Polyarticular Corticosteroid Injection Versus Systemic Administration in Treatment of Rheumatoid Arthritis Patients: A Randomized Controlled Study

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ABSTRACT. ***Objective.*** To study the effectiveness and side effects of polyarticular corticosteroid injection compared to systemic administration in patients with rheumatoid arthritis (RA), and to examine the differential response to injection among joints.

Methods. Sixty-nine RA patients presenting with 6–12 swollen joints were enrolled to participate in a randomized trial consisting of polyarticular injection in 6–8 swollen joints of intraarticular (IA) triamcinolone hexacetonide (IA group) or intramuscular (IM) mini-pulse therapy with triamcinolone acetonide in equivalent doses (IM group). Blind examination at baseline (T0), Weeks 1 (T1), 4 (T4), 12 (T12), and 24 (T24) postintervention included American College of Rheumatology improvement criteria ACR20%, 50% and 70%, visual analog scale for articular pain, pain on movement, joint count, range of motion, morning stiffness, quality of life (Medical Outcome Study Short Form-36), use of nonsteroidal antiinflammatory drugs and oral corticosteroid, blood pressure, adverse effects, calls to the physician, and hospital visits.

Results. Significantly better results were observed for IA compared to IM patients as follows: ACR20% (61.7% vs 28.5% at T1; 73.5% vs 42.8% at T4), ACR50% (29.4% vs 5.7% at T1; 44.1% vs 20% at T4), ACR70% (11.7% vs 0% at T1), patient's evaluation of disease activity, lower tender joint count, lower blood pressure, lower number of adverse effects, calls to the physician, and hospital visits ($p < 0.05$). Less significant adrenocorticotropic hormone reduction was observed for IA group at T4 and T12 ($p < 0.05$). Elbows and metacarpophalangeal joints had the best response to corticosteroid injection.

Conclusion. In the short term, polyarticular IA injection was better than IM corticosteroid, as shown by ACR improvement criteria and number of adverse effects. (J Rheumatol 2005;32:1691–8)

Key Indexing Terms:
RHEUMATOID ARTHRITIS CORTICOSTEROID INTRAARTICULAR INJECTION

Rheumatoid arthritis (RA) is a chronic disease mainly characterized by symmetric erosive synovitis particularly affecting peripheral joints[1]. Functional disability in RA patients is the consequence of articular deformity, which in turn is the result of pannus invasion of the articular cartilage, capsule, ligaments, and subchondral bone[2].

Synovectomy by chemical, radioisotopic, or surgical means has been adopted as a therapeutic option in RA[3-8]. Synovectomy has been indicated as follows: to control pauciarticular synovitis, to control the most actively tender joints in patients with polyarticular disease activity[4,9], and for patients in whom prosthetic joint replacement is contraindicated[10].

Most chemical synovectomy is performed using glucocorticosteroid (GC) intraarticular (IA) injection[11]. GC were the first class of drugs to be used in IA injection. Since their first use for synovectomy, the chemical structure of GC has undergone significant modifications that have made these drugs more potent and less soluble[5]. IA triamcinolone hexacetonide[12-15] remains active longer (6 days on average)[16], and its microcrystal disposition allows it to remain for an extended time in the IA space, which reduces its systemic absorption (only 35% is absorbed 3 days after injection)[16]. Thus, triamcinolone hexacetonide has been the most indicated drug for chemical synovectomy. Controlled chemical synovectomy trials in RA patients have demonstrated that triamcinolone hexacetonide is superior to other GC[17-21]. Chemical synovectomy with triamcinolone hexacetonide improved arthritis for periods ranging from 3[3] to 21 months[22].

The effect of polyarticular injection of IA triamcinolone hexacetonide versus that of a systemically administered corticosteroid intervention has not been compared in controlled trials. Benefits of polyarticular IA injection have not been proven. Most of the comparative studies published evaluated the effect of IA injection performed in only one joint, mostly the knee. Only 2 uncontrolled series in patients with

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Accepted for publication April 11, 2005.

RA demonstrated benefits of multiple concomitant IA injection of triamcinolone hexacetonide associated with immobilization[22,23]. Whether specific joints respond differently to chemical synovectomy is not known, since results of IA injection performed at different articular sites have not yet been studied using a controlled design.

