Intra-articular glucocorticoid injections should not be neglected in the remission targeted treatment of early rheumatoid arthritis: a post hoc analysis from the NEO-RACo trial

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Abstract

Objective

To study the effects of neglecting intra-articular glucocorticoid injections (IAGCIs) into swollen joints in early rheumatoid arthritis (RA).

Methods

Ninety-nine patients with early, DMARD naive RA were treated, aiming at remission, with methotrexate, sulfasalazine, hydroxychloroquine, low-dose oral prednisolone and, when needed, IAGCIs for 2 years, and randomised to receive infliximab or placebo from weeks 4 to 26. During each of the 15 study visits, patients were scored retrospectively 0.2–0.4 points (depending on the number of non-injected joints) if IAGCIs to all swollen joints were not given. Patients were divided into tertiles by their cumulative scores for neglected injections (CSNI) over 24 months. 28-joint disease activity score (DAS28) area under the curve (AUC) between 0–24 months, remission rates, changes in quality of life, and radiological changes during the follow-up were assessed. Trends across tertiles of CSNI were tested with generalised linear models.

Results

Higher CSNI was associated with lower strict remission rates (p=0.005), and lower quality of life (p=0.004) at 24 months, and higher DAS28 AUC (p<0.001) during the follow-up. At 24 months, DAS28 remission rates were 90%, 93% and 76% (p=0.081), and strict remission rates were 74%, 77% and 39% by tertiles of CSNI. No significant differences were observed in radiological progression (p=0.089). IAGCIs were well tolerated.

Conclusion

Neglecting IAGCIs into swollen joints is associated with lower remission rates, higher disease activity, and lower quality of life. Hence, IAGCIs should be used as an integral part of the targeted treatment of early RA.

Key words

rheumatoid arthritis, DMARDs, intra-articular injections, glucocorticoids, quality of life, protocol compliance

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Received on January 27, 2016; accepted in revised form on May 26, 2016.

Competing interests:
L. Kuusalo has received honoraria from Abbvie, Bristol-Myers Squibb, and Pfizer.
K. Puolakka has received honoraria from Abbvie, Bristol-Myers Squibb, MSD, Pfizer, Roche, and UCB.
H. Kautiainen has received honoraria from Abbvie and Pfizer.
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H. Julkunen has received honoraria from Abbvie, Berlin-Chemie, Bristol-Myers Squibb, Pfizer.
O. Kaipiainen-Seppänen has received honoraria from Abbvie, Medac, MSD, Novartis, Pfizer, Roche, and UCB.
M. Korpela has received honoraria or consulting fees from Abbott, Bristol-Myers Squibb, Celgene, GSK, Hospira, MSD, Novartis, Pfizer, Roche, UCB Pharma.
L. Paimela has received honoraria from Abbvie, Bristol-Myers Squibb, Janssen, MSD, Pfizer, Roche, UCB.
R. Peltomaa has received honoraria from Abbvie, Bristol-Myers Squibb, MSD, Roche, and UCB.
T. Möttönen has received honoraria from Abbvie, Amgen, Eli Lilly, MSD, Bristol-Myers Squibb, Novartis, Roche, and Pfizer.
T. Yli-Kerttula has received honoraria from Abbvie, MSD, Pfizer and UCB.
M. Leirisalo-Repo has received honoraria from Abbvie, Bristol-Myers Squibb, MSD, Pfizer, Regeneron and Roche.
V. Rantalaiho has received honoraria from Bristol-Myers Squibb.

Introduction

Since the introduction of glucocorticoids (GCs) into clinical practice over 60 years ago, intra-articular glucocorticoid injections (IAGCIs) as well as oral GCs have been an important part of the treatment of rheumatoid arthritis (RA) (1, 2). In recent years, the beneficial effect of oral low-dose glucocorticoids in relieving RA symptoms rapidly and reducing radiological progression has been demonstrated (3-5). Due to lack of data on the safety profile of low-dose GCs, current European League Against Rheumatism recommendations state that they should be considered as part of the initial treatment strategy, but only as a short-time bridging therapy of not more than six months (6).

