 2.72 4.63	
Reitamo[7]	Ps	CsA	34	DB, RCT	Mean percentage reduction of PASI	At 16 weeks: CsA 1.25 mg/kg: 33% CsA 5.0 mg/kg: 71%	< 0.001 comparing 2 doses	1.29 comparing 2 doses	No placebo arm
Heydendael[8]	Ps	CsA vs MTX	85	RCT, assessor blinded	PASI reduction	At 16 weeks: MTX 15–22.5 mg/wk: 64% CsA 3.0–5.0 mg/kg: 72%	p = 0.14 comparing 2 groups receiving MTX and CsA	0.35 comparing 2 groups receiving MTX and CsA	No placebo arm; doses of both MTX and CsA could be increased to achieve response; no folate supplementation in MTX arm
Kaltwasser[10]	Ps & PsA	LEF	182	DB, RPC	PASI reduction	At 24 weeks: LEF: 22% Pbo: 2%	0.003	0.33	Concomitant prednisone allowed; low mean baseline PASI score
Gupta[11]	Ps	SSZ	50	DB, RCT	Global severity scale reduction	At 8 weeks: SSZ: 48% Pbo: 4%	0.0001	Not able to calculate	Analysis not ITT; significant dropout (26%) in SSZ arm; doses escalated as per tolerability in SSZ arm
Kragballe[12]	Ps	Acitretin vs etretinate	168	DB, RCT	PASI reduction	At 12 weeks: Acitretin: 76% Etretinate: 71%	Not significant	Cannot be determined	No placebo arm; analysis not ITT; variable dosing based on response; low mean baseline PASI
Goldfarb[13]	Ps	Acitretin	38	DB, RPC	Mean improvement in BSA, percentage	At 8 weeks: Pbo: –0.8% ACT 10 mg qd: –3.0% ACT 25 mg qd: –3.2% ACT 50 mg qd: +5.5% ACT 75 mg qd: +17.4%	p = NS for 50 mg vs placebo; p = 0.03 for 75 mg vs placebo	1.0: 75 mg qd vs placebo	Small numbers of subjects in each cohort; short treatment duration during Pbo controlled portion; variable dosing and open-label after 8 wks
Layton[14]	Ps	Hydroxyurea	85	Open-label	Physician assessment of good, moderate, or poor	Good: 60% Good, but relapse on treatment: 4% Moderate: 20% Poor: 16%	No statistics	Not able to calculate	Open-label; ill-defined efficacy metric; varying dosages and treatment lengths; significant hematologic toxicity seen; reporting bias?
Zackheim & Maibach[15]	Ps	6-Thioguanine	40	Open-label	Physician assessment of complete or almost complete clearing, moderate improvement, or little or no improvement	Complete or almost complete clearing: 78% Moderate improvement: 1 Little or no improvement: 11%	No statistics	Not able to calculate	Open-label; ill-defined efficacy metric; varying dosages and treatment lengths; significant hematologic toxicity seen; reporting bias?
Zackheim[16]	Ps	6-Thioguanine	81	Open-label	Effective maintenance; discontinued	Effective maintenance: 49% Discontinued: 51%	No statistics	Not able to calculate	Open-label; ill-defined efficacy metric; varying dosages and treatment lengths; significant hematologic toxicity

ACT: acitretin; BSA: body surface area; CsA: cyclosporine, DB: double-blind; ITT: intention to treat; LEF: leflunomide; MTX: methotrexate; NS: not statistically significant; PASI: Psoriasis Area and Severity Index; Pbo: placebo; PGA: physician global assessment; Ps: psoriasis; PsA: psoriatic arthritis; RCT: randomized, controlled trial; RPC: randomized, placebo-controlled; SSZ: sulfasalazine.

analysis of acitretin (75% of subjects) versus etretinate (25% of subjects). The median baseline PASI score was 12.6 in the acitretin group. Acitretin was given at a fixed dose of 40 mg daily for the first 4 weeks, with variable dosing based on individual response allowed during the final 8 weeks of the treatment phase. After 12 weeks, the acitretin group showed a mean PASI score reduction of 76%, compared with 71% for the etretinate group. Only 78% of the enrolled subjects in the acitretin treatment group were included in the efficacy analysis (not ITT). The median dose of acitretin over the 12 weeks was about 40 mg per day and proved to be intolerable for many subjects. Mucocutaneous side effects were common, with cheilitis (99%), dry nose (84%), peeling palms and soles (83%), xerosis (70%), dry mouth (66%), conjunctivitis (49%), and alopecia (48%) occurring with high frequency. Abnormal transaminase (12%), cholesterol (10%), and triglyceride (12%) elevations occurred in acitretin-treated subjects. No quality of life assessments were reported.

A controlled study of 38 subjects evaluated 4 daily doses of acitretin (10 mg, 25 mg, 50 mg, and 75 mg)[13]. All subjects had at least 10% BSA involvement at baseline. Only the first 8 weeks were double-blind, placebo-controlled, with the remaining 16 weeks involving an open-label, variable dosing regimen based on efficacy, tolerability, and laboratory abnormalities. Clinical efficacy was notable only in subjects receiving acitretin at 50 mg daily or greater. Relative to baseline, subjects receiving acitretin 50 mg and 75 mg daily experienced 5.5% and 17.4% improvement, respectively, in their BSA involvement (statistically significant only in the 75 mg group). Higher doses of acitretin were associated with more significant mucocutaneous and alopecic side effects. Laboratory abnormalities included transaminase, triglyceride, and cholesterol elevations. No quality of life assessments were reported.

