Chapter 3

Intra articular injection with corticosteroids in patients with recent onset rheumatoid arthritis: subanalyses from the BeSt study

E. Gvozdenović, L. Dirven, M. van den Broek, K.H. Han, E.T.H. Molenaar, R. Landewé, W.F. Lems and C.F. Allaart.

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ABSTRACT

Objective

To investigate the association between intra-articular (IA) large joint corticosteroid injections and clinical outcomes in patients with recent onset rheumatoid arthritis (RA).

Methods

We compared pain (visual analogue scale (VAS)), the Disease Activity Score (44 joints) (DAS) and swollen and tender joint counts before and after IA injection. Using linear mixed models (LMM) the DAS and the Health Assessment Questionnaire (HAQ) score over time were compared in IA injected versus non-injected patients.

Results

In year 1, 93 joints were injected in 44 patients treated with initial methotrexate monotherapy, and 16 in patients treated with initial combination therapy ($p<0.01$). Three months later, swelling and tenderness were resolved in 50-58% of the injected joints but within 12 months after the injection, swelling recurred in 14% and tenderness in 41% of the injected joints. Mean (SD) DAS decreased from 4.0 (1.4) before to 3.2 (1.2) 3 months after injection ($p<0.01$) and VAS for pain from 49 (26) to 40 (27) ($p<0.01$). LMM showed a higher DAS and HAQ in patients injected in year 0-1 compared to those not injected, but no difference in subsequent years, and similar treatment adjustments. Eight year radiographs showed similar damage in injected joints (17%) and non-injected joints (14%).

Conclusion

IA corticosteroid injections are associated with symptom relief, sometimes only temporarily, in 50% of the cases. Initially DAS significantly improved, but over time DAS and HAQ were similar in injected versus non-injected patients. After 8 years there was no difference in joint damage.

INTRODUCTION

Inflammation of joints in rheumatoid arthritis (RA) causes pain and loss of physical function and eventually may result in joint destruction. Current treatment consist of disease-modifying anti rheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), biological agents and oral corticosteroids.[1] In addition, intra articular (IA) corticosteroid injections are given, mostly in the large joints, as local therapy to reduce pain and swelling.[2-6] In daily practice short term effect varies per patient due to accuracy and needle placement, type of corticosteroid, misdiagnosis of inflammation.[5,7,8] Long term, IA-injections in combination with DMARDs are suggested to have a positive effect on inflammation in RA. [9]

In the BeSt study, which compares 4 different treatment strategies aimed at a Disease Activity Score (DAS) =<2.4 in patients with recent onset RA, we investigated the association of IA-injections in the large joints with disease activity and functional ability in the first year and over 8 years of treatment including number of treatment adjustments and radiological damage at year 8.

METHODS

Patients

The BeSt is a multicenter trial including 508 patients with recent onset RA (1987 classification criteria) between April 2000 and August 2002. More details are described elsewhere.[10] In all four groups, IA injections were allowed at the rheumatologists' discretion. Intra muscular injections were not allowed. For the current analysis patients who received IA injections in the large joints during the first year, and patients who did not were compared. Early (3 months after IA injection), short term (from t=1 year to t=2 years) and long term (between t=2 years and t=8 years) outcomes were measured every three months using the three monthly swollen and tender joint counts, a visual analogue scale (VAS in mm, 0=best, 100=worst) for pain, the DAS, with local swelling (based on a 44 joint count) and tenderness (measured in 51 joints with the Ritchie Articular Index), and functional ability (Health Assessment Questionnaire HAQ).[11] Radiological damage defined as a Larsen score >=1 and the number of treatment adjustments (made when three monthly DAS as measured by trained nurses was >=2.4) were used as secondary outcome measure in the analyses.