Compared with oral GCs, evidence on the impact of IAGCIs is scarce. The efficacy of single-joint IAGCIs, most often of the knee, has been demonstrated in both osteoarthritis and RA (7-10). In addition, IAGCIs have been superior to intramuscular GCs injections in knee synovitis of RA patients in at least one randomised double-blind trial (11). Stressing the importance of suppressing inflammation, IAGCIs also seem to protect RA patients against periarticular bone loss in the small joints of the hand (12). However, only one randomised trial has compared intramuscular and polyarticular administration of GCs, finding the latter to be more effective in short term, and associated with fewer systemic side effects (13).

The use of IAGCIs instead of oral GCs may be less detrimental because of lower cumulative doses due to the administration of injections only in the presence of swollen joints. Therefore, injections may cause less short- and long-term adverse events, which are usually mild with the exception of bacterial arthritis, a feared but extremely rare complication (14-16).

The use of IAGCIs as a part of the treat-to-target strategy has yielded excellent results, as in the CIMESTRA trial. In the trial, patients with early, aggressive RA were treated with a combination of IAGCIs and methotrexate. This strategy resulted in rapid long-term control of the inflammation, which was sustained for two years, together with minimal radiological progression. Also, cumulative CG doses remained low, corresponding less than 2 mg of prednisolone daily during the first year (17, 18). Moreover, besides the CIMESTRA and the current trial, IAGCIs have been used actively as a part of the treatment strategy in a few previous studies, such as the FIN-RACo, and the TICORA trials (17, 19-22).

In the present study, we aimed to explore whether the inactive use of IAGCIs has an impact on outcomes in early RA in the NEO-RACo trial. In this trial, a remission targeted protocol was used, and the active use of IAGCIs to all swollen joints was encouraged at all times in addition to a combination of three conventional synthetic disease-modifying drugs (csDMARDs) and low-dose oral prednisolone (23).

Methods

Study design and patients

The NEO-RACo trial was an investigator initiated, randomised, controlled, double-blind, multicenter trial, which enrolled 99 patients with early, active and DMARD naive RA fulfilling the American College of Rheumatology (ACR) 1987 classification criteria for RA (24). The patients were treated with an intensified Finnish rheumatoid arthritis combination treatment strategy (FIN-RACo) consisting of methotrexate (MTX, max. 25 mg/week), sulfasalazine (2 g/day), hydroxychloroquine (35 mg/kg/week) and low-dose oral prednisolone (7.5 mg/day) for two years. In addition, the patients were randomised to receive either infliximab (FIN-RACo+INFL) or placebo (FIN-RACo+PLA) infusions at weeks 4, 6, 10, 18, and 26. According to the study protocol, in the case of non-remission or intolerability the csDMARD treatment had to be changed as per predefined instructions. In treatment failure, defined as less than ACR50 (25) improvement at two consecutive visits after week 26, the use of biological DMARDs as a salvage therapy was accepted. At all time points, the treatment was targeted to a modified ACR remission (26), named strict NEO-RACo remission, defined as no swollen (66 joint count) or tender joints (68 joint count) and presence of 5

out of the 6 following criteria: 1) morning stiffness <15 minutes, 2) no fatigue, 3) no joint pain, 4) no tender joints, 5) no swelling in joints or tendons, and 6) erythrocyte sedimentation rate <30 mm/h in women and <20 mm/h in men. Patient selection criteria, treatment protocol and 2-year outcomes of the NEO-RACo trial have been described in detail previously (23).

Use of IAGCIs into all swollen joints was recommended in both treatment arms. The type and dose of IAGCI was left to the discretion of the treating physician. Both methylprednisolone and triamcinolone hexacetonide were therefore used for injections, although in general triamcinolone is recommended for injecting large joints (*e.g.* knee, elbow) and methylprednisolone for small joints in Finland. The injected joints and the doses of glucocorticoids were recorded in the case files, including injections administered outside the scheduled study visits. The use of ultrasound during joint injections was left to the discretion of the treating physician and was not recorded.

