

Ultrasound-guided intra-articular triamcinolone acetonide injection for treating refractory small joints arthritis of rheumatoid arthritis patients

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Abstract

To investigate the efficiency and clinical safety of intra-articular triamcinolone acetonide (TA) injection under the guide of ultrasonography combined with standard treatment for treating refractory small joints arthritis in rheumatoid arthritis (RA) patients.

TA was injected upon confirmation of the needle inserting into the articular cavity. The dose was 40 mg for the wrist, 20 mg for the metacarpophalangeal (MCP) joint and 20 mg for the proximal interphalangeal (PIP) joint, respectively. Visual analogue scale (VAS) for joint pain, swelling, tenderness, synovial hyperplasia and power Doppler signal scores were evaluated at pretreatment, and post-treatment 24 hours, 1 week, 4 weeks as well as 12 weeks.

The VAS for pain and tenderness scores showed gradual improvement at 24 hours, 1 week, 4 weeks and 12 weeks after treatment compared with the baseline levels ($P < .005$). The swelling showed no changes at 24 hours after treatment compared with the baseline, and showed gradual improvement at 1 week, 4 weeks and 12 weeks after treatment ($P < .005$). Significant decrease was noticed in the synovial hyperplasia score at 4 weeks and 12 weeks compared with the baseline level. Power Doppler signal score showed significant decrease at post-treatment 24 hours, which showed further decrease at 1 week and 4 weeks.

Ultrasound-guided intra-articular TA injection is effective for treating RA patients with refractory small joints arthritis without changing the original treatment plan.

Abbreviations: DMARDs = disease-modifying antirheumatic drugs, MCP = metacarpophalangeal, MSCs = mesenchymal stem cell, PIP = proximal interphalangeal, PRP = platelet-rich plasma, RA = rheumatoid arthritis, SD = standard deviation, TA = triamcinolone acetonide, VAS = visual analogue scale.

Keywords: intra-articular injection, metacarpophalangeal joint, proximal interphalangeal joint, rheumatoid arthritis, triamcinolone acetonide, wrist

1. Introduction

Rheumatoid arthritis (RA), an inflammatory progressive disease with synovitis as the major pathological feature, is usually associated with joint destruction and disability in the absence of appropriate treatment.^[1] It shows high prevalence and morbidity worldwide. The onset of RA varies among the patients regarding the race, geographic location, type, lesion site, and pattern of

joint involvement. Meanwhile, it may be different based on the genetic background of patients and the severity of inflammatory progress.^[2,3]

Nowadays, the treatment efficiency of RA based on biological agents and small molecules shows significant improvement with the advances in the diagnosis and treatment, especially the emergence of concept of “treating rheumatoid arthritis to target”.^[4] Indeed, a large number of patients show remarkable attenuation in the symptoms after treatment, including attenuation of joint swelling, decrease of inflammatory indices and controlling of diseases. However, some patients may present refractory joint swelling with or without pain in one or two small joints, which hamper the quality of life among these cases. For these patients, alternation of treatment regimen or agents may be a treatment option, but it brings about additional treatment intensity and cost, as well as unexpected adverse events. If no additional treatment is given, the disease is in an active state persistently, which may progress to more severe forms.^[5] Intra-articular glucocorticoid injection combined with disease-modifying antirheumatic drugs (DMARDs) has been suggested to show positive effects on inflammation in RA. In this study, we included patients with refractory joint swelling with or without pain in one or two small joints after previous standard treatment using DMARDs. Then we investigated the efficiency and safety of intra-articular triamcinolone acetonide (TA) injection under the guide of ultrasonography combined with the standard treatment unchanged for treating these patients.

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The study protocols were approved by the Ethical Committee of the Yantai Yuhuangding Hospital.

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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2. Materials and methods

2.1. Patients

In this prospective, non-randomized controlled study, we included the RA patients admitted to our department from January 2013 to December 2015. The study was performed in line with the Declaration of Helsinki. The protocols were approved by the Ethics Committee of Yantai Yuhuangding Hospital (approval No. 2012–92).

The inclusion criteria were as follows:

- (i) those diagnosed with RA fulfilling the 2010 ACR/EULAR RA criteria;
- (ii) those with stable conditions after administration of DMARDs, with 1 or 2 sites (e.g., wrist joint, MCP and PIP) suffering from refractory swollen with or without pain, with no attenuation after 3-month treatment using the previous regimen;
- (iii) those with synovial hyperplasia in the joints after ultrasonography.