Statistical analyses

Descriptive analyses using X^2-test for categorical data and analysis of variance (ANOVA) or Kruskal-Wallis test for continuous data were performed, depending on normal distribution of the tested variable. Short term associations of IA injections were tested with a paired T-test. Aiming to correct for patient selection resulting in IA injected patients being more likely have more active RA, we used propensity scoring.[12] The propensity model included the following covariates: gender, age at inclusion, body mass index (BMI), rheumatoid factor (RF) status; anti-cyclic citrullinated peptide (ACPA) status; baseline total Sharp van der Heijde Score (SHS), DAS, HAQ, treatment strategy, swollen joint count, tender joint count, patient's assessments of global disease activity and pain on a visual analogue scale (VAS) and doctor's VAS for disease activity. The propensity score showed moderate to good discrimination, the area under the receiver operating characteristic (ROC) curvewas 0.73 (95% confidence interval 0.67-0.80). HAQ and DAS over time in injected and non-injected patients, adjusted for propensity score and follow-up time, were compared using a linear mixed-effects model (LMM) analysis. Logistic regression was performed to analyze the association of IA injections on radiological damage after 8 years, corrected for the propensity score. Univariate linear model building was used to measure the association between injections (yes/no) on the number of high DAS44 steered treatment adjustments within the treatment arms (post-hoc test). Software program SPSS version 17.0 was used for the analyses; p-values were reported two-sided and p-values smaller than 0.05 were considered statistically significant.

RESULTS

Of the 508 patients, 60 patients (12%) were injected in one or more large joints (n=93) during the first year of treatment, 42 (60%) of whom were women. At baseline, patients who would receive IA injections had a significantly higher mean DAS, HAQ, number of swollen and tender joints than the non-injected patients (table 1).

Of the injected joints, 32 (34%) were knees, 29 (31%) shoulders, 19 (20%) wrists, 7 (8%) ankles, 5 (5%) elbows and 1 (1%) hip. Depending on preference in the participating hospitals, 47 (52%) joints were injected with triamcinolonacetonide (Kenacort), 12 with methylprednisolone (Depo-medrol) (13%) and 32 (35%) with triamcinolonhexacetonide (Lederspan).

Table 1. Baseline characteristics in injected patients versus the rest of the patients.

	IA-injection during first year, n=60	**No IA injection during first year, n=447**	**p-value**
Women, n (%)	42 (60)	301 (67)	0.66
Age (years), mean (SD)	55 (14)	54 (13)	0.64
BMI, mean (SD)	26 (4)	26 (4)	0.37
Symptom duration (wks) median (IQR)	21 (12 to 57)	24 (14 to 53)	0.46
ACPA positive, n (%)	34 (57)	266 (62)	0.15
RF positive, n(%)	39 (65)	290 (65)	0.97
Smoking, n (%)	35 (58)	292 (66)	0.26
Alcohol, n (%)	33 (55)	229 (52)	0.64
DAS_{44}, mean (SD)	4.7 (0.8)	4.4 (0.9)	<0.01
HAQ, mean (SD)	1.6 (0.6)	1.4 (0.7)	<0.01
VAS pain, mean (SD)	58 (25)	53 (21)	0.10
VAS disease activity (patient) mean (SD)	65 (21)	59 (22)	0.07
VAS morning stiffness, mean (SD)	62 (23)	59 (24)	0.48
VAS general well-being, mean (SD)	55 (19)	52 (20)	0.19
Swollen joint count large joints, mean (SD)	3.7 (1.9)	3.0 (1.9)	<0.01
Tender joint count large joints, mean (SD)	5.4 (2.6)	4.7 (2.7)	0.05
VAS disease activity (physician), mean (SD)	62 (17)	56 (18)	0.06
Treatment strategy, n (%)			<0.01
Sequential monotherapy	21 (35)	105 (23)	
Step-up combination therapy	23 (38)	98 (22)	
Initial combination with prednisone	5 (8)	128 (29)	
Initial combination with infliximab	11 (18)	111 (25)	

n=number, SD=standard deviation, IQR = interquartile range, BMI= body mass index, ACPA = anti−citrullinated protein antibody, RF = rheumatoid factor, DAS44= Disease Activity Score in 44 joints, HAQ= Health Assessment Questionnaire, VAS = visual analogue scale

Recurrence of symptoms was similar after these types of injections (data not shown). Significantly ($p<0.01$) more injected patients, n=44, had been allocated to initial monotherapy in strategy arms 1 and 2 than to the initial combination therapy in strategy arms 3 and 4 (n=16) (Figure1).