Outcomes and follow-up

The patients were assessed at weeks 0, 4, 6, 10, 14, 18, 22, 26, and at months 8, 10, 12, 15, 18, 21, and 24. The ACR core data were gathered at all visits (27). Strict NEO-RACo remissions, disease activity, health-related quality of life, and radiological progression were used as outcome measures. The 28-joint disease activity score (DAS28) (28) and DAS28 area under the curve (AUC) between 0 and 24 months, and remissions at 24 months were used to assess disease activity. Health-related quality of life was assessed at 0, 8, 12 and 24 months using the Short-Form 36 questionnaire (SF-36) and the scores were converted into SF6Ds and quality adjusted life-years (QALYs) for analysis (29). Radiographs of the hands and feet were taken at 0, 8 and 24 months, and scored according to the modified Sharp/van der Heijde method (SvdH) (30).

Score for neglected IAGCIs

A scoring system that would not depend solely on the number of missed injections was created to quantify the impact of the missed IAGCIs. All given IAGCIs on each of the 15 study visits between 0 and 24 months were carefully assessed and scored by 2 reviewers as follows: If one or several large swollen joints or more than 2 small swollen joints were not injected 0.4 points were given (gross negligence), and if only 1–2 small joints were not injected 0.2 points were given (minor negligence). Also, if the patient refused injections points were given according to the same rules as this was thought to reflect the physician's inability to motivate the patient to receive treatment. However, points for the lack of IAGCIs were not given if 1) a minimum of 2 ml of glucocorticoids were injected as rheumatologists in Finland have in general been recommended to avoid injecting larger amounts than 2 ml of IAGCIs during one day to avoid systemic adverse effects; 2) if distal interphalangeal joints of hands, or proximal or distal interphalangeal joints of feet were not injected as these joints are seldom affected by RA but can be swollen because of osteoarthritis; 3) if the treating physician had reported that the effusion in the joint was due to osteoarthritis; or 4) if the joint had been injected multiple times without improvement as the expected benefit of injections would be low while the risks of repeated injections would increase. The maximum score for the lack of IAGCIs was 0.4 points/visit, and 6 points for the whole follow-up.

Ethical considerations

Informed written consent was obtained from all patients. Study protocol was approved by the national health authorities and by the ethics committee of the Hospital District of Helsinki and Uusimaa, and the study was conducted according to the declaration of Helsinki. The study has been registered at http://www.clintrials.gov (NCT00908089).

Statistical analysis

The data are presented as means with standard deviations (SD) or as counts with percentages. For analysis, the patients were divided into tertiles according to the score for neglected IAGCIs. Statistical comparisons were made using analysis of variance (ANOVA), Kruskall-Wallis test or chi-square test. Statistical significance for the hypotheses of linearity was evaluated by using generalised linear models with appropriate distribution and link function. The normality of the variables was tested using the Shapiro-Wilk W test. In the case of violation of the assumptions (*e.g.* non-normality), a bootstrap-type test was used. The bootstrap method is beneficial when the theoretical distribution of the test statistic is unknown and in the case of violation of the assumptions. STATA 13.1, StataCorp LP (College Station, TX, USA) statistical package was used for the analyses.

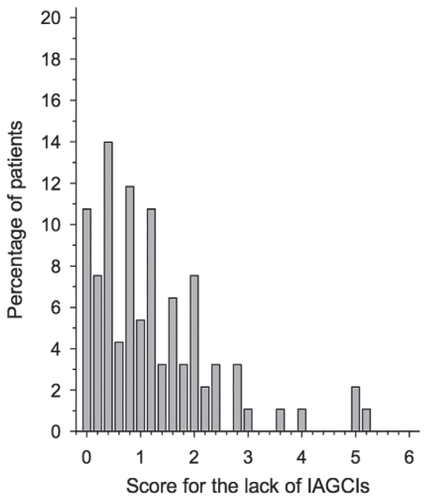

Fig. 1. Distribution of the patients with respect to the score for the neglected intra-articular glucocorticoid injections (IAGCIs).

