Flares in Lupus: Outcome Assessment Trial (FLOAT), A Comparison Between Oral Methylprednisolone and Intramuscular Triamcinolone

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ABSTRACT. ***Objective.*** Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by a relapsing-remitting course. When a mild/moderate flare occurs, treatment with corticosteroids is often instituted. There are 2 methods of acutely giving a boost of steroids: triamcinolone injection or a short-term boost of oral prednisone or methylprednisolone. We investigated whether triamcinolone is superior to oral corticosteroids for mild/moderate flare in patients with lupus.

Methods. In a clinical trial, 50 patients with SLE presenting with a mild or moderate flare [defined using the Safety of Estrogens in Lupus Erythematosus: National Assessment–SLE Disease Activity Index (SELENA-SLEDAI) flare instrument] were randomized to receive oral methylprednisolone with rapid tapering (medrol dose-pack) or triamcinolone 100 mg, given intramuscularly. The patients completed a Likert scale of activity and the Medical Outcomes Study Short Form-36 health status questionnaire on the randomization day, and repeated them the next day, 2 days, one week, 2 weeks, 3 weeks, and one month later.

Results. Complete improvement occurred in 0% at one day, 0% at 2 days, 8.3% at one week, 20.8% at 2 weeks, 20.8% at 3 weeks, and 25% at 4 weeks in the methylprednisolone group versus 4.3% at one day, 4.3% at 2 days, 8.6% at one week, 12.5% at 2 weeks, 30.4% at 3 weeks, and 34.7% at 4 weeks in the triamcinolone group. Improvement in health status by Week 4 occurred in 66.6% of the patients in the methylprednisolone group versus 73.9% in the triamcinolone group.

Conclusion. The triamcinolone and oral methylprednisolone groups did equally well. Triamcinolone may lead to a more rapid response than the oral methylprednisolone (69.5% vs 41.6% with some improvement at day one). (J Rheumatol 2006;33:57–60)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS CORTICOSTEROIDS FLARES

Systemic lupus erythematosus (SLE) is a multisystem disease often characterized by periods of remission and then acute exacerbations. Corticosteroids are often the treatment of choice in acute flares because of their rapid onset, with dosage schedules depending on the severity of the manifestation.

Currently, there are 2 traditional ways to acutely give a "boost" of corticosteroids for a mild to moderate lupus flare: a medrol dose-pack, which gives methylprednisolone orally in a rapid taper, or an intramuscular (IM) triamcinolone injection, which gives a one-time dose of a long-acting corticosteroid**.** There is no evidence to indicate that one corticosteroid preparation is superior to another when comparable dosage is used. Both triamcinolone and methylprednisolone have been used in open trials with satisfactory results[1]. If effective, a single IM dose of triamcinolone given in the outpatient setting could provide the advocated steroid dosage and exclude the issue of patient compliance.

Despite the widespread use of corticosteroids in SLE, there is a dearth of research on their benefit for mild to moderate lupus flares. We conducted a randomized controlled study comparing 2 methods of acutely giving a boost of steroids: triamcinolone injection versus oral methylprednisolone with rapid taper (medrol dose-pack).

MATERIALS AND METHODS

A randomized clinical trial was conducted between May and July of 2003 at Johns Hopkins University. Fifty patients with SLE diagnosed with mild to moderate flare were randomized to a 100 mg IM triamcinolone acetonide injection versus a medrol dose-pack (oral methylprednisolone tapered in one week). All patients fulfilled the American College of Rheumatology (ACR) criteria for SLE[2]. All patients gave informed consent to participate.

Mild to moderate flare was defined using the Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) SLE Disease Activity Index (SLEDAI) flare instrument, proven to be a reliable and valid measure. The SELENA-SLEDAI composite[3] comprised 3 elements: (1) SELENA-SLEDAI instrument defined above; (2) new/worse activity, med-

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ication changes, and hospitalizations not recorded in the instrument (b, c, and d below); and (3) the physician's global assessment by visual analog scale.