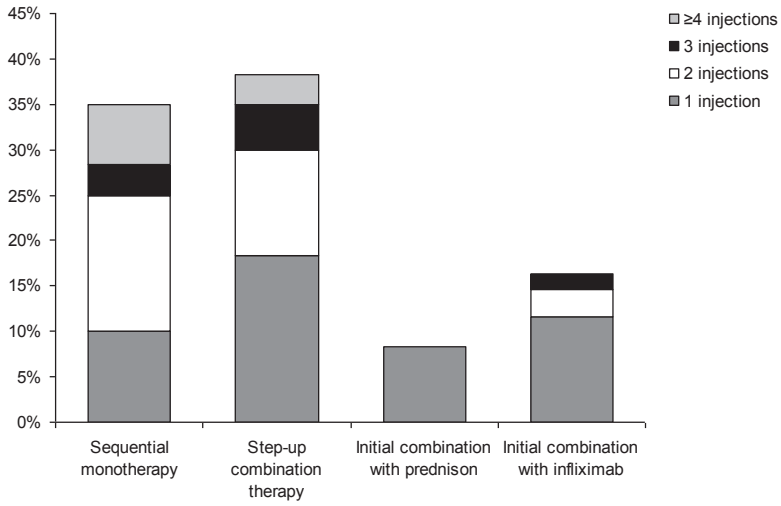

Figure 1. Percentage of injected joints in patients per treatment group.

Pre-injection, local joint swelling as assessed by the study nurses was present in 41 (46%) of injected joints, local tenderness in 56 (63%), and both local tenderness and joint swelling in 31 (36%) of the injected joints. 24 joints were deemed by the research nurse to be neither swollen nor tender. Three months after the first injection, 27(50%) of the swollen joints were no longer swollen and 23 (58%) of the tender joints were no longer tender. Mean (SD) DAS before and 3 months after IA injection was 4.0 (1.4) and 3.2 (1.2), respectively ($p<0.01$) and VAS for pain before and 3 months after IA injection was 49 (26) and 40 (27), respectively ($p<0.01$).

Within 12 months after the injection, swelling recurred in 3/12 (14%) of the resolved swollen joints after injection and tenderness recurred in 11/27 (41%) of the resolved tender joints after injection.

Seventeen joints were injected twice in the first year of treatment. Three months after the second injection, 3/9 of the tender joints were no longer tender, and 2/6 of the swollen joints were no longer swollen. Five joints were injected a third time, resulting in non-tenderness three months later in 1/5. In 10 (38%) of the injected patients that reached a DAS44 =<2.4 in the first year, no systemic treatment adjustment occurred. During year 0-1, IA injected patients had a higher DAS44 than non-injected patients, mean (95% CI) 3.66 (3.48 to 3.84) versus 2.80 (2.73 to 2.87) and higher HAQ 0.96 (0.84 to 1.08) versus 0.78 (0.74 to 0.82)

($p<0.01$), after propensity scoring. However these were less than the minimal clinically significant difference.[13, 14] Between t=1 year and t=2 years, and between t=2 years and t=8 years, there were no significant differences in DAS and HAQ over time between injected and non-injected patients (Figure 2).