Aggressive early multifocal intervention is currently advocated for treatment of RA. An approach including multiple IA injections and combination therapy with disease modifying antirheumatic drugs (DMARD) may be a reasonable option for these patients. In a controlled trial, Proudman, *et al*[24] have demonstrated better results for patients undergoing polyarticular IA injection with methylprednisolone.

Systemic effects as well as local adverse reactions have been reported after IA injection of GC[4,9,25-28]. The effect of multiple IA injections with triamcinolone hexacetonide on the hypothalamic-pituitary-adrenal axis has not been evaluated.

We conducted a controlled trial in patients with RA with polyarticular disease activity comparing medium term effectiveness of IA injection versus systemic administration of GC.

MATERIALS AND METHODS

Patients. We conducted a prospective single-blind randomized controlled trial to compare the effectiveness of 2 GC treatment programs and to evaluate the effectiveness of GC IA injection in different joints. A total of 70 patients with RA diagnosis according to American College of Rheumatology (ACR) criteria[29] were included from the Rheumatology Outpatient Clinic of the Universidade Federal de São Paulo, São Paulo, Brazil. Inclusion criteria included: RA diagnosed for more than 6 months; age between 18 and 65 years; functional class II or III according to the ACR criteria[30]; presence of 6 to 12 swollen joints including the following: elbow, wrist, second and third metacarpophalangeal (MCP) joints, knee, and ankle; and use of stable doses of oral corticosteroid for the last 30 days and of stable doses of DMARD for the last 3 months. Exclusion criteria: parenteral GC in the last 3 months; IA GC injection in the last 6 months; diabetes mellitus; history of psychosis or psychotic symptoms; uncontrolled hypertension; glaucoma; history of surgical procedure in the swollen joints; presence of skin lesion on the affected joints; and suspected microcrystal or septic arthritis. Written informed consent was obtained from all subjects, and the Universidade Federal de São Paulo Ethics Committee approved the study.

Intervention. Patients were screened for entry into the study by one investigator (JN) blinded to the patients' treatment allocation. Patients were randomly allocated to treatment groups by drawing lots. Folded pieces of paper indicating the intervention were placed in sealed envelopes in a container. One of the investigators (LMO) selected the envelopes to see who would go to which group.

Patients were randomized to participate in 2 intervention groups of 35 patients each: the IA group and the intramuscular (IM) group. Interventions in both groups were performed by the same investigator (RNVF). In the IA group, patients received multiple concomitant IA injections with triamcinolone hexacetonide in a concentration of 20 mg/ml. A minimum of 6 (patients with 6 swollen joints) and a maximum of 8 joints (patients with 7–12 swollen joints) per patient were injected at one time. In the IM group, patients received triamcinolone acetonide (20 mg/ml) IM injection in a total single dose equivalent to the amount of IA triamcinolone hexacetonide they would have received if they had been thus randomized. As the patients had 6 or more swollen joints, the IM group received a minimum dose of 160 mg of triamcinolone acetonide (corresponding to 4 MCP joints and 2 large joints) and this intervention was considered a mini-pulse therapy. Bed rest for 48 hours after the intervention was ordered for patients in both groups. While patients were followed for 24 weeks after intervention they were asked not to start or stop DMARD or change DMARD dose. Adverse effects were reported by telephone, and patients were allowed to use sodium diclofenac (maximum dose 150 mg/day) and oral prednisone as needed; patients kept a daily record of drug use.

IA injection. The IA group underwent IA injection under aseptic conditions. Injection was performed by the same physician (RNVF), and joints were systematically emptied before injection. Injections were performed without fluoroscopic monitoring. Elbow, wrist, knee, and ankle were injected with 40 mg of triamcinolone hexacetonide, while MCP joints received doses of 20 mg.

Evaluation. Patients were evaluated by a blinded physician (JN) at baseline (T0) and 1, 4, 12, and 24 weeks after intervention (T1, T4, T12, and T24, respectively). The number of sodium diclofenac tablets and oral prednisone doses used were counted at each timepoint and average daily doses for these drugs were assessed. Blood samples (10 ml) were also collected.