Mild/moderate flares were defined as one or more of the following: (a) change in SELENA-SLEDAI instrument score of > 3 points, with total score ≤ 12; (b) new or worsening discoid, photosensitive, or other rash attributable to lupus (including lupus profundus, cutaneous vasculitis, or bullous lupus), nasopharyngeal ulcers, pleuritis, pericarditis, arthritis, or fever not attributable to infection; (c) increase in prednisone, but not to > 0.5 mg/kg/day; (d) initiation of either hydroxychloroquine or nonsteroidal antiinflammatory agents, without an increase in prednisone; and (e) change in the physician's global assessment by ≥ 1.0 but remaining ≤ 2.5.

Severe flares were defined as one or more of the following: (a) SELENA-SLEDAI instrument score > 12; (b) new or worsening central nervous system involvement, vasculitis, glomerulonephritis, myositis, thrombocytopenia (platelet count < 60,000/mm^3), or hemolytic anemia (hemoglobin < 70 g/l, or drop in hemoglobin > 30 g/l over a 2 week period), each requiring doubling of corticosteroids to a final dose of > 0.5 mg/kg/day or acute hospitalization; (c) any manifestation requiring an increase in prednisone or equivalent dose to > 0.5 mg/kg/day, or initiation of cyclophosphamide, azathioprine, mycophenolate mofetil, or methotrexate; (d) hospitalization for lupus activity; and (e) change in physician's global assessment from baseline to > 2.5.

These definitions were agreed upon by the SELENA investigators to reliably discriminate severe flare from mild/moderate flare. Symptoms attributed to menopause such as hot flashes, fatigue, and irritability did not overlap with the definitions of flares. These new definitions (the SELENA-SLEDAI composite) were then tested among the core investigators using patient scenarios from the Hopkins Lupus Cohort.

On the day of the flare visit, each participant completed a Medical Outcomes Study Short Form-36 (SF-36) Health Status Survey and a 5-choice Likert scale of SLE activity. At one day, 2 days, one week, 2 weeks, 3 weeks, and one month, each participant was contacted by telephone to repeat the SF-36 and the Likert scale of SLE disease activity (worse, the same, a little better, much better, completely better; compared to baseline). If assigned to methylprednisolone, the patient was given the prescription and told to fill it and to take the first dose the same day; if assigned to triamcinolone the injection was given in the clinic that day.

Demographic data collection included age, sex, ethnicity, SELENA-SLEDAI, Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index, and current medications.

Statistical analysis included Fisher's exact test for comparison of categorical variables and Student t test for comparison of continuous variables. The primary outcome variable was improvement of the mild to moderate flare at the one-day telephone followup. The sample size was powered to determine if the triamcinolone group would have 50% more improvement than the methylprednisolone group for the primary outcome variable (self-report of improvement one day after treatment based on a Likert scale).

RESULTS

Fifty patients were enrolled (45 women, 5 men), 26 in the oral methylprednisolone group and 24 in the triamcinolone group. Three patients were removed from the study for noncompliance: 2 in the oral methylprednisolone group and one in the triamcinolone group. These patients did not answer any of the telephone calls but were included in the analysis (intention to treat).

Patients' ages varied between 19 and 72 years, with an average of 41.5 years. Twenty-eight patients were Caucasian, 21 African American, and one Asian. The SLICC/ACR Damage Index varied from 0 to 11 (average 1.596) and the SLEDAI at baseline from 0 to 14 (average 3.085). Forty-eight patients were taking medications for lupus disease activity, including prednisone, hydroxychloroquine, mycophenolate mofetil, azathioprine, methotrexate, and/or nonsteroidal antiinflammatory drugs (NSAID). Disease duration varied from 1 to 33 years of disease, with an average of 10.15 years.

There were no significant differences between the 2 study groups by age, sex, ethnicity, years of disease, SLICC/ACR Damage Index, or SELENA-SLEDAI score (Table 1).

Organ involvement of patients (Table 2) included primarily polyarthralgia/polyarthritis, rash, and pleurisy.

In the oral methylprednisolone group, 41.6% of patients had some improvement at Day 1, 87.5% at Day 2, 79.1% at Week 1, 58.3% at Week 2, 83.3% at Week 3, and 75% at Week 4. In terms of complete improvement in the methylprednisolone group, we found 0% at Day 1, 0% at Day 2, 8.3% at Week 1, 20.8% at Week 2, 20.8% at Week 3, and 25% at Week 4 (Table 3).

