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Radiosynoviorthesis of acromioclavicular joint using ^{169}Er-citrate: prospective evaluation of efficacy

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Abstract

BACKGROUND: There is a clinical need for therapeutic alternative in patients with persisting painful arthritis of AC-joint and failure of previous treatments. However, no radiopharmaceutical is currently explicitly approved for radiosynoviorthesis of acromioclavicular joint. The aim of our study was to prospectively assess the efficacy and safety of radiosynoviorthesis of acromioclavicular joint using erbium-169 citrate.

MATERIAL AND METHODS: Radiosynoviorthesis of acromioclavicular joint was performed in 51 consecutive patients (18 males, 33 females) mean age 64.3 (range 43.8–82.6, median 63.6) years with clinically confirmed arthritis of 85 acromioclavicular joints. The efficacy of RSO was reported by patients according to 10-step visual analogue scale of pain (VAS) (0 = no pain, 10 = most severe pain) at 6 months after radiosynoviorthesis and by ranking the global therapeutic effect of RSO in 4 categories (1 = the best effect, 4 = no change). To assess the variation of blood perfusion in treated joints, the efficacy of RSO was also evaluated by variation of target (acromioclavicular joint)/non-target (soft tissue) uptake ratio (T/NTR) of metylendiphosphonate (^{99m}Tc) measured as number of counts over region of interest on blood pool phase of two-phase bone scintigraphy performed before and 6 months after RSO.

RESULTS: Radiosynoviorthesis was followed by significant decrease in VAS, mean — 3.1 (-47%). Excellent, good, moderate and bad response was observed in 57 (67%), 25 (29%), 1 (1%) and in 2 (2%) of acromioclavicular joints respectively. A significant correlation between decrease of T/NTR and variation of VAS in % ($\rho = 0.532$, $p < 0.0001$) and between T/NTR and subjective evaluation of therapeutic effect in scale 1–4 ($\rho = 0.388$, $p = 0.0002$) was observed. However, it was not possible to identify the cut-off value of relative decrease in T/NTR showing sufficient sensitivity and specificity to detect the therapeutic response.

CONCLUSION: Results of this prospective study permit to conclude a good efficacy and safety of radiosynoviorthesis using erbium-169 citrate in a series of patients with arthritis of acromioclavicular joint in whom previous line(s) of treatment did not lead to satisfactory pain relief.

KEY words: radiosynoviorthesis, arthritis, acromioclavicular joint, ^{169}Er-citrate, pain relief

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Introduction

Acromioclavicular joint (AC-joint) as a part of the shoulder girdle complex permits in conjunction with the sternoclavicular joint the clavicular rotation and gliding into antero-posterior direction. These two articulations represent the only articulation between the shoulder girdle, the upper extremities and the trunk. During normal activities of daily living the AC-joint experiences significant loading on small surface and is frequently subjected to trauma as well.

Furthermore, as other synovial articulations, AC-joint can be involved in rheumatoid arthritis and the seronegative arthropathies. In case of persisting seropositive or seronegative arthritis despite previous treatments including intraarticular administration of corticosteroids, surgical, chemical or radiation synovectomy of inflamed hypertrophic synovial membrane can be proposed. To avoid surgical synovectomy, several drugs were proposed for chemical synovectomy, e.g. rifampicin [1] or osmium acid [2]. The main drawback of the chemical synovectomy is its painfulness and

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relatively low long-term response rate [2]. The bibliographic data support the intraarticular administration of appropriate β^- emitting therapeutic radiopharmaceutical (RSO) as the simple, mini-invasive and effective therapeutic option performed in out-patients for the local treatment of arthritis, without need for anaesthesia or long rehabilitation [3–5]. The low tissue penetration of β^- particles up to 10 mm minimizes the radiation absorbed dose to non-target tissue. The absorbed dose of radiation about 100 Gy leads to a synovectomy similar to surgical synovectomy [6]. The leakage rate is low, if the joint is immobilized and if particles with an appropriate size of 5–10 μm are used [5, 7, 8]. The pain reduction typically occurs up to 4 weeks after RSO. In approximately 3 months the radiation leads to reducing of effusion, an inflammatory process and a fibrosis of synovia. If necessary, the procedure can be repeated, but not earlier than 6 months after previous RSO; two failed RSOs should not be followed by subsequent one [5].