Disease related variables. Improvement in disease activity variables was measured using ACR improvement criteria — ACR20%, 50%, and 70%[31]. Individual analysis for each of the 7 components of the above criteria was also performed [tender and swollen joint counts, global pain by visual analog scale (VAS), patient and physician evaluation of disease activity using VAS, function as determined by Stanford Health Assessment Questionnaire (HAQ), and erythrocyte sedimentation rate (ESR)]. VAS pain was also used for each of the 12 joints studied as well as pain on movement joint count and Escola Paulista de Medicina range of motion scale (EPM-ROM)[32] to evaluate range of motion. All patients completed the Brazilian version for the Medical Outcome Study Short Form-36 (SF-36) quality of life questionnaire[33].

Adverse effects. The following variables were analyzed: number of systemic and local adverse effects; number of telephone calls to the physician and hospital visits for related events; and diastolic and systolic blood pressure (mm Hg). Adverse effects were systematically and actively searched for during medical visits.

Laboratory tests. ESR was measured at each timepoint. Plasma samples taken at each timepoint were frozen at –80°C, and adrenocorticotropic hormone (ACTH) levels were measured at the end of the study. ACTH was measured by immunoassay[34] using a commercial kit (ELSA-ACTH, CIS Bio International, Schering, Gif sur Yvette, France). Serum ACTH levels < 10 pg/ml were considered below normal.

Patients lost to followup before timepoint T12 and those who started new DMARD or stopped use of DMARD for more than 15 days during the study were considered dropouts and were excluded from statistical analysis.

Statistical analysis. Data are presented as mean ± standard deviation. Chi-squared analysis was used to evaluate differences between categorical variables. Student t test was used to determine potential differences among numerical nonrepeated measurements while 2-way analysis of variance (ANOVA) was performed to evaluate differences among repeated measurements. When 2-way ANOVA showed significant differences between groups (intergroup analysis), one-way ANOVA was performed to evaluate statistically significant differences among repeated intragroup measurements. ANOVA provide one p value evaluating the variable in a given group during followup versus the other group (intergroup analysis) and another p value evaluating the variable in each group compared to their respective values at baseline T0 (intragroup analysis). Mann-Whitney test was used to evaluate differences among nonparametric variables. Proportion test was used to compare articular response to IA injection among different injected joints. Significance level was set as $p < 0.05$.

RESULTS

We studied 75 patients with RA of whom 69 were considered for statistical analysis. One patient who died during the protocol course was the only dropout. Mean age was 47.55 ± 9.65 years and mean time since diagnosis was 11.39 ± 7.6 years. Most patients were women (92.75%) and non-Caucasian (55.72%). No statistically significant difference in any variable was observed between groups at baseline (T0). Table 1 shows clinical data and demographic characteristics of RA patients treated with GC at baseline. Dose of GC administered was not significantly different between groups. A total of 253 swollen joints were injected with triamcinolone hexacetonide in the IA group. In the IM group a total of 267 swollen joints were noted for the purpose of the intervention.

Disease related variables. Table 2 shows clinical variables that differed significantly between IM group patients treated with IM triamcinolone acetonide or IA group patients treated with IA triamcinolone hexacetonide. We observed that patients who received IA injection with triamcinolone hexacetonide had significantly smaller number of tender joints compared to the IM group ($p < 0.05$) during the study. After IA injection, patients also reported lower disease activity levels than their IM counterparts ($p < 0.05$). Intragroup analysis for these 2 variables (number of tender joints and patient evaluation of disease activity) showed statistically significant difference at each timepoint compared to baseline (T0), suggesting that both interventions were effective with time. For all other disease related variables (swollen joint count, global pain, physician evaluation of disease activity, ESR, HAQ functional subscale) we observed no statistically significant difference between groups during the study.

Comparison analysis for the ACR response criteria used to evaluate progression in disease activity (ACR20%, ACR50%, and ACR70%) revealed statistically significant improvement by ACR20% and ACR50% for the IA group at

Table 1. Clinical and demographic characteristics of RA patients treated with triamcinolone at baseline.

