ORIGINAL ARTICLE

Comparison of Intra-articular Glucocorticoid Injections with DMARDs versus DMARDs alone in Rheumatoid Arthritis

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Abstract

Background: Intra-articular triamcinolone in combination with DMARDs may be able to achieve faster and tighter control of disease activity in early rheumatoid arthritis that may be the key to preventing or minimizing later deformities.

Objective: To compare the efficacy of a combination of Disease Modifying Anti-Rheumatoid Drugs (DMARDs) with Intra-articular Glucocorticoids versus only DMARDs in a group of patients with early Rheumatoid Arthritis.(RA)

Methods: Fifty patients diagnosed as Rheumatoid Arthritis (RA) by American Rheumatology Association (ARA) criteria (1987) with disease duration less than two years were randomized into two groups. The Control group received a combination of Methotrexate 15 mg daily with Sulfasalazine 2 gm daily for 3 months and the Study group received the above combination along with Intra-articular injections of Triamcinolone acetate (40mg per ml) in each of the swollen joints at the start of the study. Outcome was assessed in terms of Disease Activity Score (DAS-28), American College of Rheumatology (ACR) 20/50/70 criteria and number of rescue medications used at the end of 3 months.

Results: The study group had significant reductions in DAS 28 scores (3.39 versus 4.99 in control group) and significantly more subjects achieved the ACR 20/50/70 criteria at the end of 3 months (100/60/36% versus 84/20/0%) Secondary end-points like tender and swollen joint count, ESR, early morning stiffness, health assessment questionnaire (HAQ) scores and general health status were significantly reduced in the study group. Also, significantly lesser rescue medications were needed in the study group.

Conclusion: Combination of DMARDs with Intra-articular corticosteroids is significantly better than DMARDs alone in early RA.

Introduction

Rheumatoid Arthritis, (RA) is the most common systemic autoimmune disease affecting 0.75% of the population, predominantly females, causing inflammation, cartilage destruction and bony erosions in synovial joints.[1-3] Activation of T- Lymphocytes by an unknown antigen stimulates monocytes, macrophages and synovial fibroblasts to produce the cytokines interleukin (IL-1), IL-6 and tumor necrosis factor (TNF-α) in the synovial fluid which in turn are potent stimulators of mesenchymal cells such as synovial fibroblasts, osteoclasts and chondrocytes that release matrix metalloproteases (MMP).[4,5] MMP in conjunction with elastases and proteases secreted by neutrophils degrade the cartilage and weaken it which ultimately leading to joint destruction.[4] Activated T-cells also cause an osteoprotegerin ligand (OPGL) mediated osteoclastogenesis and consequent bone loss.[6]

Early RA, which is characterized by joint swelling, stiffness and presence of inflammatory markers in the blood and synovium without radiographic

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Table 1 : Baseline comparison between the two groups

Characteristics	Control Group (n=25)	Study Group (n=25)	p-value
Demographic Characteristics			
Age (in years)	37 (Range 18-60)	37.36 (Range18-64)	0.734
Sex (M:F)	3:22	3:22	1.000
Smokers	4(16%)	3(12%)	0.684
Disease Characteristics			
Duration (in months)	14.44	13.24	0.575
Rheumatoid Factor Positive	13(52%)	18(72%)	0.145
Early Morning Stiffness (in minutes)	81.6	80.4	0.404
ESR (mm)	47.32	42.68	0.13
Tender Joint Count	17.96	17.4	0.793
Swollen Joint Count	7.88	8.44	0.464
Health Assessment Questionnaire (HAQ) scores	1.256	1.386	0.47
General Health Condition (VAS on a scale from 0 to 100, 100 being worst)	62.6	69	0.143
Disease Activity Score (DAS 28)	6.631	6.65	0.977

p < 0.05 taken as statistically significant

bony changes represents a therapeutic "window of opportunity".[7] Rapid control of early inflammation may conceivably limit or prevent subsequent joint destruction or deformity. The older "pyramidal approach" to treatment has changed in recent years to achievement of remission with early use of DMARDs.[8]

Studies using corticosteroids in various forms have proven efficacy in retarding radiographic progression and achieving a tight control of the disease in combination with traditional DMARDs.[9,10] Triamcinolone is the least water soluble of all steroid preparations and tends to remain in the joint for long periods, thus producing its effects locally.[11] Intra-articular steroids impair the ability of monocytes to release TNF-α and suppress levels of other mediators like IL-1, IL-6 and IL-8.[12,13] It also decreases levels of RANKL, a member of TNF-α family, thus leading to fewer erosions.[14] Biologic DMARDs and intra-articular steroids are the only two agents acting on the RANKL/OPGL and MMP systems, leading to greater bone and cartilage preserving effects.[15]

With this background in mind, we decided to design a study to assess the efficacy of a combination of intra-articular steroids with DMARDs versus DMARDs alone in early RA.