The exclusion criteria were as follows:

- (i) patients with more than 2 swollen joints;
- (ii) those underwent intra-articular corticosteroid hormone injection;
- (iii) those with systemic or local joint infection.

2.2. Treatment

Intra-articular injection of TA was carried out under the ultrasonic guidance by an experienced surgeon. TA was injected only upon confirmation of the needle inserting into the articular cavity. Each joint received single injection for treatment. The dose was 40 mg for the wrist, 20 mg for the MCP and 20 mg for the PIP, respectively. The patients were suggested to limit the excessive movement of the target joints within 30 days. The previous treatment regimen (DMARDs) was still carried out according to the treatment schedule with no alternations even during this study.

2.3. Outcome evaluation

Visual analogue scale (VAS), a common method for evaluating joint pain,^{16,71} swelling, tenderness, synovial hyperplasia and power Doppler signal scores were evaluated at pre-treatment, and 24 hours, 1 week, 4 weeks as well as 12 weeks after injection. The clinical evaluation was performed by a rheumatologist blinded to the treatment regimen based on the following criteria:

- (i) VAS for joint pain at rest: 0, no pain; 10 cm, severe pain;
- (ii) swelling score: 0, no joint swelling; 1, slight joint swelling, not exceeding the bony protruding part of the joint; 2, obvious joint swelling; 3, severe joint swelling;
- (iii) tenderness: 0, no tenderness in the presence of high pressure and maximal passive activity; 1, showing tenderness at the joint margin or pressing the ligament; 2, tolerable tenderness in the presence of hard pressure or maximal passive activity, with adverse events such as frowning; 3, severe tenderness, not tolerable.

2.4. Ultrasonography

Ultrasonography was carried out by a well-trained rheumatologist blinded to the clinical symptoms of the patients. Ultrasonic

examination was performed using the Color Doppler ultrasound imaging device (LOGIQ-P5, GE Healthcare, CA), using a linear array transducer with a frequency of 10 MHz. Dorsal and volar sections (longitudinal and transverse views) of wrist, metacarpophalangeal (MCP) or proximal interphalangeal (PIP) joints were scanned according to the description by Backhaus.¹⁴ Synovial hyperplasia score and Color Doppler ultrasound score were evaluated as previously described.¹⁵ Synovial hyperplasia was defined presence of uncompressed hypoechoic region in the joint capsule. The criteria were as follows: 0, no synovial hyperplasia; 1, slight synovial hyperplasia; 2, synovial thickening bulging over the line linking tops of the periarticular bones but without extension along the bone diaphyses; 3, synovial thickening bulging over the line linking tops of the periarticular bones and with extension to at least one of the bone diaphyses. The intra-articular power Doppler signal score was as follows: 0, no flow in the synovium; 1, single vessel signals; 2, confluent vessel signals in less than half of the area of the synovium; 3, vessel signals in more than half of the area of the synovium.

2.5. Safety evaluation

We collected all the adverse events during the study. Besides, the severity of the adverse events was recorded, together with the perceived relationship with the drug and the treatment. Meanwhile, the correlation between the severity and the medication was investigated.

2.6. Follow up

The patients were followed up once every 1 to 3 month. Recurrence of joint pain was recorded. The patients were followed up with the duration of 3 years.

2.7. Statistical analysis

Data analysis was used for the SPSS16.0 software. The continuous variables were presented as mean \pm standard deviation (SD). The paired Student's *t* test was used to compare the measurements of VAS, swelling, tenderness, synovial hyperplasia and power Doppler signal scores at different time points, and the Bonferroni method was used to adjust the test level. The corrected $P < .005$ was used.

3. Results

3.1. Patient characteristics

In total, 30 cases (male: 7; female: 23; 18–70 years; mean age, 38.7 \pm 2.8 years) admitted to our department of Yantai Yuhuangding Hospital were included in this study. The disease course duration was in a range of 0.6 to 10 years (2.7 \pm 0.6 years). Seventeen (56.67%) showed positivity for the rheumatoid factor, and twenty-three (76.67%) showed positivity for the anti-cyclic citrullinated peptide antibodies. A total of 39 joints (wrist: 21; MCP: 6; PIP: 12) had intractable arthritis.