	IM Group (N = 35)	IA Group (N = 34)	p*
Age, yrs (mean ± SD)	49.28 ± 8.2	45.82 ± 11.10	0.144
Female:male	33:2	31:3	0.643
Caucasian	19	12	0.314
Time since diagnosis, yrs (mean ± SD)	10.32 ± 6.7	12.47 ± 85	0.218
Rheumatoid factor-positive, n	23	22	0.869
Functional class II, n	26	24	0.788
Funcational class III, n	9	10	0.788
Swollen joint count (mean ± SD)	7.62 ± 1.75	7.85 ± 1.41	0.109
Tender joint count (mean ± SD)	7.14 ± 2.76	5.88 ± 3.04	0.102
Global pain, VAS (mean ± SD)	5.57 ± 2.06	6.04 ± 1.95	0.399
Patient's evaluation of disease activity, VAS (mean ± SD)	5.68 ± 1.40	4.73 ± 2.04	0.060
Physician's evaluation of disease activity, VAS (mean ± SD)	5.51 ± 1.77	4.54 ± 1.86	0.051
Stanford Health Assessment Questionnaire	1.32 ± 0.56	1.00 ± 0.60	0.053
Erythrocyte sedimentation rate	38.57 ± 25.18	39.21 ± 29.60	0.818
Patients using chloroquine	7	11	0.274
Patients using methotrexate	19	22	0.329
Patients with hypertension	10	12	0.934
Daily oral prednisone dose, mg (mean ± SD)	7.36 ± 6.6	7.79 ± 6.64	0.131
Serum ACTH, pg/ml (mean ± SD)	17.88 ± 20.68	14.10 ± 16.57	0.145
Triamcinolone dose, ml (mean ± SD)	11.11 ± 1.6†	11.71 ± 1.31††	0.103
Triamcinolone dose, mg (mean ± SD)	222.2 ± 32†	234.2 ± 26.2††	0.103

SD: standard deviation; VAS: visual analog scale; * chi-squared, ANOVA, and Student t test. † triamcinolone acetonide; †† triamcinolone hexacetonide.

Table 2. Tender joint count, patients assessment of disease activity, ACR20%, ACR50%, and ACR70% in RA patients after triamcinolone intraarticular (IA) versus intramuscular (IM) intervention.

Timepoints	IM Group (N = 35)	IA Group (N = 34)	Intergroup p*
Tender joint count (mean ± SD)			0.011
T0	7.14 ± 2.76	5.88 ± 3.04	
T1	4.91 ± 3.2	2.58 ± 2.90	
T4	3.31 ± 2.76	2.05 ± 2.44	
T12	4.57 ± 3.15	3.38 ± 3.29	
T24	5.11 ± 3.68	3.88 ± 3.31	
	Intra group p < 0.001	Intra group p < 0.001	
Patient assessment of disease activity, VAS (mean ± SD)			0.04
T0	5.68 ± 1.40	4.73 ± 2.04	
T1	3.88 ± 1.76	2.69 ± 1.71	
T4	3.15 ± 1.93	2.47 ± 2.06	
T12	3.65 ± 2.16	3.79 ± 2.62	
T24	4.75 ± 2.23	3.94 ± 2.65	
	Intra group p < 0.001	Intra group p < 0.001	
ACR20%, No. of patients (%)			
T0			
T1	10 (28.57)	21 (61.76)	0.04
T4	15 (42.85)	25 (73.52)	0.01
T12	12 (34.28)	16 (47)	0.234
T24	8 (22.85)	13 (32.23)	0.165
ACR50%, No. of patients (%)			
T0			
T1	2 (5.71)	10 (29.41)	0.009
T4	7 (20)	15 (44.11)	0.032
T12	4 (11.42)	8 (23.52)	0.166
T24	4 (11.42)	7 (20.58)	0.299
ACR70%, No. of patients (%)			
T0			
T1	0	4 (11.76)	0.039
T4	4 (11.42)	5 (17.70)	0.686
T12	0	1 (2.94)	0.299
T24	0	3 (8.82)	0.07

SD: standard deviation; VAS: visual analog scale; ACR: American College of Rheumatology improvement criteria. * ANOVA for repeated measurements and chi-squared test.

timepoints T1 and T4 and by ACR70% at T1, compared to the IM group ($p < 0.05$). A trend for better results by ACR70% criteria for the IA group compared to the IM group was also observed at T24 ($p = 0.07$; Table 2).

Daily use of sodium diclofenac and oral prednisone, morning stiffness, articular range of motion measured by EPM-ROM scale, pain on movement joint count, and quality of life (SF-36) did not differ significantly between groups during the followup period.