According to the guideline of the European Association of Nuclear Medicine, candidates for RSO should have been under a six-month systemic treatment without encouraging results or should have undergone at least one unsuccessful intra-articular injection of a long acting glucocorticoid [5]. However, earlier in the course of the disease the RSO is indicated, the better results can be expected [8].

Several radiopharmaceuticals are currently approved in several European countries for RSO: yttrium-90 for knee, rhenium-186 for medium joints (e.g. ankle, shoulder, elbow, and wrist) and erbium-169 for small joints (e.g. fingers, metacarpophalangeal and metatarsophalangeal joints). Radionuclides with higher energy of β^- particles and longer soft tissue range (^{90}Y, ^{186}Re) are used for RSO of large/medium articulations and the radionuclides with lower energy of β^- particles and shorter soft tissue range (^{169}Er) are used for RSO of small articulations.

No radiopharmaceutical is currently explicitly approved for RSO of AC-joint. However, there is an unmet clinical need for therapeutic alternative in patients with persisting painful arthritis of AC-joint and failure of previous treatment(s).

The documented efficacy of RSO in significant proportion of patients (average response 73 ± 17%) [8] with persistent chronic arthritis despite previous line(s) of treatment including intraarticular administration of corticosteroids encouraged us to launch this first prospective study of feasibility, efficacy and safety of RSO in arthritis of AC-joint.

The aim of our study was to prospectively assess the efficacy and safety of RSO of AC-joint using erbium-169 citrate.

Material and methods

The inclusion criteria for performing RSO using ^{169}Er-citrate were pain and clinically confirmed persistent arthritis of AC-joint during more than 6 months, failure of previous systemic treatment, availability of two-phase bone scintigraphy (BS) consisting of blood pool imaging (BPI) phase and bone phase less than 2 months prior RSO with increased tracer uptake in concerned AC joint observed on BPI phase.

The underlying cause of aseptic arthritis of AC joint (e.g. rheumatoid arthritis vs. osteoarthritis) was not taken into consideration.

The exclusion criteria for performing RSO using ^{169}Er-citrate were persisting pain less than 6 months, negative finding on BPI phase of two phase bone scintigraphy, personal history of traumatism of concerned shoulder, pregnancy, breast feeding and age less than 18 years.

Prior RSO, all patients gave their written consent.

The control two phase BS was performed 4–8 months after RSO.

The efficacy of procedure was subjectively reported by patients; the criterion for efficacy of RSO was relief of pain assessed prior RSO and during follow up at 6 months using a 10-step visual analogue scale of pain (VAS) [9]. The VAS was divided into 10 steps, from a level of no-pain (scale 0) to most severe pain imaginable (scale 10). The pain was documented by nuclear medicine physician in conjunction with referring physician; a pain relief by more than 2 steps on the VAS lasting for 12 consecutive weeks was used as a criterion for response. The variation of VAS in percent before and after RSO was assessed.

The global effect of RSO was ranked by patients in 4 subjective categories adapted according to Liepe et al. [10]: excellent response (no symptoms, score 1); good response (significant reduction of symptoms, score 2); moderate response (slight decrease, score 3); and bad response (no change or worsening, score 4), of pain in treated joint 6 months after procedure.