Results

Of the 99 patients randomised to the study, follow-up data at 24 months was available for 93 patients (92%). The points given from the neglected IAGCIs ranged from 0 to 5.2 and are shown as percentages in Figure 1. The patients were divided into tertiles by the score for neglected IAGCIs. The clinical and demographic baseline characteristics of the patients by tertiles are shown in Table I. The median number of IAGCIs in the first, the second, and the third tertile was 5.5, 1.5, and 2.0, respectively (p=0.007).

We found a statistically significant linear relationship across the tertiles of neglected injections and NEO-RACo remission rates at 24 months, DAS28 AUC, and quality of life (Fig. 2, ad-

Table I. Baseline characteristics of the patients categorised into tertiles by neglected intra-articular glucocorticoid-injections.

Characteristic	Tertiles by neglected IAGCIs			*p*-value
	I (n=30) score 0–0.4	II (n=30) score 0.6–1.2	III (n=33) score ≥1.4	
Demographic data at baseline				
Female, n (%)	22 (73)	23 (77)	18 (56)	0.11
Age (years), mean±SD	43 ± 10	47 ± 11	48 ± 10	0.12
BMI, mean±SD	26.1 ± 4.2	25.9 ± 4.0	26.0 ± 4.5	0.93
Duration of symptoms (months), median (IQR)	4 (2,6)	3 (2,5)	4 (3,6)	0.99
Rheumatoid factor present, n (%)	21 (70)	25 (85)	23 (70)	0.95
Measures of disease activity at baseline				
Number of swollen joints, mean±SD	14.9 ± 7.1	14.9 ± 5.2	16.0 ± 7.0	0.53
Number of tender joints, mean±SD	18.3 ± 10.6	19.0 ± 9.4	22.5 ± 11.2	0.12
Erythrocyte sedimentation rate (mm/h), mean±SD	35.2 ± 24.6	34.3 ± 21.2	29.5 ± 20.0	0.29
Patient's global assessment (VAS, mm), mean±SD	51 ± 27	42 ± 22	53 ± 25	0.77
Pain (VAS, mm), mean±SD	57 ± 26	47 ± 25	56 ± 28	0.90
Physician's global assessment (VAS, mm), mean±SD	48 ± 23	49 ± 17	56 ± 19	0.09
Physical function (HAQ), mean±SD	0.9 ± 0.7	0.8 ± 0.7	1.2 ± 0.6	0.16
DAS28, mean±SD	5.5 ± 1.6	5.5 ± 0.9	5.6 ± 1.0	0.66
Radiography at baseline (SvdH score)				
Total score, mean±SD	1.1 ± 2.0	2.4 ± 5.0	2.7 ± 8.9	0.32
Erosion score, mean±SD	1.0 ± 1.9	2.2 ± 4.4	2.3 ± 7.7	0.35
Narrowing score, mean±SD	0.3 ± 1.3	0.2 ± 0.7	0.4 ± 1.3	0.78
The initial randomisation group				
FIN-RACo+Placebo, n (%)	16 (53)	9 (30)	21 (64)	0.38
FIN-RACo+Infliximab, n (%)	14 (47)	21 (70)	12 (36)	

IAGCIs: intra-articular glucocorticoid injections; IQR: interquartile range; VAS: visual analogue scale; HAQ: Health Assessment Questionnaire; DAS28: 28-joint disease activity score; SvdH score: Sharp/van der Heijde score.