3.2. Comparison of VAS, swelling, tenderness, synovial hyperplasia and power Doppler signal scores

In regards to the longitudinal views of the dorsal part of the wrists, significant decrease was noticed in the thickness and blood flow signals of the synovial membrane at post-treatment

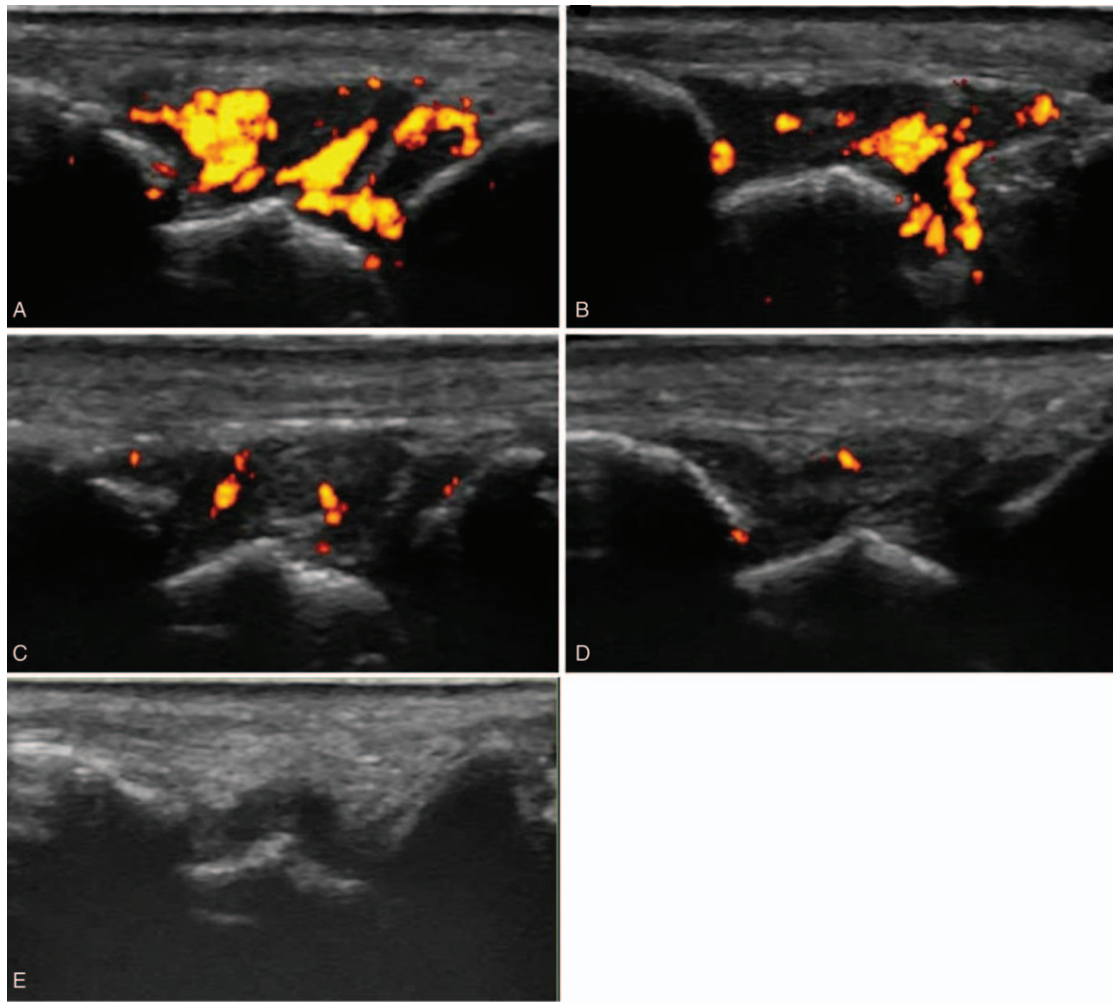


Figure 1. A 44-year-old male RA patient with a course of 2 years presented to our department for treatment. The symptoms showed attenuation after treating with methotrexate and iguratimod, but swelling pain was felt in the right wrist. (A) Longitudinal view of the dorsal part of the right wrist: grade 3 synovial hyperplasia and blood flow signals; (B–D) Blood flow signals at 24 hours, 1 week, and 4 weeks after intra-articular TA injection. (E) Synovial hyperplasia and blood flow signals at post-treatment 12 weeks. The synovial hyperplasia showed attenuation (grade 2) and no blood flow signals were observed.

24 hours, 1 week, 4 weeks, and 12 weeks compared with the baseline level (Fig. 1).