To assess the variation of blood pool perfusion in treated joints, the efficacy of RSO was also evaluated by variation of target (AC-joint)/non-target (soft tissue) uptake ratio (T/NTR) of metylendiphosphonate-^{99m}Tc. For this assessment, the following approach was used: the average count rate was calculated in manually drawn circular region of interest (ROI) covering the area of increased tracer uptake in the area of AC joint (target) on anterior view of pre-RSO planar BPI (Figure 1A). The average count rate was also calculated in corresponding ROI (target) on anterior view of post-RSO planar BPI (target) (Figure 1E). The activity of background (non-target) was calculated as the average count rate in manually drawn elliptic ROI on anterior view of pre- and post-RSO planar BPI (Figure 1A, E), covering approximately middle third of soft tissue of left femur excluding the large vessel area.

The T/NTR and the variation of T/NTR in percent on pre- and post-RSO BPI were subsequently calculated.

The statistical analysis was performed using software MedCalc v17.6. For determining a significant change in the VAS and in T/NTR, the non-parametric Wilcoxon's test was used to compare unpaired or paired quantitative data, respectively. A probability level $p < 0.05$ was considered significant.

RSO of AC-joint

Given the size of AC-joint (comparable with that of small joints of hand or feet), the ^{169}Er-citrate was designed as an optimal radiopharmaceutical in this indication [11].

After fluoroscopic verification of needle position, 0.1 mL of contrast agent was intra-articularly administered of to confirm the intraarticular position of the needle (Figure 1C).

Subsequently the activity of 37 MBq of ^{169}Er-citrate (CIS bio International, Gif-Sur-Yvette, France) in a volume of 0.1 mL was administered and the needle was flushed by 0.1 mL of triamicinolone (20 mg/mL) (Figure 1D). After procedure the puncture site was sterilely covered and the shoulder was immobilised for 48 hours. It was recommended to not to overload the treated extremity during 7–10 days following procedure.

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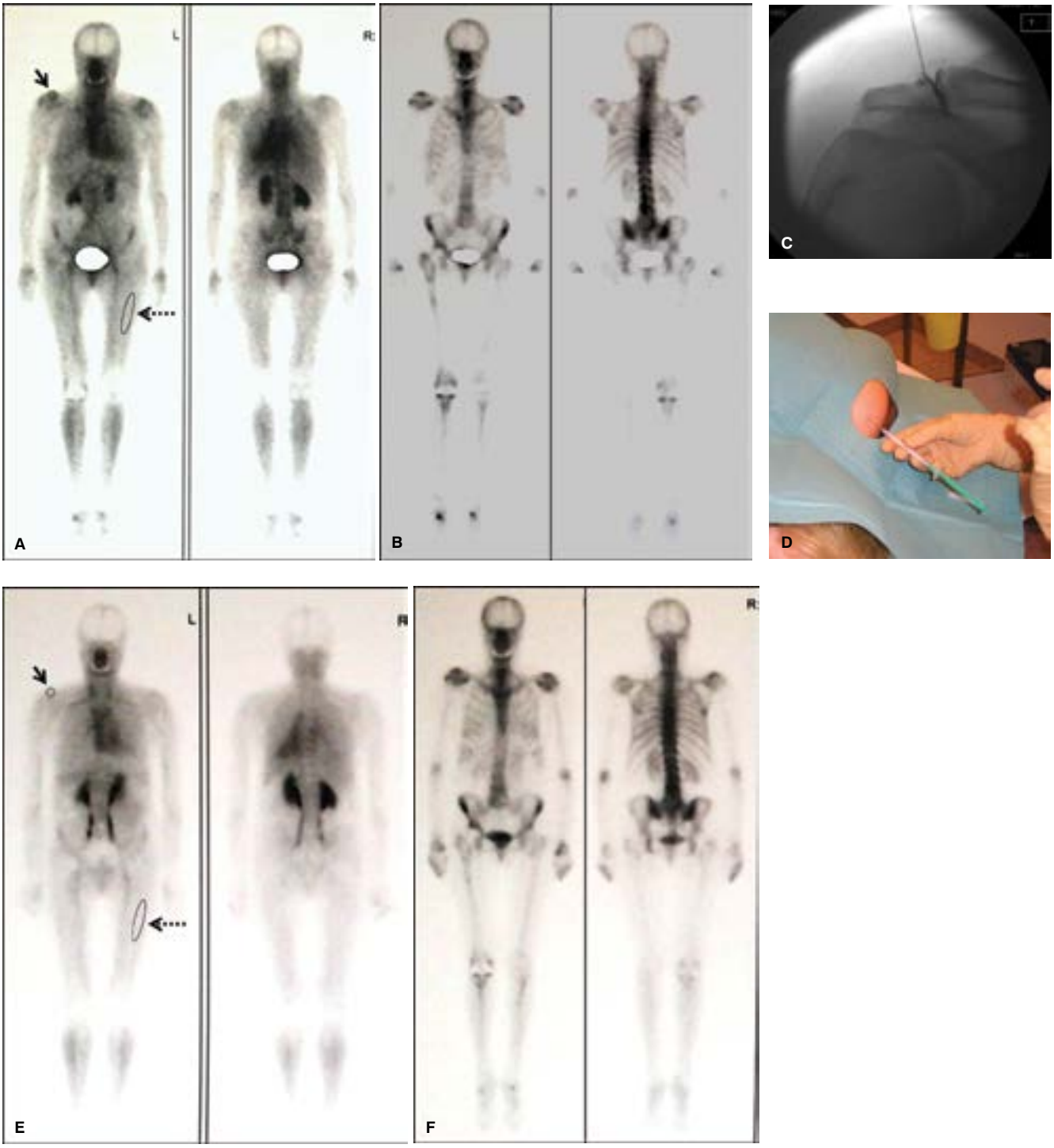

