^{169}Erbium-citrate synoviorthesis after failure of local corticosteroid injections to treat rheumatoid arthritis-affected finger joints

A. Kahan[1], G. Mödder[2], C.J. Menkes[1], P. Verrier[1], J.-Y. Devaux[4], A. Bonmartin[5], Y. De Rycke[6], L. Manil[6], F. Chossat[7], J. Tebib[3]

[1]Paris V University, Rheumatology A Department, Hôpital Cochin, AP – HP, Paris, France; [2]Nuclear Medicine, Max Planck Institute, Köln-Marsdorf, Germany; [3]Rheumatology Department, Centre Hospitalier Lyon-Sud, Lyon; [4]Paris V University, Nuclear Medicine Department, Hôpital Cochin, AP – HP, Paris; [5]Nuclear Medicine Department, Centre Hospitalier Lyon-Sud, Lyon; [6]Consultants for Schering – CIS bio international, Gif-sur-Yvette; [7]Schering – CIS bio international, Gif-sur-Yvette, France.

Abstract

Objectives

Intra-articular injection of ^{169}Erbium-citrate (^{169}Er-citrate; radiosynoviorthesis or radiosynovectomy) is an effective local treatment of rheumatic joint diseases. However, its efficacy in corticosteroid-resistant rheumatoid arthritis-affected joints has not been clearly demonstrated.

Methods

A double-blind, randomised, placebo-controlled, international multicentre study was conducted in patients with rheumatoid arthritis with recent (≤ 24 months) ineffective corticosteroid injection(s) into their finger joint(s). Eighty-five finger joints of 44 patients were randomised to receive a single injection of placebo (NaCl 0.9%) or ^{169}Er-citrate. Results of evaluation 6 months later were available for 82 joints (46 metacarpophalangeal and 36 proximal interphalangeal joints) of 42 patients: 39 ^{169}Er-citrate-injected joints and 43 placebo-injected joints. Efficacy was assessed using a rating scale for joint pain, swelling and mobility.

Results

Intent-to-treat analysis of the results of the 82 joints showed a significant effect of ^{169}Er-citrate compared to placebo for the principal criteria decreased pain or swelling (95 vs 79%; p = 0.038) and decreased pain and swelling (79 vs 47%; p = 0.0024) and for the secondary criteria decreased pain (92 vs 72%; p = 0.017), decreased swelling (82 vs 53%; p = 0.0065) and increased mobility (64 vs 42%; p = 0.036). Per-protocol analysis, excluding 18 joints of patients who markedly changed their usual systemic treatment for arthritis, gave similar percentages of improvement but statistical significance was lower owing the reduced power of the statistical tests.

Conclusion

These results confirm the clinical efficacy of ^{169}Er-citrate synoviorthesis of rheumatoid arthritis-diseased finger joints after recent failure of intra-articular corticotherapy.

Key words

Radiosynoviorthesis, erbium, rheumatoid arthritis.

André Kahan, MD; Gynter Mödder, MD; Charles Joël Menkes, MD; Pierre Verrier, MD; Jean-Yves Devaux, MD; Alain Bonmartin, MD; Yann De Rycke, MD; Luc Manil, MD; Florence Chossat, MD; Jacques Tebib, MD.

Please address correspondence to: Professeur André Kahan, Hôpital Cochin, Service de Rhumatologie A, 27 rue du Faubourg Saint Jacques, 75014 Paris, France.
E-mail: andre.kahan@cch.ap-hop-paris.fr

Introduction

Rheumatoid arthritis is a chronic disease characterized by an inflammation of the peripheral joints. The inflammation with hyperproliferation of cells and hypervascularisation of the synovial membrane leads to a progressive destruction of joints (1–3). The evolution of the disease may be severe with gradual loss of joint functions (4, 5).