Table 1 showed the comparison for VAS, swelling, tenderness, synovial hyperplasia and power Doppler signal scores at pre-treatment and post-treatment 24 hours, 1 week, 4 weeks as well as 12 weeks, respectively. The VAS and tenderness scores showed

significant differences at 24-hours, 1 week, 4 weeks, and 12 weeks after treatment compared with the baseline levels ($P < .005$). The swelling score showed no changes at 24 hours after treatment compared with the baseline and showed significant differences at 1 week, 4 weeks, and 12 weeks after treatment ($P < .005$). Significant decrease was noticed in the

Table 1
Comparison of observed indices before and after treatment.

Variables	before and after the intervention				
	pre	post 24 h	post 1 w	post 4 w	post 12 w
VAS	6.41 ± 2.04	4.49 ± 1.65*	2.82 ± 1.68* [†]	1.31 ± 1.24* ^{†,‡}	0.54 ± 0.68* ^{†,‡,§}
Swelling	3.00 ± 0.00	2.92 ± 0.27	2.13 ± 0.41* [†]	1.08 ± 0.74* ^{†,‡}	0.62 ± 0.59* ^{†,‡,§}
Tenderness	5.64 ± 2.89	4.41 ± 2.26*	2.72 ± 1.86* [†]	1.28 ± 1.11* ^{†,‡}	0.82 ± 0.97* ^{†,‡,§}
Synovial hyperplasia	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00	1.95 ± 0.86* ^{†,‡}	1.49 ± 1.10* ^{†,‡,§}
Power Doppler signal	2.62 ± 0.49	1.85 ± 0.49*	1.08 ± 0.70* [†]	0.51 ± 0.60* ^{†,‡}	0.28 ± 0.46* ^{†,‡}

* $P < .005$ vs pre.
[†] $P < .005$ vs post 24 h.
[‡] $P < .005$ vs post 1w.
[§] $P < .005$ vs post 4 w.

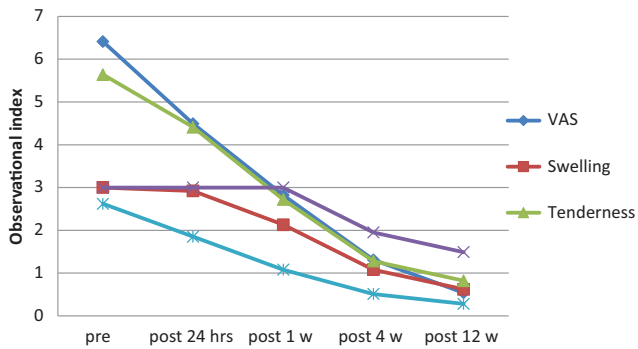


Figure 2. Dynamic changes of each observational index.

synovial hyperplasia score at 4 weeks and 12 weeks compared with the baseline level, while no statistical difference was noticed at post-treatment 24 hours and 1 week compared with the baseline level. Power Doppler signal score showed significant decrease at post-treatment 24 hours, which showed further decrease at 1 week and 4 weeks. The improvement was not obvious at post-treatment 12 weeks (Table 1). The changes of the observed indices were shown in Figure 2.

3.3. Safety evaluation

There were no infections at the injection sites and nearby tissues. No tendon tear was noticed. One case showed depigmentation at the puncture site, and such condition was relieved spontaneously 6 months later with no treatment.

3.4. Follow up of recurrence of swelling and pain in target joints

The follow-up duration was 3 years. Only two cases (6.67%) showed occurrence. A female patient showed attenuation of pain and swelling in the right second and third PIP joints after treatment. About 1.5 years later, she showed joint swelling and then received additional intra-articular injections, after which the conditions showed reduction. Since then, no recurrence was reported. A male patient showed right wrist flaring 8 months after injection following excessive wrist use. He showed symptomatic relief after application of non-steroidal drug. The other subjects showed no recurrence of joint swelling and pain during the follow-up.

4. Discussion

Many patients show persistent inflammation in the small joints despite attenuation in the symptoms after conventional standard therapy. Intra-articular injection of DMARD and/or glucocorticoid has been reported to attenuate the disease conditions.^[8,9] However, no clinical trials have been conducted to investigate whether single intra-articular injection could management the small joints inflammation, with an aim to attenuate the conditions without adjusting the treatment regimen and avoid the adverse events and treatment cost induced by adding or changing the drugs.