Hydroxyurea. In a nonprospective study, 85 patients received hydroxyurea over 8 years, with no placebo or active control group[14]. Dosing was varied according to clinical response, although a "maintenance dose" of 0.5–1.5 g daily was achieved in most subjects. The efficacy metric was atypical. Of the 85 subjects, 60% achieved a "good" response to therapy ("complete to near complete clearing" of psoriasis), 20% showed a "moderate" response ("residual lesions that could be managed at home"), and only 16% showed a "poor" response. The mean duration of therapy was not described for the total subject group. Adverse effects were seen in 43% of subjects, with most requiring either a reduced dose or treatment cessation. Clinically significant hematologic adverse effects, defined as anemia (hemoglobin < 11 g/dl), leukopenia (white blood cell count < 3500/mm^3), and/or thrombocytopenia (platelets < 150,000/mm^3), occurred in 35% of subjects.

6-Thioguanine. The efficacy of 6-thioguanine was evaluated in a retrospective, open-label study of 40 subjects who received 6-thioguanine with varying treatment courses and dosages[15]. The efficacy metric was atypical. In this population, 78% were described as achieving "complete or almost complete" clearing, 11% showed "moderate" improvement, and only 11% showed "little or no" improvement. Reversible "hemopoietic depression" was seen in about two-thirds of subjects. No quality of life assessments were reported.

A subsequent open-label analysis evaluated 81 subjects who were treated with a varying dose of 6-thioguanine according to initial disease severity and response during therapy[16]. Duration of therapy ranged from 1 to 220 months (median 16 mo). The efficacy metric was atypical and was reported as "effective maintenance" in 49% of subjects, while the other 51% of treated subjects discontinued therapy due to initial failure of therapy (5%), side effects (36%), or relapse of psoriasis (10%). Myelosuppression was the most frequent side effect, occurring in 47% of subjects, and requiring discontinuation in 21% of subjects. Serum transaminase levels were elevated in 25% of evaluated subjects. No quality of life assessments were reported.

Treatment Recommendations

For the treatment of plaque-type psoriasis:

- Cyclosporine is highly effective (level 1b, grade A)
- Methotrexate is highly effective (level 1b, grade A)
- Acitretin is moderately effective (level 1b, grade A)
- Leflunomide is minimally effective (level 1b, grade A)
- Sulfasalazine is minimally effective (level 1b, grade A)
- Hydroxyurea may be minimally effective (level 3, grade C)
- 6-Thioguanine may be minimally effective (level 3, grade C)

CONCLUSIONS

Perhaps with the exception of cyclosporine, every agent discussed in this article warrants larger, prospective, well powered placebo-controlled studies that use the standards of evidence-based medicine. MTX is effective and well tolerated in appropriately selected patients who are receiving folate supplementation, and who are adequately monitored for potential toxicities[17]. Patients receiving MTX should be monitored for hematology values and liver function at baseline and every 4–8 weeks of therapy, with less intensive monitoring (every 8–12 weeks) for patients consistently showing no ill effects over the long term. Renal function should be measured at baseline and every 6 months, as alterations in renal function can have a profound effect on the clearance of MTX, potentially leading to increased toxicity[18]. At baseline, evaluations for the presence of hepatitis B and C and a tuberculin skin test should be performed. The cumulative dose of MTX should be updated regularly, and patients should be considered for liver biopsy as per the guidelines of the American Academy of Dermatology[17]. Patients should be encouraged to avoid alcohol intake and attempts at conception, and also should be reminded about potential drug interactions.

Cyclosporine suffers from dose-related nephrotoxicity and hypertension that impede its use as a longterm agent for most

patients. Nevertheless, cyclosporine is an effective drug for rapid clearing in most patients. Cyclosporine, when used in the appropriate patient at the appropriate dose (usually 2.5 to 5.5 mg/kg daily), is an excellent "bridging agent" that can be used safely for periods of 2–12 months. Ultimately, however, most patients should be transitioned to other agents that have better longterm safety profiles. Patients receiving cyclosporine should be monitored using laboratory measures of renal and liver function and serum magnesium level at baseline and every 4–8 weeks of therapy, with less intensive monitoring (every 8–12 weeks) for patients consistently showing no ill effects over the long term. A fasting lipid panel of tests should be done at baseline and followed about every 8–12 weeks. At baseline, evaluations for the presence of hepatitis B and C and a tuberculin skin test should be performed. The blood pressure must be regularly monitored. A yearly 24 hour collection of urine for the calculation of the creatinine clearance should be performed for treatment courses longer than 12 months. Patients also should be reminded about potential drug interactions.

Acitretin is less effective when used as monotherapy for plaque psoriasis. Doses required to achieve significant improvement (> 40 mg daily) are accompanied by often intolerable mucocutaneous side effects and alopecia, and result in more frequent laboratory abnormalities. Further, acitretin is not an option in women of childbearing potential. When used in lower doses (10–25 mg daily), acitretin remains an agent that may be combined effectively with ultraviolet phototherapy, MTX, cyclosporine, or the biologic agents. At higher doses, acitretin requires periodic (every 6–12 weeks) monitoring of the liver function tests and fasting lipids. Combination therapy with low-dose acitretin may allow for dose-sparing of the second agent and often provides better efficacy with good tolerability.

Sulfasalazine and leflunomide have poor evidence substantiating their use as monotherapy in plaque psoriasis. Sulfasalazine appears to have poor tolerability at the higher doses required for efficacy. These therapies likely need to be combined with other drugs in order to achieve better efficacy.

Both hydroxyurea and 6-thioguanine are older systemic therapies that display efficacy in open-label studies. But these studies, perhaps reflecting reporting bias, may overstate efficacy and understate significant toxicity. For this reason, these 2 agents may be reserved for patients who fail or cannot receive most other therapies.

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