Figure 1. A case of 58-years old female patient with polyarthritis. Two-phase bone scintigraphy with 519 MBq of ^{99m}Tc-metylenbisphosphonate including blood pool imaging phase (**A**) and bone phase (**B**); Whole body anterior (left) and posterior (right) views confirmed increased blood pool and increased osteoblastic activity in both AC (more pronounced on the right side), both I. carpometacarpal joints and in metatarsophalangeal joints on both sides; prosthesis of right hip and right knee. The RSO of right AC joint was indicated. After intraarticular instillation of 0.1 mL of contrast agent to confirm optimal needle position (**C**) the syringe was changed and ^{169}Er-citrate was administered into articular cavity (**D**). After next change of syringes, the needle was flushed by 0.1 mL of triamicinolone 20 mg/mL. Six months after RSO of right AC joint the patient reported decrease in VAS from 8 to 2 and global effect of treatment was ranked as excellent. Follow-up two-phase BS was performed 6 months after treatment: BPI phase (**E**) and bone phase (**F**); Whole body anterior (left) and posterior (right) views. For calculation of target/non target ratio, the circular region of interest was drawn in the area of increased tracer uptake in the area of AC joint (target) (**A, E** arrow) and elliptical region of interest (non-target, background) (**A, E** dashed arrow) covering approximately medial third of soft tissues of the left femur, avoiding area of large vessels was drawn, both on planar anterior view of BPI. On semiquantitative assessment of blood pool perfusion of AC joint prior and after RSO the target/non target ratio decreased from 1.39 to 1.14 (by 17%). Persistent osteoblastic activity in both acromioclavicular joints (**B, F**), still more pronounced on the right side

Results

Between March 2008 and December 2014, the RSO of clinically confirmed arthritis of AC-joint was performed in 51 patients (18 males, 33 females) mean age 64.3 (range 43.8–82.6, median 63.6) years.

Two-phase bone scintigraphy using ^{99m}Tc-metylenbisphosphonate including BPI and bone phase was performed in all patients.

A total of 85 AC-joints were treated: 69 AC-joints were treated once, 12 AC-joints were treated twice, 3 AC-joints were treated three times, and one AC-joint was treated four times. Both left and right AC-joints were treated in 18 patients.

The therapeutic effect of RSO was assessed 6 months after the treatment.