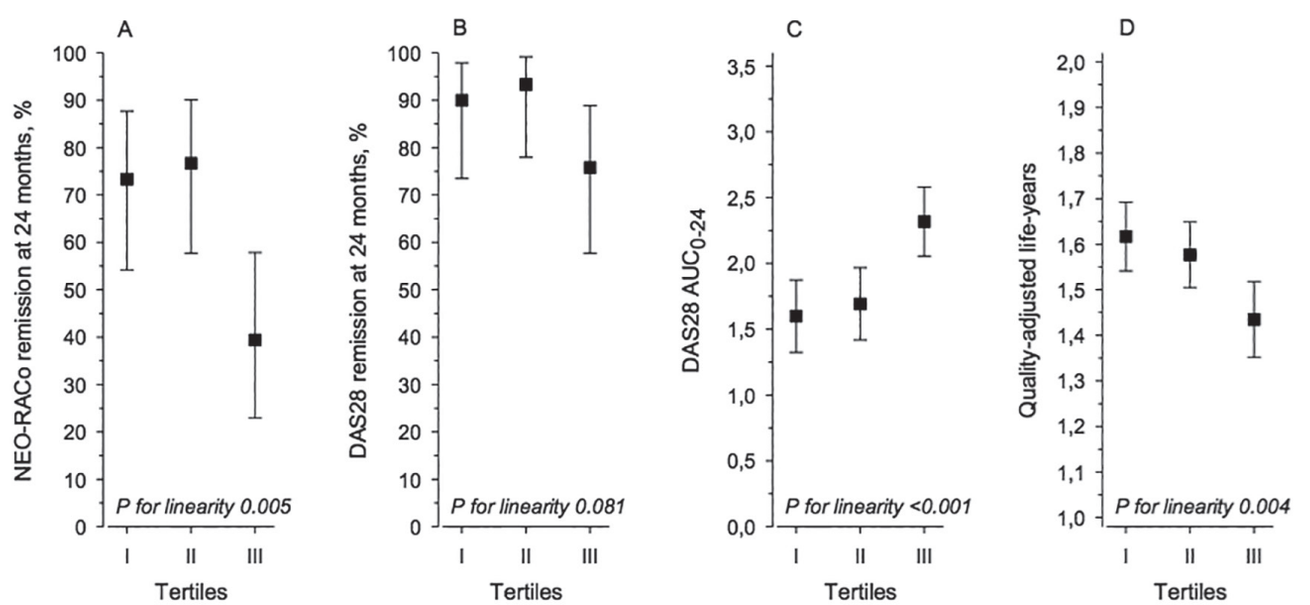

Fig. 2. Remission rates, disease activity and quality of life by tertiles of neglected intra-articular glucocorticoid injections.
(**A**) Strict NEO-RACo remissions and (**B**) 28-joint disease activity score (DAS28) remissions at 24 months, (**C**) DAS28 area under the curve (AUC) 0–24 months, and (**D**) the gain in quality of life as quality adjusted life years (QALY) by tertiles of neglected injections. During the follow-up, 0–4 injections were neglected in the first tertile. Adjusted for age, sex, rheumatoid factor status, baseline disease activity, and the use of infliximab.

justed for age, sex, rheumatoid factor status, baseline disease activity, and the use of infliximab). Also, DAS28 at 24 months by tertiles of neglected injections behaved respectively (*p* for linearity 0.021). The correlation coefficient between DAS28 AUC and neglected IAGCIs was 0.51 (95% CI 0.34–0.64). DAS28 remission rates at 24 months were 90% in the first, 93% in the second, and 76% in the third tertile, and respective NEO-RACo remission rates were 74%, 77% and 39% (Fig. 2).

The average radiological changes during follow-up were marginal. We found no

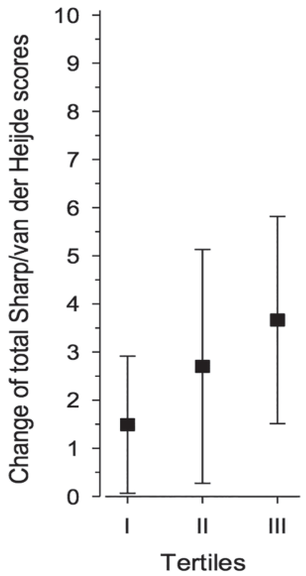

Fig. 3. Change of total Sharp/van der Heijde (SvdH) score by tertiles of neglected intra-articular glucocorticoid injections. During the follow-up, 0–4 injections were neglected in the first tertile. P for linearity 0.089, adjusted for baseline SvdH score, sum of injections and the use of infliximab.

statistically significant linear relationship across the tertiles in radiological progression (Fig. 3). Only one adverse event due to IAGCIs was reported. This was a suspected septic arthritis with a flare of multiple joints after a carpometacarpal joint injection at 8 months.