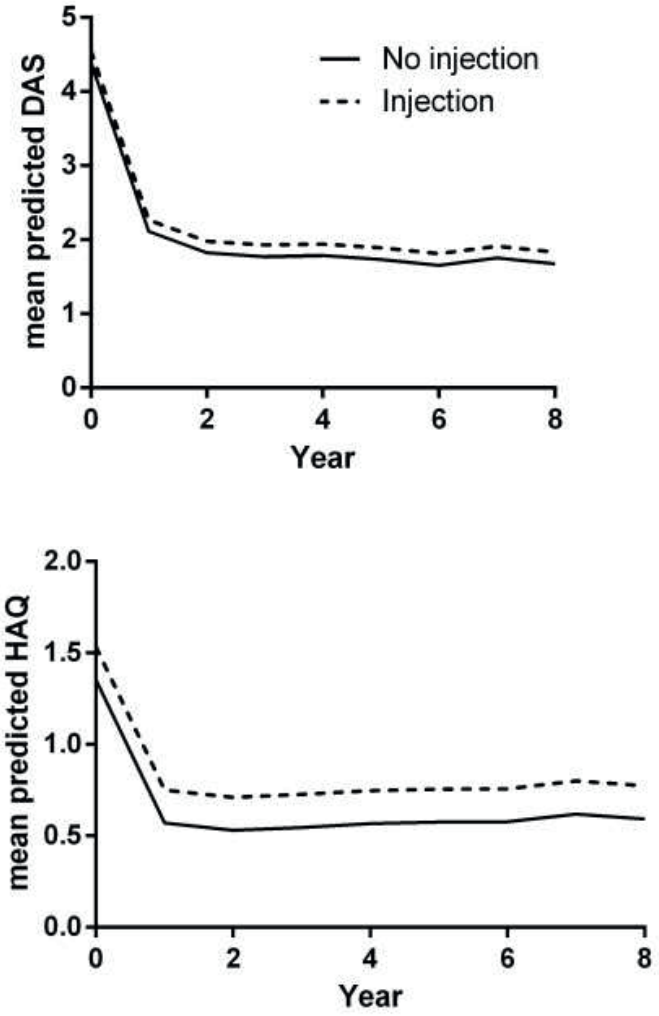

Figure 2. Predicted mean HAQ (Health Assessment Questionnaire and mean DAS44 (Disease activity score in 44 joints) based on a linear mixed models analysis in injected patients versus non injected patients during the eight years of follow-up.

From baseline until year 8, the number of treatment steps taken in the four strategy groups was similar in the injected patients and the non-injected patients (table 2).

Radiographs, assessed at t=8 years in the BeSt protocol, were available for 51% (n=46) of the injected joints, and 53% (n=3179) of the non-injected joints, in 28 (47%) injected and 262 (58%) non-injected patients.

Radiological damage was present in 17% (n=8) of the radiographs of injected joints, and in 14% (n=453) of the radiographs of non-injected joints. Since there were no baseline radiographs, progression could not be scored. On patient level, no significant (p=0.67) association between IA injection and damage was present, adjusted for propensity score (OR: 0.82, 95% CI 0.33 to 2.03).

Table 2. Univariate linear model showing number of treatment steps after 8 years for injected versus non injected patients, per treatment strategy.

	Injected in the first year (yes/no)		
	Yes	**No**	**p-value**
Sequential monotherapy,	3.7	2.3	0.10
mean (95% CI)	(2.02 to 4.43)	(1.38 to 3.35)	
Step-up combination therapy,	3.5	2.4	0.12
mean (95% CI)	(1.99 to 5.08)	(1.40 to 3.46)	
Initial combination with prednisone, mean	1.0	1.7	0.49
(95% CI)	(-0.99 to 2.98)	(1.10 to 2.30)	
Initial combination with infliximab,	1.0	2.2	0.14
mean (95% CI)	(-0.50 to 2,47)	(1.66 to 2.76)	

CI=confidence interval.