Prior RSO, no significant difference between 10-step VAS level in patients referred for first or for repeated RSO of the same AC-joint was observed ($p = 0.15$). In patients in whom both AC-joints were treated there was no significant difference between VAS level for the left and right AC-joint ($p = 0.84$).

The criterion for efficacy of RSO was pain relief assessed in a 10-step VAS during follow up at 6 months after RSO, the decrease by more than 2 steps being considered as therapeutic response. The results are summarised in Table 1.

Overall, the RSO led to a significant decrease in VAS. Mean VAS prior RSO was 6.5 (range 3–10, median 6) vs. 3.4 (range 0–8, median 3) after treatment ($p < 0.0001$). The response to RSO was significantly more pronounced in patients referred for first RSO ($n = 69$) than in repeated RSO of the same articulation ($n = 16$); mean variation of VAS in patients referred for one single RSO was -3.2 (-50%) vs. -2.3 (-39%) in patients referred for repeated RSO ($p = 0.02$ (0.049)).

The interval between two consecutive RSO was mean 7 (range 4.6–14.5, median 6) months.

The global subjective effect of RSO was assessed by patients in 4-grade scale. Excellent response or no symptoms of pain (score 1) was observed in 57 (67%) (48 first and 9 repeated RSO), good response or significant reduction of symptoms of pain (score 2) in 25 (19 first and 6 repeated RSO) (29%), moderate response

Table 1. Visual analogue scale of pain and variation of target/non-target ratio prior and after radiosynoviorthesis of acromioclavicular joint and subjective evaluation of radiosynoviorthesis of each treated acromioclavicular joint

Number of treated AC-joints	Overall n = 85	1st RSO n = 69	2nd RSO of the same AC-joint n = 12	3rd RSO of the same AC-joint n = 3	4th RSO of the same AC-joint n = 1
VAS prior RSO	Mean 6.4	Mean 6.6	Mean 5.8	Mean 6.3	8
	Range 3–10	Range 3–10	Range 4–7	Range 5–7	
	Median 6	Median 6	Median 6		
VAS after RSO	Mean 3.4	Mean 3.2	Mean 3.5	Mean 3.7	6
	Range 0–8	Range 0–8	Range 2–5	Range 3–5	
	Median 3	Median 3	Median 3.5		
Variation of VAS	Mean -3.1	Mean -3.2	Mean -2.3	Mean -2.7	-2
	Range 0 to -9	Range 0 to -9	Range 0 to -4	Range -2 to -4	
	Median -3	Median -3	Median -2	Median -2	
Variation of VAS in %	Mean 47%	Mean -50.3%	Mean -39.5%	Mean -42%	Mean -25%
	Range -50% to -100%	Range -100% to 0%	Range -67% to 0%	Range -57% to -29%	Median -25%
	Median -43%	Median -50%	Median -40%	Median -40%	
VAS prior vs. after RSO	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	—	—
Subjective evaluation 1-4	Mean 3.6	Mean 3.7	Mean 3.4	Mean 3.7	Mean 3
	Median 4	Median 4	Median 4	Median 4	Median 3
T/NTR prior RSO	Mean 1.17	Mean 1.17	Mean 1.09	Mean 1.35	Mean 1.86
	Range 0.21–2.6	Range 0.21–2.6	Range 0.24–2.5	Range 0.54–2.6	Median 1.86
	Median 1.03	Median 1.15	Median 0.89	Median 0.9	
T/NTR after RSO	Mean 1.03	Mean 1.04	Mean 0.99	Mean 1.01	Mean 1.69
	Range 0.05–2.7	Range 0.05–2.7	Range 0.22–2.4	Range 0.47–1.95	Median 1.69
	Median 0.94	Median 0.95	Median 0.74	Median 0.62	
Variation of T/NTR prior vs. after RSO	Mean -11%	Mean -11%	Mean -4%	Mean -23%	Mean -9%
	Range -91% to -81%	Range -91% to -81%	Range -78% to -61%	Range -30% to -14%	Median -9%
	Median -0.1	Median -12%	Median -5%	Median -25%	
T/NTR prior vs. after RSO	$p < 0.0001$	$p < 0.0001$	$p = 0.5$	—	—