ACTH serum concentrations presented great variance in our sample and thus ACTH was considered a nonparametric variable for statistical purposes. No significant difference was observed in ACTH serum levels between the 2 groups at the timepoints analyzed. However, the effect of interventions on secretion of ACTH, measured as the percentage difference in ACTH levels compared to baseline ($\Delta\%$ = final ACTH – initial ACTH/initial ACTH × 100), was significantly different between groups. Compared to patients undergoing IA injection with triamcinolone hexacetonide, patients in the IM group presented significantly more pronounced reduction in ACTH serum levels at T4 and T12 (compared to baseline; $p < 0.05$). No significant difference in percentage change to baseline was observed between groups at T1 and at T24.

Adverse effects. Table 3 details adverse effects reported by patients during the course of the study. A total of 38 different adverse effects were reported, and the most prevalent were dyspepsia (47.14%), dizziness (18.57%), insomnia (17.14%), headache (14.28%), edema (11.42%), and somnolence (11.42%). One patient from the IA injection group died during the study. The patient was a 46-year-old obese woman who came to the first visit after intervention (T1) without complaints and presenting blood pressure of 150 × 80 mm Hg. She was found dead by the family 26 days after randomization in the study. Necropsy and toxicological tests did not find a specific cause of death. This was the only dropout in our study.

As shown in Table 4, intergroup analysis showed that patients undergoing IA injection with triamcinolone hexacetonide had significantly fewer side effects compared to those who received IM triamcinolone acetonide at all timepoints evaluated. Intragroup analysis did not show statistically significant change in number of side effects in the groups during the study. Accordingly, patients in the IA group presented significantly lower blood pressure values during the study compared to the IM group. Average number of patients with blood pressure of 140 × 90 mm Hg or higher at each timepoint was 5.75 and 15.75 for the IA and IM groups, respectively. Intragroup comparison analysis showed significant reduction of systolic blood pressure during the study in the IA group, while a substantial increase was observed for diastolic blood pressure in the IM group (Table 4).

Table 5 shows that the number of telephone calls to the physician and number of hospital visits due to disease or to side effects were all significantly lower in the IA group compared to the IM group. Skin hypopigmentation areas around the articular injection site were observed in 25 out of 253 joints that underwent the IA injection (9.88% of joints, 0.7 hypochromic areas per patient in the IA group). Identified by a blinded physician, hypopigmentation areas in the articular surface were reported as complaints by only 2 patients. Most of the hypopigmentation areas were observed in MCP joints (22), ankle (2), and wrist (1). A total of 23 instances of joint instability were observed after intervention, but there was no statistically significant difference between groups (10 in IA and 13 in IM group). Most instances of joint instability were volar subluxation of the wrist (15,

Table 3. Adverse effects in RA patients according to administration [intramuscular (IM) versus intraarticular (IA)].

	Percent of Total	IM Group No. of Patients (%)	IA Group No. of Patients (%)
Dyspepsia	47.14	23 (65.7)	10 (28.7)
Dizziness	18.57	12 (34.3)	1 (2.8)
Insomnia	17.14	12 (34.3)	
Headache	14.28	9 (25.7)	1 (2.8)
Edema	11.42	6 (17.1)	2 (5.7)
Somnolence	11.42	5 (18.3)	3 (8.5)
Uterine bleeding	8.57	5 (18.3)	1 (2.8)
Weight gain	5.71	4 (11.42)	
Palpitation	5.71	3 (8.5)	1 (2.8)
Muscle cramps	2.85	2 (5.7)	
Striae	2.85	2 (5.7)	
Paresthesia	2.85	2 (5.7)	
Pruritus	2.85	2 (5.7)	
Pneumonia	4.28	3 (8.5)	
Dyspnea	2.85	2 (5.7)	
Typical precordialgia	2.85	2 (5.7)	
Purpura	2.85	2 (5.7)	
Gastrointestinal bleeding	1.42	1 (2.8)	
Hidradenitis	1.42	1 (2.8)	
Sinus infection	1.42	1 (2.8)	
Baker's cyst dissection	1.42	1 (2.8)	
Hypertensive emergency	1.42	1 (2.8)	
Hemiparesthesia	1.42	1 (2.8)	
Onychomycosis	1.42	1 (2.8)	
Erysipela	1.42	1 (2.8)	
Persistent vomiting	1.42	1 (2.8)	
Femoral osteonecrosis	1.42	1 (2.8)	
Hirsutism	1.42	1 (2.8)	
Acne	1.42	1 (2.8)	
Amenorrhea	1.42	1 (2.8)	
Vaginal candidiasis	1.42	1 (2.8)	
Erectile dysfunction	1.42	1 (2.8)	
Blurred vision	1.42	1 (2.8)	
Echymosis	1.42		1 (2.8)
Facial plethora	1.42		1 (2.8)
Scabiosis	1.42		1 (2.8)
Death	1.42		1 (2.8)
Stomatitis	1.42		1 (2.8)