DISCUSSION

In recent onset RA patients, randomized in the BeSt study to start treatment with either methotrexate mono-or with combination therapy, intra-articular corticosteroid injections were allowed at the discretion of the rheumatologists. Joint swelling and tenderness outcomes were assessed at 3-monthly intervals by trained nurses who calculated the Disease Activity Score (DAS). The 12% injected patients improved in clinical outcomes (VAS pain, DAS, HAQ)

after three months and a year after injection. Local swelling resolved in 50% and tenderness in 58% of injected joints, but within 12 months recurred in 14% of previously swollen and 41% of previously tender injected joints. Injected patients had a higher baseline DAS and HAQ, and were more often randomized to the initial monotherapy arms of the BeSt trial. These arms overall required more treatment adjustments than the initial combination therapy arms in year 1. After propensity scoring to correct for differences between the injected and non-injected patients using, we found that in the years following the injections there were no significant differences in DAS and HAQ over time between injected and non-injected patients. Also number of three-monthly treatment adjustments that were required if DAS was >=2.4 were similar between injected and non-injected patients within the treatment strategies over 8 years. In the linear mixed model analysis, IA injections were not associated with DAS and HAQ reduction in the subsequent years after IA injection.

Our data suggest that IA injections are associated with short term symptom relief in patients with early RA. Assuming that injected patients had more active disease than non-injected patients, IA injections in year 1 also seem to be associated with suppression of disease activity in the longer term, as injected and non-injected patients had over time similar disease activity and functional ability, required similar number of systemic treatment adjustments and had similar prevalent local joint damage at t=8 years.

One may argue that an early success rate of 50% to 58% of a local anti-inflammatory treatment is disappointing, in particular when symptoms sometimes rapidly return. Although previously described[15] we found no association between recurrence of symptoms and type of corticosteroid used for the injections. However, incorrect placement of some injections, which in our study were almost all given blind, may have occurred. Previous studies have shown that 'blind' injections are misplaced in 18-63% of cases.[16, 17] However, some reports described that incorrect located injection still results in local symptom relief.[18] Furthermore, the treating rheumatologists may have injected joints that were most severely or persistently inflamed and were less likely to show a complete and lasting immediate response. Since our study relies on joint assessments from study nurses (unaware of treatment strategy) rather than those of treating rheumatologists, some discrepancies may be explained. On the other hand, some joints injected might not have been inflamed with rheumatoid arthritis. The fact that some were injected more than once and never responded might also indicate non-inflammatory osteoarthritis or cuff lesions.

The BeSt protocol required radiographs to be taken of all large joints after 8 years, but was found only available in 51% of the injected joints (and 53% of non-injected joints). We cannot verify if damage was already present at baseline, which might have triggered the injections, nor can we evaluate whether damage has developed or progressed over time in relation to the injections. The fact that damage was found in 17% of available injected joints and in 14% of available non-injected joints suggests that injected joints do not have more damage than non-injected joints, and that the injections at least were not detrimental to the integrity of the joints. A further limitation of the study was the incomplete data on intra articular injections in the years 2-8. We estimate that this occurred less often than in year 1, as during treat-to-target therapy, in the majority of patients disease activity was well suppressed,[19, 20] and few joints in year 1 were repeatedly injected, but we verify this for lack of details. The small number of injections the second and the third time and the available data of swollen and tender joints 1 year after injection may be a limitation in itself.

In conclusion, rheumatologists injected large joints with corticosteroids predominantly in recent onset RA patients with high disease activity, resulting in an adequate local response in about 50% of the injected joints. Joint swelling recurred within 1 year in only 14% which suggests that in early RA, joint injections with corticosteroid are associated with symptom relief and adequate suppression of local inflammation. Overall DAS and HAQ were reduced and over following years similar to DAS and HAQ in non-injected patients, and the numbers of three-monthly systemic treatment adjustments in this treat to target study were similar. Finally, radiographs of injected versus non-injected joints at 8 years suggests that there is similar damage in these joints. Thus, IA injections might provide both short and long term benefit.

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