In the triamcinolone group, some improvement was found in 69.5% of patients at Day 1, 79.1% at Day 2, 78.2% at Week 1, 91.3% at Week 2, 75% at Week 3, and 79.1% at Week 4. For complete improvement, we found 4.3% patients at Day 1, 4.3% at Day 2, 8.6% at Week 1, 12.5% at Week 2, 30.4% at Week 3, and 34.7% at Week 4 (Table 4).

There was no statistically significant difference in "any response" or in "complete response" between the 2 groups. Although triamcinolone appeared to lead to faster improvement, the only p value that reached statistical significance was at Week 2 ($p = 0.006$).

There was no difference between the 2 groups in the SF-36 health status questionnaire. At Week 4, 66.6% of the patients in the oral methylprednisolone group and 73.9% in the triamcinolone group had some improvement (Figure 1).

Two patients (one from each group) were considered treatment failures (no improvement).

No side effects were seen with either treatment. In terms of adherence, 3 patients from the methylprednisolone group did not start the medication on the first day. Two patients in the methylprednisolone group withdrew without starting the medication.

DISCUSSION

This is the first randomized trial comparing 2 methods of giving a boost of corticosteroid for a mild to moderate SLE flare. Exacerbations of disease activity are an integral part of the SLE course. The incidence of flares is 0.65 per patient per year of followup[4]. Mild/moderate flares are often treated with a short course of corticosteroids, but noncompliance may reduce its effectiveness. Even in solid-organ transplants, when success depends on patient adherence to treatment, a fraction of patients do not comply appropriately with medical advice[5]. In this trial, 5 patients in the oral methylprednisolone group were noncompliant, with 2 starting the medication one day late and 2 not starting it at all.

Table 1. Characteristics of the patients with SLE.

	Oral Methylprednisolone Group, n = 26	Triamcinolone Group, n = 24
Sex	25 F, 1M	20 F, 4M
Ethnicity, %		
Caucasian	65.3	50
African American	30.7	50
Asian	3.8	
Age, yrs, range (mean)	19–72 (43)	20–66 (40)
SLICC/ACR damage index, range (mean)	0–11 (2)	0–5 (1.18)
SELENA-SLEDAI, range (mean)	0–13 (3)	0–14 (2.81)
Duration of disease, yrs, range (mean)	1–33 (11.8)	1–21 (9.04)

Table 2. Organ involvement.

Symptom/Signs	No. of Patients
Alopecia, pleurisy	1
Alopecia	1
Polyarthralgias	12
Polyarthralgias, fatigue	6
Polyarthralgias, fatigue, cutaneous rash	2
Polyarthralgias, cutaneous rash, alopecia	1
Polyarthralgias, lymphadenopathy	1
Polyarthralgias, cutaneous rash	1
Polyarthritis	5
Polyarthritis, fatigue	1
Polyarthritis, hand vasculitis	1
Polyarthritis, oral ulcers	2
Polyarthritis, fatigue, rash	1
Monoarthritis	1
Discoid rash	4
Cutaneous rash	2
Cutaneous rash, pleurisy, fever, headache	1
Pleurisy, oral ulcers	1
Pleurisy	4

Although corticosteroid therapy has a clear beneficial effect on many acute SLE manifestations, controlled studies of corticosteroids are scarce, especially in the setting of mild to moderate flares of nonrenal lupus[6]. Few open series have evaluated oral corticosteroid use[7-11], and 2 controlled trials have specifically assessed the use of intravenous methylprednisolone, comparing either high and low dose[12] or placebo[13].

However, trials similar to ours have been done in other disease states. One study[14] compared IM triamcinolone versus oral prednisone in treating adult patients for mild to moderate exacerbation of asthma, and concluded that the triamcinolone arm had a similar relapse rate to the oral prednisone arm. Another study[15] investigated the efficacy of the use of IM triamcinolone acetonide in patients with pseudogout who had contraindications to NSAID.

We found comparable response rates between the 2 regimens in our trial at Day 2 and at Weeks 1, 3, and 4. Triamcinolone had a greater response only at Day 1 (69.5% vs 41.6%) and Week 2 (91.3% vs 58.3%). There was no statistical difference in health status between the 2 groups, although the triamcinoline group was numerically superior at all timepoints except Week 3.

Our results showed that the majority of flares involved only one organ system (60%), in close agreement with Ehrenstein, *et al*[16], who found single-organ involvement in 70% of flares.