Several drugs have been used for the intra-articular injection such as glucocorticoid, methotrexate, hyaluronic acid and hyaluronate sodium. Recently, several biological agents have

been also utilized for the intra-articular injection, which confirmed to be effective for the disease.^[10–15] In a case report, intra-articular Botulinum toxin A as an adjunctive therapy benefited to the patients with refractory joint pain.^[16] Meanwhile, intra-articular injection of platelet-rich plasma (PRP) and mesenchymal stem cell (MSCs) contributed to the attenuation of inflammation, but further large sample studies are needed to investigate the safety and efficiency of these treatment regimens.^[17–19]

To date, most of the studies of intra-articular injection have been carried out in knee joints,^[13,14,20–24] while only a small number of studies are carried out in the small joints.^[15,25] This may be related to the difficulty of small joint puncture, especially the administration of hormones. In certain cases, injection of hormones into the adjacent tendon and tissues may induce tendon rupture, which may hamper the treatment efficiency. Sonographic needle guidance can significantly improve the performance and outcomes of IA injections.^[26] Unlike the previous study by Pereifa et al,^[15] in our clinical practice, we tried to perform the small joint puncture at the sites with obvious synovial hyperplasia under the sonographic guidance. On this basis, the drugs could be injected into the joint cavity with no puncture failure. No severe side events (e.g., tendon rupture) were noticed. These indicated that ultrasound guided intra-articular injection was effective for treating small joint lesions. For the side events, one patient showed puncture site depigmentation, which may be related to the increased intra-articular pressure after injection and subsequent incorrect pressure resulting in drug extravasation into the skin. On this basis, in our future procedures, we would inform the patients about accurate compressing the puncture sites, with an aim to avoid similar complications.

The treatment efficiency of intra-articular injection is highly relied on the changes of clinical symptoms and signs, VAS visual score, DAS28 score, as well as the alternations of inflammation indicators. Recently, increasing studies have been focusing on the evaluation of treatment outcome of RA, with the advances of musculoskeletal ultrasound.^[25] The EULAR recommendations indicated that ultrasound was superior to clinical examination in regard to the detection of joint inflammation.^[27] For the ultrasonic parameters, hydrops thickness, synovial thickness and power Doppler signals were considered to be important.^[25] In this study, semi-quantitative evaluation based on the synovial hyperplasia and power Doppler signal was carried out, which showed significant decrease in the power Doppler signals 24 hours, especially 1 week after steroid injection that could accurately reflect the disease changes. No significant change in the synovial hyperplasia score at the beginning of the treatment (1 week), but statistical decrease was noticed at 4 weeks and 12 weeks, respectively. Therefore, joint ultrasonic parameters could be used to evaluate the outcome of patients underwent joint cavity treatment, among which the power Doppler signal score showed a higher accuracy and sensitivity compared to the synovial hyperplasia score.

In this study, the patients' conditions showed rapid improvement 24 hours after treatment, which showed further improvement at 1 week, 4 weeks and 12 weeks after treatment. The occurrence rate was not high (6.67%). No case received re-treatment within 1 year, avoiding the risk of cartilage damage caused by repeated injection of corticosteroid therapy. The patients showed 1 or 2 small joints swelling, and showed attenuation after TA injection without changing the previous

treatment regimen. This contributed to the treatment efficiency without inducing additional expenditures or side events.

In a previous meta-analysis, intra-articular injection of TA was shown to provide clinical benefits for up to 6 months and even longer.^[28] Meanwhile, its treatment efficiency was comparable to that of the intra-articular injection of biological agents such as Etanercept.^[12] The recommended dose of TA in treating small joints was 20 mg in the wrist joint, 5 mg-10 mg in the MCP and PIP joint single injection.^[29] In this study, the patients showed obvious joint swelling in the wrist joints, MCP and PIP joints, together with 3 grade synovial hyperplasia. On this basis, we selected a higher dose compared to the previous study. Our data showed TA triggered clinical benefits significantly in a persistent manner without causing obvious side events.

Indeed, there are limitations in this study. Right now, we cannot confirm the exact dose for TA as a dose of 40 mg or 20 mg was reported to be effective in a previous description.^[15] In future, large sample sizes randomized clinical trials were needed.

5. Conclusions

In conclusion, ultrasound-guided intra-articular TA injection is effective for treating RA patients with refractory small joints arthritis without changing the original treatment plan. It shows satisfactory safety with less side events. Ultrasonography contributed to the small joint puncture of the RA patients, which contributes to the monitoring of the disease conditions.

Author contributions

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Supervision: Yanchun Tang.

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Visualization: Yanchun Tang.

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