Table 4. Side effects and blood pressure in RA patients treated with triamcinolone according to administration scheme [intramuscular (IM) versus intraarticular (IA)].

Timepoints	IM Group	IA Group	p
Side effects (mean ± SD)			< 0.001*
T1	0.94 ± 0.94	0.09 ± 0.38	< 0.001
T4	1.06 ± 1.21	0.26 ± 0.45	0.03
T12	1.31 ± 1.25	0.21 ± 0.41	< 0.001
T24	0.97 ± 1.15	0.18 ± 0.39	0.004
	Intragroup p = 0.306	Intragroup p = 0.106	
Systolic blood pressure, mm Hg (mean ± SD)			0.02*
T0	126.57 ± 13.49	125.14 ± 14.38	0.80
T1	131.11 ± 18.61	123.38 ± 15.98	0.013
T4	129.57 ± 16.99	119.55 ± 17.07	0.017
T12	133.28 ± 19.36	118.38 ± 15.40	< 0.001
T24	132.14 ± 18.75	119.26 ± 15.57	< 0.001
	Intragroup p = 0.097	Intragroup p = 0.028	
Diastolic blood pressure, mm Hg (mean ± SD)			< 0.001*
T0	74.71 ± 9.31	73.82 ± 10.44	0.77
T1	81.57 ± 10.31	69.70 ± 8.69	< 0.001
T4	79.71 ± 10.70	69.11 ± 8.39	< 0.001
T12	82.28 ± 13.46	71.17 ± 10.94	< 0.001
T24	81.14 ± 10.29	73.08 ± 9.53	0.0015
	Intragroup p = 0.006	Intragroup p = 0.089	

ANOVA: * global intergroup p value.

Table 5. Clinical events and local side effects in RA patients treated with triamcinolone according to type of intervention [intramuscular (IM) versus intraarticular (IA)].

	IM Group	IA Group	p*
No. of phone calls to physician (mean ± SD)	0.88 ± 1.05	0.25 ± 0.56	< 0.01
No. of hospital visits (mean ± SD)	0.31 ± 0.58	0	< 0.01
No. of joint instabilities (mean ± SD)	0.37 ± 0.81	0.29 ± 0.68	0.801
No. of hypopigmentation areas per patient (mean ± SD)	0	0.71 ± 1.07	< 0.01

SD: standard deviation. * Student t test.

65.21%). The remaining cases were ulnar deviations of MCP joints with ulnar subluxation of the finger extensor complex (8, 34.78%). We also observed transient worsening of pain and articular edema in 25 IA patients (73.52%). Articular flare post-IA injection occurred 1.04 ± 1.08 days after the injection procedure and was reported only when asked by the blinded investigator. Articular flare post-IA injection was not reported as an adverse effect by any participant. No septic arthritis, skin atrophy, or tendon rupture occurred in any patient during the study.

Articular response to IA triamcinolone hexacetonide injection. A total of 253 IA injections were performed including elbows (18), knees (25), ankles (44), third MCP joints (48), second MCP joints (55), and wrists (63). To determine potential differences in response of specific joints to the IA injection procedure, a comparison analysis was performed evaluating percentage reduction in the number of tender joints, number of joints with pain on movement, and number of swollen joints. As shown in Table 6, better IA injection results with more significant reduction in number of tender joints were observed in the elbow and MCP joints at both T12 and T24 ($p < 0.05$). Elbows, MCP joints, and knees showed better results after IA triamcinolone hexacetonide injection, presenting more significant percentage reduction in the number of joints with pain on movement and of swollen joints at T12 and T24 ($p < 0.05$). As seen for tender joints, wrists (at T12 and T24) and ankles (at T24) showed less significant improvement after injection, presenting less impressive percentage reduction in the number of joints with pain on movement and swollen joints.