Materials and Methods

Patients satisfying the American Rheumatology Association (ARA) 1987 criteria for diagnosis of RA aged over 18 years with disease duration less than two years and attending the Physical Medicine and Rehabilitation department of Safdarjang Hospital, New Delhi were enrolled in this prospective, randomized study which commenced in October 2009 and ended in July 2011. The study was approved by the institution review board. After screening for exclusion criteria, written, informed consent was obtained and patients were randomized into two groups (control and study) by lots drawn. At baseline, Complete Blood Counts (CBC), Erythrocyte Sedimentation Rate (ESR), Liver and Kidney Function Tests, Rheumatoid Factor (RF), and radiographs of affected joints were performed. Number of Tender Joints (TJC), Swollen Joints (SJC), duration of early morning stiffness (EMS), patients assessment of pain and patients and physicians assessment of disease activity (VAS scale 0 to 100, 0=best, 100=worst) and Health Assessment Questionnaire (HAQ) modified in the Indian scenario was also recorded.

Study group received oral Methotrexate (MTX) 15mg per week, oral Folic Acid 5 mg per day, (except on day of MTX administration) oral Sulfasalazine (SSZ) 2gm per day and intra-articular injections of Triamcinolone acetonide (40mg per ml) in each of the swollen joints (small joints of hand = 0.2 ml, wrist, elbow and ankle joints = 0.5 ml and knee and shoulder = 1 ml each) and Control group received oral MTX (15mg per week), oral folic acid (5mg per day, except on the day of MTX intake) and oral SSZ (2gm daily). Oral Diclofenac (50mg) was offered as rescue medication on an "as needed" basis. Subjects were followed up at 6 and 12 weeks and TJC, SJC, ESR, disease activity (as recorded by patient and physician), pain score and HAQ scores were recorded. In addition, CBC and LFT were done at each follow-up. A count of oral NSAIDs used was maintained. Exclusion criteria were contraindications to steroids like Diabetes, acute infections, peptic ulcer disease and renal disease, joint deformity or erosions, treatment with oral or intra-articular steroids in the last one year, treatment with any other DMARD combination and pregnant and lactating women.

Disease Activity Score (DAS-28) and ACR20/50/70 score at 12 weeks was considered as primary outcome measures. In addition, ESR, EMS, HAQ scores, TJC, SJC, general health status (patient reported on VAS scale 0 to 100, 0=best, 100=worst) and number of rescue medication tablets used were considered as secondary outcome variables. Data was managed on Microsoft Excel© and tested on SPSS for windows version 15 software. Independent T test, Chi-Square test and Wilcoxon rank sum was used for data analysis. Results were considered significant at p<0.05.

Table 2 : Primary and secondary end point variables at 6 and 12 weeks

Parameters	At 6 Weeks			At 12 Weeks		
	Control	Study	p-value	Control	Study	p-value
ESR (mm/hour)	39.68 (±12.12)	28.32 (±13.47)	0.004	32.68 (±13.42)	26.6 (±12.91)	0.134
Tender Joint Count	12.28 (±5.56)	3.12 (±3.56)	0.001	8.36 (±4.8)	3 (±3.14)	0.001
Swollen Joint Count	4 (±1.5)	0.36 (±1.03)	0.001	3 (±1.25)	0.6 (±2.08)	0.001
General Health Status (VAS 0 to 100)	51.8 (±12.57)	30 (±14.64)	0.001	42.4 (±15.95)	27.8 (±14.36)	0.002
DAS 28 scores	5.71 (±0.72)	3.48 (±1.07)	0.001	4.99 (±0.93)	3.39 (±1.26)	0.001

p < 0.05 taken as statistically significant

Results

In all, 56 patients were enrolled in the study out of which 50 completed 3 months follow-up. (25 in each group) There were 6 drop-outs (2 due to allergic reactions to SSZ, 3 due to lack of follow-up and one developed amenorrhea).

Baseline characteristics of both groups are summed up in Table 1.