Drugs are used to control the pain, to decrease inflammation and to modify the natural evolution of the disease (6). NSAIDs, aspirin and analgesics allow the reduction of joint pain, stiffness and swelling. Disease-modifying anti-rheumatic drugs (DMARDS) aimed at modifying the disease include methotrexate, sulfasalazine, antimalarial agents (hydroxychloroquine), gold salts, D-penicillamine, cyclosporin A, azathioprine, leflunomide, TNF-inhibitors and anakinra. Corticosteroids induce a rapid anti-inflammatory effect; a reduction in radiographic destruction has also been reported with low-dose corticosteroid therapy. If some joints remain inflamed despite systemic therapy, local treatments are prescribed. The most common first-intention local treatment is intra-articular injection of corticosteroids, which usually provides pain relief and diminished inflammation. When drugs are unsuccessful, surgical or arthroscopic synovectomy might help to reduce inflammation and to maintain joint function (7).

Synovectomy by intra-articular injection of β-emitting radioisotopes (also called radiosynovectomy or radiosynoviorthesis) was proposed in the 1960s as an efficient means to destroy proliferating inflammatory synovial membrane. For small joints, ^{169}Erbium (^{169}Er) was shown to be the best adapted. This radionuclide is an almost pure beta-ray emitter with a half-life of 9.4 days. The mean range of beta-ray penetration into soft tissues is 0.3 mm and the maximum range is 1 mm (8).

Combined with prednisolone, ^{169}Er-citrate injection into rheumatoid arthritis-affected finger joints was shown, in a double-blind clinical trial, to give significantly better results than prednisolone alone (9). Moreover, in another double-blind study, pain and inflammation of rheumatoid arthritis joints were more effectively reduced by ^{169}Er-citrate than placebo (10). A more recent retrospective study indicated that ^{169}Er synoviorthesis was an effective treatment of rheumatoid arthritis in patients who did not respond to local corticosteroid therapy (11).

The present controlled prospective study was undertaken to evaluate the efficacy of an injection of ^{169}Er-citrate versus placebo in rheumatoid arthritis-affected joints that had recently failed to respond to local corticosteroid treatment.

Materials and methods

Patients

Patients with rheumatoid arthritis were included in 3 centres (two in France and one in Germany). All patients met the criteria established by the American Rheumatism Association (2). Only metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints that had never been subjected to radiosynoviorthesis or surgery of the joint and had recently (≤ 24 months) failed to respond to intra-articular corticosteroid injection were eligible. This failure could be primary (no relief of symptoms) or secondary (relapse of the symptoms after a transient relief of symptoms for < 3 months). Eighty-five joints from 44 patients who signed an informed consent were randomised and 83 joints (43 patients) were injected with placebo or ^{169}Er-citrate. Evaluation data obtained 6 months later were available for 82 joints (46 MCP and 36 PIP joints of 42 patients). The randomised and treated study population was composed of 40 women and 3 men (mean age ± SD: 51.2 ± 13.1 years), whose mean disease duration was 87 ± 55 months. The mean time elapsed since the last corticosteroid joint injection was 6.7 ± 5.5 months. There was a primary or a secondary failure for 48 and 52% of the 85 randomised joints, respectively. No injection into the joints under investigation was allowed during the study. Concomitant treatments were authorised (oral corticosteroids, up to the equivalent of 10 mg of prednisone/day), but dose could not be changed dramatically during the observation period, except in case of absolute necessity. Concomitant

baseline treatments (expressed as percentages of the 85 randomised joints in placebo and active treatment groups, respectively) included low dose corticosteroids (78 and 66%), non-steroidal anti-inflammatory drugs (63 and 66%), analgesic drugs (32 and 25%), methotrexate (61 and 61%), hydroxychloroquine (39 and 30%), gold salts (12 and 16%), azathioprine (20 and 11%), cyclophosphamide (5 and 0%) or D-penicillamine (2 and 0%). No significant differences between the treatment groups was found for demographic, disease parameters and concomitant treatments.

Injection methodology

Intra-articular injections were performed under radiographic control after administration of a small amount of contrast medium. ^{169}Er-citrate was purchased from CIS bio international (Gif-sur-Yvette, France) as a colloidal suspension with an activity of 110 MBq/mL at the date of calibration. The placebo solution was a sterile apyrogenic and isotonic solution of 0.9% NaCl. The volume injected (using a 1-mL syringe) was 0.23 ± 0.50 mL corresponding to 28.0 ± 4.8 MBq in the 22 ^{169}Er-treated MCP joints and 0.14 ± 0.23 mL corresponding to 18.4 ± 3.1 MBq in the 17 ^{169}Er-treated PIP joints. Injected joints were immobilised with a splint for 48 h.