Side effects of chronic exposure to corticosteroids are

Table 3. Likert scale results for the oral methylprednisolone group. Data are n (%).

	Day 1	Day 2	Week 1	Week 2	Week 3	Week 4
Lupus flare gone	0 (0)	0 (0)	2 (8.3)	5 (20.8)	5 (20.8)	6 (25)
Lupus flare much better	3 (12.5)	8 (33.3)	9 (37.5)	3 (12.5)	8 (33.3)	7 (29.1)
Lupus flare a little better	7 (29.1)	13 (54.1)	8 (33.3)	6 (25)	7 (29.1)	5 (20.8)
No change	14 (58.3)	3 (12.5)	3 (12.5)	8 (33.3)	3 (12.5)	4 (16.6)
Lupus flare even worse	0 (0)	0 (0)	4 (16.6)	2 (8.3)	1 (4.1)	2 (8.3)

Table 4. Likert scale results for the intramuscular triamcinolone group. Data are no. (%).

	Day 1	Day 2	Week 1	Week 2	Week 3	Week 4
Lupus flare gone	1 (4.3)	1 (4.5)	2 (8.6)	3 (13.6)	7 (31.8)	8 (38)
Lupus flare much better	2 (8.7)	6 (27.2)	7 (30.4)	13 (59)	6 (27.2)	5 (23.8)
Lupus flare a little better	13 (56.5)	12 (54.5)	9 (39.1)	5 (22.7)	5 (22.7)	6 (23.5)
No change	6 (26)	2 (9)	4 (17.4)	1 (4.5)	2 (9)	2 (9.5)
Lupus flare even worse	1 (4.3)	1 (4.5)	1 (4.3)	0 (0)	2 (9)	0 (0)

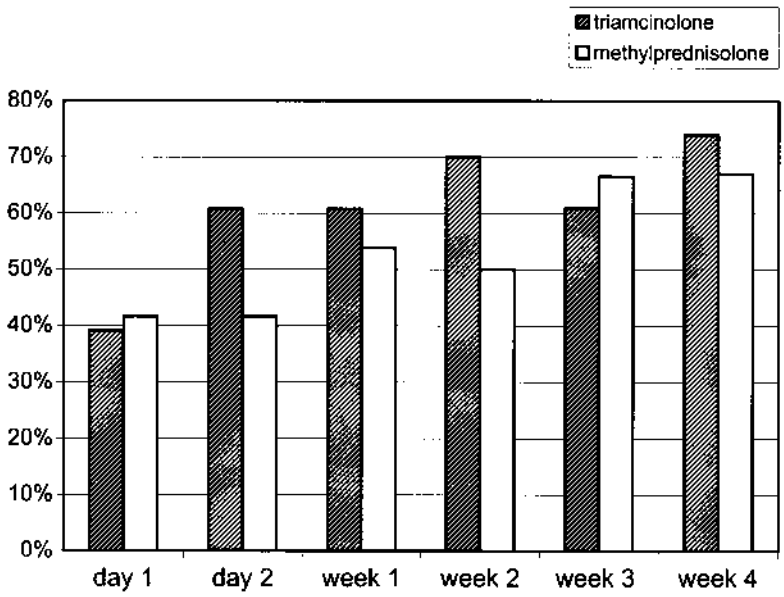

Figure 1. At Week 4, 66.6% of patients in the oral methylprednisolone group and 73.9% in the triamcinolone group had some improvement in SF-36.

well known, including cushingoid features, cataracts, glaucoma, premature atherosclerotic disease, hypertension, osteoporosis, osteonecrosis, myopathy, diabetes, depression, and psychosis[17]. The Optic Neuritis Treatment Trial[18] studied side effects of short-term glucocorticoid exposure. Minor side effects were common, and included sleep disturbances, mild mood change, stomach upset, and facial flushing. Jansen and van Roon[19] reported 4 cases of cushingoid habitus after triamcinolone acetonide injections. IM triamcinolone can cause localized lipodystrophy at the site of injection, as well as hypopigmentation. In our study, no side effects were reported in either group.

This study indicates the utility of patient-driven outcomes in a large, simple study. Our study design is practical in mild to moderate lupus flares that do not require repetitive laboratory monitoring.

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