Discussion

Our results indicate that neglecting IAGCIs is associated with lower remission rates, higher disease activity, and lower quality of life in patients with early RA. In our study, IAGCIs were also well tolerated, and therefore these results promote the active use of IAGCIs together with combination therapy of csDMARDs in the treatment of early RA.

This study was conducted in Finland, where liberal use of IAGCIs has been and currently is an important part of the treatment scheme in early RA. Traditionally, rheumatology fellows have been taught to inject all swollen joints of early RA patients unless contraindications are present. Injecting only one or two most swollen joints is generally not considered sufficient. Therefore, in this study, the use of IAGCIs into all swollen joints was only recommended, as it is considered an intimate part of the Finnish rheumatology clinical practice.

Despite the high remission rates in this study, we were able to demonstrate the effect of inactive use of IAGCIs. We found a trend towards lower NEO-RACo remission rates and higher disease activity in patients who were not given IAGCIs into all swollen joints. Furthermore, due to the aggressive treatment strategy of this study, most patients did not have inflamed joints after 6 months, which substantially lowered the need for IAGCIs. The overall treatment responses were very good, and radiological progression was minimal in both treatment arms (no progression in 80% of the patients randomised to infliximab, no progression in 53% of the patients randomised to placebo) (23). We found a trend in the radiological progression (Fig. 3), but due to the relatively small sample size the study was underpowered to reach statistical significance.

Previous results of the NEO-RACo study demonstrated that it is possible to reach very high DAS28 remission rates of 82% at 2 years with intensive, remission targeted, csDMARD combination treatment (23). Based on the results of the present study, the liberal, active use of IAGCIs in the trial most likely contributed substantially to these excellent results. Furthermore, the IAGCIs increased the cumulative daily prednisolone dose only slightly. As published earlier, the mean cumulative doses of intra-articular methylprednisolone equivalents over 2 years were 212 mg in the FIN-RACo+PLA group, and 92 mg in the FIN-RACo+INFL group (23). Thus, the IAGCIs added only 0.1–0.4 mg to the mean cumulative daily prednisolone dose.

We did not find earlier studies focusing on the impact of IAGCIs on quality of life in RA, but lower disease activity has been shown to be strongly associated with improved quality of life (31, 32). Also, RA has often a negative impact on health-related quality of life, which is consequently inferior in RA patients compared with the general population (33, 34).

Overall, the literature on the impact of IAGCIs is very limited. Our study did not compare different administration routes of GCs and, to our knowledge, only one randomised, controlled trial has compared the effectiveness of polyarticular *versus* intramuscular GCs. In this study by Furtado *et al*., 69 patients were randomised to receive equivalent doses of either IAGCIs or intramuscular GCs. In the intra-articular group, 267 swollen joints were injected with triamcinolone, whereas patients in the intramuscular triamcinolone group had 253 swollen joints. After four weeks, 44% of the patients in the IAGCI group had achieved ACR50 response with less adverse events, compared with 20% in the intramuscular GC group (13).

Our results are most comparable with other treatment strategy trials, in which IAGCIs have been used. In the TICORA trial patients were randomised to intensive treatment or to routine care (20). In contrast to our study, the patients were given IAGCIs into a limited number of joints (max. 3/visit) with a cumulative maximum of 120 mg of triamcinolone acetonide in three months. However, if the maximum dose of IAGCIs was not applied within three months after starting a new DMARD, intra-muscular GCs were given to reach the cumulative dose of 120 mg. At the end of follow-up, the disease activity was lower, DMARD treatment more intensive and the number of received IAGCIs higher in the intensive group than in the routine care group. The mean cumulative dose of GCs in the intensive group remained low and corresponded to less than 1.5 mg of prednisolone daily.