Randomisation and blinding

Each joint was randomly assigned to receive ^{169}Er-citrate or placebo. Randomisation was equilibrated (by groups of 4 joints) and stratified according to joint type (MCP or PIP) and centres (3 centres). In the case of multiple injections for a single patient, each joint was separately randomised. The placebo and ^{169}Er-citrate solutions were prepared and labelled so that the active compound could not be identified. All study participants were blinded to treatment assignment for the duration of the study.

Evaluation of the functional and radiological parameters of rheumatoid arthritis

Six months after the injection, disease manifestations were evaluated by the investigator (swelling and mobility) or by the patient under the investigator supervision (pain) using a 4-step rating scale (0: absence; 1: slight; 2: moderate; 3: severe). Improvement was defined as a decrease of at least one step of the score. Pain was also quantitatively evaluated using a 100-mm visual analog scale (0 mm: no pain; 100 mm: unbearable pain).

The radiological parameters were evaluated according to the Steinbrocker index, which distinguishes 4 grades for joint lesions (12). The evolution of the radiological signs was assessed using a 2-step rating scale (0: regression or stabilisation; 1: aggravation).

Statistical analyses

At baseline, comparability of the groups was assessed using a chi-square test or Student's t-test for qualitative or quantitative values, respectively. Intent-to-treat analysis was performed with patients who received injection and whose evaluation parameters were available at inclusion and at 6 months. Per-protocol analysis was performed for joints from the intent-to-treat analysis who did not dramatically modify their treatment. Two main criteria for efficacy were predefined: decreased pain or swelling and decreased pain and swelling. The secondary criteria were decreased pain assessed qualitatively and quantitatively, decreased swelling and increased mobility. The Mantel–Haenszel test was used to compare the qualitative values of assessment criteria between treatment groups, stratified according to joint type (MCP or PIP). A chi-square test (or Fisher's exact test) was used for comparisons of qualitative variables in MCP or PIP joint subgroups. A one-sided Student's t-test was used for between-group comparisons of quantitative variables (evaluation of pain). A p value ≤ 0.05 was considered significant.

Results

Effect of ^{169}Er-citrate 6 months after injection (intent-to-treat analysis)

At baseline, placebo and ^{169}Er-citrate groups were comparable for functional (pain, swelling and decreased mobility) and radiological (Steinbrocker index) signs of the disease (Table I).

Intent-to-treat analysis of the principal criteria, decreased pain or swelling and decreased pain and swelling on all joints demonstrated a significant effect of ^{169}Er-citrate vs placebo (Table II). Subgroup analysis for the former criterion according to joint type also indicated a significant effect of ^{169}Er-citrate (95%) as compared to placebo (71%; p = 0.032) on MCP joints, but not on PIP joints (94 vs 89%, respectively). Subgroup analysis for the other principal criterion decreased pain and swelling also indicated a significant difference on MCP joints (86 vs 37%; p = 0.0003) but not on PIP joints (70 vs 58%, respectively).

The evaluation of the secondary criteria for efficacy on all joints demonstrated significant therapeutic effects of ^{169}Er-citrate as compared to placebo on the qualitative evaluation of decreased pain, decreased swelling and increased mobility (Table II). Separate analysis of MCPjoints again showed significant improvement for ^{169}Er-citrate-treated patients for all three criteria and quantitative evaluation of decreased pain. However, no significant difference between treatment groups was found for PIPjoints.

No significant differences between the treatment groups concerning radiological signs were expected only 6 months after injection and data analysis confirmed this (data not shown).

Swelling and pain at the inclusion were not prognostic factors of efficacy at 6 months.