DISCUSSION

We compared polyarticular injection of intraarticular triamcinolone hexacetonide with the effects of systemic intramuscular triamcinolone acetonide in patients with RA. IA triamcinolone hexacetonide effectiveness has been compared to many other corticosteroid drugs including triamcinolone acetonide[20,21] and has always been considered superior. For that reason, triamcinolone hexacetonide was chosen in our study to be used in the IA group. Triamcinolone hexacetonide could not be injected intramuscularly due to atrophic effects. Triamcinolone acetonide, which is more soluble and pharmacologically similar to triamcinolone hexacetonide, was selected for IM use. To obtain equivalent doses in both interventions, patients in the IM group received triamcinolone acetonide doses that are considered glucocorticoid mini-pulse therapy. IA injection in RA is usually reserved for patients with mono or pauciarticular synovitis. We investigated whether a more aggressive approach using localized, polyarticular injection would be as effective as and be associated with fewer adverse effects compared to the similarly aggressive systemic approach of mini-pulse therapy.

Our results revealed that, for the medium term and at equivalent doses, the polyarticular IA injection was generally as effective as the IM administration. However, the polyarticular IA injection was superior to the IM scheme when the following variables were compared: disease activity according to the patient; number of tender joints; number of systemic side effects; systolic and diastolic blood pressure; number of hospital visits; number of telephone calls to the physician; and number of potentially related events. In the short term, polyarticular IA injection was associated with more significant disease improvement by ACR20%, 50%, and 70% compared to IM administration.

Only a few uncontrolled studies have evaluated the use of polyarticular IA injection in RA patients[22,23,35]. To our knowledge, this is the first study designed to compare polyarticular IA injection of triamcinolone hexacetonide to a

Table 6. Articular improvement in RA patients treated with intraarticular (IA) triamcinolone hexacetonide injection according to injection site.

	No. of Tender Joints N (Δ%)			No. of Joints with Pain on Movement N (Δ%)			No. of Swollen Joints N (Δ%)	
	T0	T12	T24	T0	T12	T24	T12	T24
Injected Swollen Joints at T0 (N)								
Elbow (18)	13	6 (53.8)	6 (53.8)	7	1 (85.8)	3 (57.1)	5 (72.2)	5 (72.2)
Wrist (63)	28	28 (0)*	30 (–7.14)#	22	12 (45.4)*	22 (0)#	42 (33)#	47 (25.3)#
Knee (25)	20	10 (50)	14 (30)*	10	5 (50)	7 (30)	8 (68)	9 (64)
Ankle (44)	29	20 (31)*	24 (17.2)#	22	15 (31.8)#	21 (4.5)*	24 (45.4)*	25 (43.2)*
2nd MCP (55)	28	7 (75)	10 (64.2)	17	4 (76.4)	9 (47)	23 (58.1)	23 (58.2)
3rd MCP (48)	19	8 (57.8)	7 (63)	13	4 (69.2)	6 (53.8)	15 (68.7)	17 (64.6)

T0: baseline; T12 and T24: 12 and 24 weeks after IA injection, respectively; MCP: metacarpophalangeal joint; Δ%: improvement percentage; * $p < 0.05$; # $p < 0.01$ vs joint with best improvement percentatge (Δ%), proportion test.

systemic intervention in terms of effectiveness and local and systemic side effects.

McCarty, *et al* evaluated the effect of polyarticular injection in RA patients in open studies and observed good results[22,23]. In an open prospective study including several rheumatic diseases, Green, *et al*[35] observed that response to IA injection at the second week was the best variable to predict response 12 and 26 weeks postintervention. Their results showed less improvement (ACR20%, 29% of patients) than our results. In our sample, significant improvement after polyarticular IA triamcinolone hexacetonide injection was observed at the first (ACR20%, 61.76%) and fourth week postinjection (ACR20%, 73.69%).