The mean age of patients in the study group was 37.36 years (range=18 to 60 years) and the control group was 37 years (range=18 to 64 years) with a female to male ratio of 22:3 in both groups. Three patients in the study group (12%) and 4 patients in the control group (16%) were smokers. The mean disease duration was 13.24 months in the study group (range=3 to 24 months) and 14.44 months (range=3 to 24 months) in the control group. Eighteen patients (72%) were rheumatoid factor positive in the study group while it was 13 patients (52%) in the control group. Both groups were comparable in all baseline characteristics.

At the end of 6 and 12 weeks, significant reduction in all disease parameters was seen in the study group. (Table 2 and 3) Patients who received steroid injections with DMARDs showed an initial quick fall in all parameters which improved further at 12 weeks. Patients who were treated with only DMARDs also improved in all parameters but did so, slowly in comparison to the study group across the duration of the study.

We used an average dose of 340 mg of triamcinolone acetonide in our study group. (Range=80mg-640mg) Injections were given with standard sterile precautions using anatomical landmarks for needle placement. Apart from giddiness and nausea in a few patients and pain during needle entry, there were no other side-effects during the injection procedure itself.

Adverse effects in both groups included

Table 3 : Selected End Point Variables at 12 Weeks

Parameters	Control Group	Study Group	p-value
Early Morning Stiffness (minutes)	40.8(±15.32)	13.6(±12.2)	0.001
Fall in HAQ scores	0.45(±0.31)	0.69(±0.34)	0.009
ACR 20	21(84%)	25(100%)	0.037
ACR 50	5(20%)	15(60%)	0.004
ACR 70	0	9(36%)	0.001
Rescue Medications (Diclofenac tablets)	43.84(±17.31)	14.4(±7.17)	0.001

p <0.05 taken as statistically significant

gastritis, mouth ulcers, acneiform lesions and skin hypopigmentation at injection sites in the study group which were all managed conservatively without dropping out from the study.

Discussion

The goal of treatment in RA is to achieve remission or low disease activity state.

Modern approach to treatment favours the "reverse pyramid" concept for achievement of this goal which entails starting with a combination of DMARDs with or without steroids and then tapering to maintenance levels or using biologic agents.[8]

Both the groups in our study were comparable at baseline in all parameters. At the end of 6 weeks, the study group showed a significant improvement in both the primary and secondary outcome measures as compared to the control group. This effect was carried over till 12 weeks. This result is in agreement with a number of studies which showed significantly more improvement when a combination of DMARDs was used with local and oral steroids.[10,16,17]

ESR showed improvement in the study group which was significant at 6 weeks but not significant at 12 weeks. This is because ESR has low discriminatory power and is a poor predictor of patient's long term prognosis.[18] Hence an improvement in ESR ought to be looked for rather than its absolute value. At 12 weeks the DAS-28 score was 3.39 which indicates moderate disease activity. This is close to the low disease activity score (2.6 to 3.1) which is the aim of treatment. Although significantly more patients achieved the ACR 20 and ACR 50 criteria in the study group, greater achievement of ACR 70 criteria in the study group (36% in the study group compared to 0% in the control group) was considered as a highly desirable goal in the management of patients with RA. All the secondary end-points, that is tender joint count, swollen joint count, general health status scores and early morning stiffness showed significantly more improvement in the study group signifying across the board improvement when DMARDs were used with intra-articular steroids. Our study also showed significantly lower HAQ scores in the study

group which entails a better functional outcome in these patients. We have used a validated modified HAQ for Indian population which focuses on tasks specific to our population.[19] At the end of 12 weeks, the study group required significantly lesser rescue medication tablets thus lessening the cost of therapy and minimising potential risk of added side-effects.

We have come across several studies which have used various combinations of oral and/or intra-articular steroids in RA but we have not come across any study with intra-articular triamcinolone acetonide. Triamcinolone was used in our study because of its property of staying in the joint for long periods and thus producing more local effects. The ideal agent to be used would be triamcinolone hexacetonide but it is not available in India and both the acetonide and hexacetonide compounds have similar fractions of systemic absorption.

In conclusion, it can be stated that a combination of intra-articular steroids with DMARDs is significantly better than only DMARDs in controlling disease activity of patients with early RA. They might also turn out to be an effective alternative to more expensive options like biologic agents in achieving desired disease control. However, more studies especially those comparing biologics with combination of DMARDs and intra-articular steroids are needed to support this claim.

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