In two Danish strategy trials, the CIMESTRA and the OPERA, IAGCIs were an important part of the treatment strategy, but oral GCs were not allowed (17, 22). In CIMESTRA, early RA patients were treated with MTX, IAGCIs, and randomised to receive either cyclosporine or placebo. Intra-articular betamethasone was given into maximum of four swollen joints every two to four weeks. During the first year, the cumulative median amount of betamethasone corresponded to less than 2 mg of prednisolone per day, and respectively less than 0.5 mg per day during the second year (17). Injections led to long-lasting remission of the individual joints, and 64% and 57% of the joints injected once

were in remission at 12 and 24 months. In joints injected for a second or third time, 31–43% reached remission at 24 months (18). In the OPERA trial, early RA patients were treated with MTX, IAGCIs, and adalimumab or placebo. At every visit, swollen joints (max. 4 joints) were injected with triamcinolone hexacetonide. Adding adalimumab to the treatment did not increase the proportion of patients who reached low disease activity at 12 months, but improved remission rates and quality of life. Cumulative triamcinolone doses at 12 months remained low, corresponding to less than 1 mg of prednisolone/day (22). The impact of not injecting swollen joints compared with injecting has not been studied earlier. Hence, comparison of the results of the abovementioned trials to our results is challenging. In the NEO-RACo, besides triple therapy of csDMARDs, 7.5 mg of prednisolone/day was used. However, despite of the use of oral prednisolone, IAGCIs were required but they increased the cumulative daily prednisolone dose only slightly.

Our study has strengths and weaknesses. First, this trial was not originally designed to investigate the independent effect of IAGCIs. Thus, we analysed the effects of not injecting the swollen joints, and only implicitly the efficacy of IAGCIs. Second, patient adherence was not measured systematically, and the patients with poor adherence to medication may have more likely refused injections as well. However, the completion rate of the study was high (92%), reflecting good patient adherence. Third, unreported injection treatments performed by general practitioners could be a possible source of error. However, the patients were assessed often during the study and all injections, including those administered outside the study, had to be recorded in the case files which makes bias unlikely. Fourth, some patients may have received IAGCIs for joint effusion caused by osteoarthritis instead of RA as their differentiation was based on the best clinical assessment of the treating physician (all experienced rheumatologists). Conjointly, when generalising our results to daily clinical practice, it must be remembered that patients rarely see their rheumatologist as often as in a clinical trial, which reduces the feasibility of IAGCIs, unless they are given by a primary care physician or by a trained rheumatology nurse. Hence, if follow-up visits to rheumatology clinics cannot be arranged monthly after RA diagnosis, we suggest that primary care physicians should be trained to give IAGCIs to early RA patients in the presence of swollen joints.

To sum up, our results suggest that when IAGCIs into swollen joints are neglected, early RA patients are less likely to achieve remission, have higher disease activity, and suffer from lower quality of life. IAGCIs are well tolerated with limited systemic effects. These results allow us to implicitly conclude that IAGCIs are very useful in the treatment of RA. Subsequently, in order to reach remission in as many early RA patients as possible, IAGCIs should not be forgotten but given vigorously into all swollen joints following RA diagnosis in addition to effective combinations of DMARDs. Even though old and inexpensive, IAGCIs are feasible to use. We encourage the active use of IAGCIs as a part of the targeted treatment of early RA.

Acknowledgements

The authors would like to thank all participating patients, other members of the NEO-RACo study group [Harri Blåfield, Kari K. Eklund, Mikko Hakola, Kirsti Ilva, Anna Karjalainen, Markku Kauppi, Aulikki Kononoff, Maija-Liisa Krogerus, Kari Laiho, Riitta Luosujärvi, Reijo Luukkainen, Timo Malmi, Helena Niinisalo, Jari Pöllänen, Tea Uusitalo, Toini Uutela, Heikki Valleala, and Kaisa Vuori (rheumatologists), Leena Laasonen (radiologist), Eeva Moilanen, Riina Nieminen, and Katariina Vuolteenaho (pharmacologists)], and the study nurses for their skilled contribution.

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