Most studies evaluating the use of IA triamcinolone hexacetonide injection compared this drug to other corticosteroid medication for mono or oligoarticular procedures in RA patients[3,17-21,36-38]. None of these studies performed a systemic intervention with corticosteroid as the control group. All these trials have confirmed triamcinolone hexacetonide superiority in relation to other corticosteroids or antiinflammatory drugs for IA use. Triamcinolone hexacetonide pharmacokinetics seems to favor this drug for IA use and corroborate its superiority. Compared to triamcinolone acetonide and betamethasone, triamcinolone hexacetonide stays longer in the IA environment, presenting significant delay in IA clearance[16].

A study on aggressive management of RA has recently been published[24]. Aggressive therapy including cyclosporine, methotrexate, and polyarticular injection of all swollen joints (15 on average) was compared to monotherapy with sulfasalazine. Unlike our study, the authors used methylprednisolone for IA injection. Combined therapy was superior to monotherapy during the first 12 weeks of the study. The authors did not find statistically significant differences between the groups in ACR20% and ACR50% improvement criteria. In our study, polyarticular corticosteroid injection was associated with better results as assessed by ACR20% and ACR50% at 1 and 4 weeks postintervention and by ACR70% 1 week postintervention. In spite of some differences, our study and that from Proudman, *et al*[24] suggest that polyarticular GC injection is a reasonable approach in RA patients with polyarticular disease activity, especially when associated with combination DMARD therapy.

Systemic effects of IA GC injection have been reported[4,27,39] and are usually seen in clinical practice. Patients undergoing IA GC injection commonly experience improvement in other noninjected joints. Most of these systemic effects have been reported with IA methylprednisolone injection. A controlled study showed that IA methylprednisolone injection led to a significant decrease in cortisol levels starting 24 hours after procedure and lasting 7 days[25].

Intravenous and IM GC pulse therapy is associated with multiple systemic side effects[40-49]. Patients undergoing polyarticular IA triamcinolone hexacetonide injection had significantly fewer systemic side effects compared to those receiving IM triamcinolone acetonide pulse therapy in our study.

In our study IM triamcinolone acetonide had more significant effects on blood pressure than polyarticular injection. Taken together with analysis of related events and side effects, these findings suggest that polyarticular IA triamcinolone hexacetonide injection may be the best administration option for use in patients with comorbidity potentially worsened by GC use.

Local side effects have been reported with the use of IA triamcinolone hexacetonide, including skin atrophy and hypopigmentation (1–11.8%), tendon rupture (1%), septic arthritis (0–0.0072%), osteonecrosis/steroid arthropathy (0.8%), postinjection flare (2–6%), periarticular calcification (43% in interphalangeal joints), transient paresis of satellite muscles (rare), and articular instability[4,9,12,13,19,21,27,28,50].

We did not find statistically significant differences in the prevalence of joint instability and articular subluxation between the 2 study groups. Articular subluxation occurred mainly in the wrist (65.21%) and in MCP joints (34.78%), as would be expected in a disease that preferentially affects the hands.

Skin hypopigmentation on the articular surface was more

prevalent in the polyarticular IA injection group (9.88%), but this was a real complaint in only 2 patients. Jalava and Saario's results[19] were similar to ours (11.8% atrophy/hypopigmentation in 59 injected joints). Most of the hypochromic lesions in our study were seen on the MCP joint extensor surface, and this could be explained by the higher dose of triamcinolone hexacetonide used in these joints compared to other studies[22,23].

Improvement of synovitis after IA triamcinolone hexacetonide injection was statistically better in the elbow and MCP joints compared to other joints in our study. Wrists and ankles had the worst improvement indices after IA injection. These findings are in agreement with a study[21] in which juvenile RA ankles showed worse response to corticosteroid injection than knees. Aspects related to the specific joint injected such as level of difficulty to approach, volume of triamcinolone hexacetonide, joint load, and IA compartment communication might all affect response to IA injection.

Our results indicate that polyarticular IA triamcinolone hexacetonide injection is more effective in the short term than IM triamcinolone acetonide pulse therapy to control disease activity in patients with RA. In the medium term, both interventions had similar effectiveness; however, polyarticular injection was associated with significantly fewer systemic side effects than the IM intervention.

Our study supports the notion that a more aggressive approach to the treatment of patients with RA using combined DMARD therapy can also include polyarticular injection to increase treatment effectiveness.

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