AC joint — acromioclavicular joint; RSO — radiosynoviorthesis; T/NTR — target/non-target ratio; VAS — visual analogue scale of pain; vs. — versus

or slight decrease of pain (score 3) in 1 (first RSO) (1%) and bad response or no change or worsening of pain (score 4) in 2 (1 first and 1 repeated RSO) (2%) of treated AC-joints.

No significant difference in subjective evaluation of effect in case of first or repeated RSO was observed.

The score of subjective effect of RSO was significantly correlated with variation of pain measured in 10-step VAS ($\rho = 0.487$ in case of first and $\rho = 0.478$ in case of repeated RSO, $p < 0.001$).

The target to background ratio (T/NTR) measured on BPI of the two-phase bone scintigraphy decreased by mean -11% (range -91% to +81%, median -10%).

A significant correlation between decrease of T/NTR and variation of VAS in % ($\rho = 0.532$, $p < 0.0001$) and between T/NTR and subjective evaluation of therapeutic effect in scale 1–4 ($\rho = 0.388$, $p = 0.0002$) was observed. However, it was not possible to identify the cut-off value of relative decrease in T/NTR permitting to detect the therapeutic response with sufficient sensitivity and specificity.

The RSO of AC-joint(s) was perfectly tolerated by all patients. No complications, side effects or adverse reactions were observed.

Discussion

To the best of our knowledge, this is the first study of efficacy and safety of RSO to reduce inflammatory pain of AC-joint in a series of patients.

In the context of lack of standard of truth to objectively determine the therapeutic response to RSO, similarly to other studies, the subjective parameters had to be proposed including the VAS to observe the pain [9, 10] or ranking method subdividing the therapeutic effect in excellent, good, moderate, and bad response [10, 12]. Considering the decrease in VAS by more than 2 as a criterion for RSO efficacy, the response rate at 6 months in our series of patients in whom previous line(s) of treatment have failed was 47/85 (55%). The global evaluation of the effect of RSO by patients was excellent or good (score 1–2) by 82 (97%) of patients.

In arthritis of small articulations of hand and feet treated by ^{169}Er-citrate, the pooled patient´s global evaluation of the effect of RSO using ^{169}Er-citrate was excellent or good in 187/344 (54%) in the study of Liepe [10] vs. 82 (97%) of patients in our study, suggesting also eventual differences in subjective perception of pain concerning different joints (e.g. pain of small articulations of hand and feet vs. pain of AC-joint).

Increased articular blood pool perfusion in patients with rheumatologic conditions is indicative of active inflammation and has been suggested as a strong predictor of response to RSO [13]. In patients with rheumatoid arthritis and osteoarthritis, the clinical and scintigraphic outcomes were observed mainly in joints with decreasing blood pool indices and the response to RSO according to BPI was associated with subjective response in 129/157 (82.2 %) in the study of Zuderman et al. [13], underlining the BS as a valuable tool for monitoring RSO efficacy [8, 13]. In our study the two-phase BS including BPI and bone phase was performed less than 2 months prior and 4–8 months after RSO. The T/NTR decreased by mean -11% (range -91% to +81%, median -10%); a significant correlation between decrease of T/NTR and variation of VAS in % as well as between T/NTR and subjective evaluation of therapeutic effect in scale 1–4 was observed ($p < 0.05$); however, similarly as in other studies, it was not possible to identify the cut-off value of T/NTR variation permitting to identify a therapeutic response with sufficient sensitivity and specificity.

In our series, a corticosteroid was administered during RSO. Using the similar approach the RSO of small articulations of hand resulted in good therapeutic effect in 25/36 (69%) of patients at 6 months [14] and 128/154 (83%) of patients at 12 months [14, 15] vs. 131/157 (83%) of patients at 6 months [12, 16, 17] and 135/186 (73%) of patients at 12 months [12, 16, 18] when RSO was performed using ^{169}Er-citrate alone, suggesting from pooled data of therapeutic effect at 12 months a significantly more frequent response to ^{169}Er-citrate+corticosteroid than to ^{169}Er-citrate alone ($p = 0.019$).

In case of persistent symptoms, repeated RSO can be repeated after 6 months; two failed RSOs should not be followed by subsequent administration of radionucliude [5].

Intraarticular treatment of persistent arthritis of AC joint by local instillation of corticosteroids is not a part of routine practice; therefore our data on efficacy of RSO of AC joint cannot be compared with systematic data on efficacy of local intraarticular treatment by corticosteroids.

In our series, after careful consideration, the RSO of the same AC-joint was performed more than twice in four patients: in 3 patients three times and in 1 patient four times. In all cases the repeated RSO was performed within 6–14.5 months; the variation in VAS six months after each respective procedure was -2 in three cases and -4 in one case. The repeated procedure was perfectly tolerated in all cases; patients quoted the global efficacy of procedure as excellent response in two cases and good response in two cases and the T/NTR decreased by -9% to -25%.

From dosimetry point of view the intraarticular administration of 20–80 MBq of ^{169}Er-citrate into trapeziometacarpal joint, in the absence of extra-articular diffusion leads to radiation dose of 1820–7280, 660–2640, 260–1040 and 100–400 Gy at 0.1, 0.2, 0.3 and 0.4 mm respectively. With intraarticular administration of 80 MBq of ^{169}Er-citrate and with an assumed accumulation of 3% in the regional lymph nodes, radiation exposure in the lymph nodes can vary between 45.6 and 11.5 Gy for 1–4 accumulating lymph nodes. The whole body effective dose after intra-articular application of 20–80 MBq of ^{169}Er-citrate is 1.65–6.6 mSv with an assumed activity leakage from the joint of not more than 10% [11].

The maximal recommended activity of ^{169}Er-citrate to be administered to one joint is 80 MBq (i.e. 160 MBq in case of two consecutive administrations within interval of more than 6 months) [11]. In our series, the constant activity of 37 MBq (corresponding to 46% of maximal recommended activity) was administered at each RSO. Therefore, the total activity in patients receiving more than two RSOs of the same AC-joint ranged between 111 and 148 MBq corresponding to 69–93% of total cumulative recommended activity for two consecutive administrations. In the study of Manil et al. [19] the biological dosimetry of ^{169}Er-citrate measured by scoring dicentrics in lymphocytes cultured from blood samples withdrawn just before and 6 hours, 24 hours and 7 days after RSO was negative in all 18 interpretable patients.

It is debatable whether higher administered activities of ^{169}Er-citrate in RSO of AC-joint would lead to better therapeutic effect. No such data are currently available.

Finally, RSO of AC-joint using ^{169}Er-citrate is an affordable procedure. From our experience, the overall costs of RSO of one

AC-joint in are estimated on 180 €, including 130 € for ^{169}Er-citrate and 50€ for disposable material.

A limitation of present pilot study consist in impossibility of evaluation of therapeutic effect of RSO of AC joint according to underlying cause of arthritis (e.g. rheumatoid arthritis vs. osteoarthritis). However, in our heterogeneous series of patients not responding to previous treatments, the favourable results of RSO of AC joint encourage further evaluation of its efficacy according to underlying aetiology of aseptic arthritis.

Conclusion

The results of this first prospective study of therapeutic effect of radiosynoviorthesis of acromioclavicular joint using ^{169}Er-citrate in a series of patients with clinically confirmed arthritis of AC-joint permit to conclude the perfect tolerability in all patients and a good therapeutic efficacy in more than half patients in whom previous line(s) of treatment did not lead to satisfactory pain relief.

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

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