Effect of ^{169}Er-citrate 6 months after injection (per-protocol analysis)

The per-protocol analysis was based on 64 joints (30 in ^{169}Er-citrate-treated and 34 in placebo-treated groups). Indeed, a major modification of the systemic treatment (addition or suppression of treatment, change of dose) of some patients during the study led to the exclusion of 18 joints (9 in ^{169}Er-citrate-treated and 9 in placebo-treated groups). Per-protocol analysis for decreased pain and swelling of all joints showed ^{169}Er-citrate to be significantly more effective than the placebo (Table II). Its effect was also significantly better than

Table I. Baseline manifestations of rheumatoid arthritis patients randomised to receive ^{169}Er-citrate or placebo.

Manifestation	Er	P	Pvalue
Number of joints	39	44	
Pain (rating scale)[1], n (%)			
0	0 (0)	1 (2)	0.70
1	9 (23)	11 (25)	
2	27 (69)	27 (61)	
3	3 (8)	5 (11)	
Pain (visual analog scale in mm)[1], mean ±SD	42.2 ± 20.0	43.2 ± 20.7	0.83
Swelling (rating scale) [1], n (%)			
0	0 (0)	0 (0)	0.25
1	6 (15)	12 (27)	
2	22 (56)	25 (57)	
3	11 (28)	7 (16)	
Decrease of mobility (rating scale)[1], n (%)			
0	4 (10)	3 (7)	0.78
1	7 (18)	11 (25)	
2	23 (59)	23 (52)	
3	5 (13)	7 (16)	
Radiological signs for joint lesions (Steinbrocker index)[2], n (%)			
1	2 (5)	5 (11)	0.29
2	26 (67)	26 (59)	
3	9 (23)	13 (30)	
4	2 (5)	0 (0)	

[1] 0: absence; 1: slight; 2: moderate; 3: severe. [2] Classification according to (10). Er: ^{169}Er-citrate; P: placebo.

placebo in MCP joints (93 vs 50%; p = 0.01), but no difference was found between groups for PIPjoints (67 vs 56%, respectively; p = 0.28). No significant differences could be established for decreased pain or swelling for all joints or according to joint type (data not shown).

Per-protocol analyses of the secondary criteria indicated a significant therapeutic effect of ^{169}Er-citrate as compared to placebo only for the qualitative evaluation of decreased pain (Table II), while subgroup analysis revealed significant effects of ^{169}Er-citrate on MCP joints for decreased swelling (93 vs 61%, respectively; p = 0.04), increased mobility (73 vs 39%; p=0.024) and qualitative evaluation of decreased pain (100 vs 67%; p = 0.017). No significant differences were observed between treatment groups for any of the secondary parameters for PIPjoints.

Safety

Joint injections were well tolerated. Only transient pain or swelling after injection occurred in 5 PIP joints (2 patients) which did not require treatment: 2 injected with ^{169}Er-citrate and 3 with placebo.

Discussion

Based on the results of a retrospective study (11), ^{169}Er-citrate synoviorthesis was previously reported to be effective in rheumatoid arthritis patients after failure of intra-articular corticotherapy. Six months after ^{169}Er-citrate injection into digital joints, pain was decreased for 95% of the joints, mobility was improved for 83% and joint swelling was reduced for 83% (11). These results warranted confirmation in a controlled, prospective clinical trial. Indeed, after failure of intra-articular corticotherapy, few therapeutic options remain and radiosynoviorthesis is the only one that avoids surgical synovectomy, arthroplasty or arthrodesis. Consequently, we selected rheumatoid arthritis patients

Table II. Intent-to-treat and per-protocol analyses of a ^{169}Er-citrate versus placebo injection into the finger joints of rheumatoid arthritis patients 6 months after treatment.

Parameters	Intent-to-treat analysis									Per-protocol analysis		
	All joints			MCP			PIP			All joints		
	Er	P	p	Er	P	p	Er	P	p	Er	P	p
Number of joints	39	43*		22	24		17	19		30	34	
Principal criteria												
Decreased pain or swelling, %	95	79	0.038	95	71	0.032	94	89	0.54	97	82	0.081
Decreased pain and swelling, %	79	47	0.0024	86	37	0.0003	70	58	0.21	80	53	0.023
Secondary criteria												
Decreased swelling, %	82	53	0.0065	91	50	0.0013	71	58	0.21	80	59	0.055
Increased mobility, %	64	42	0.036	64	29	0.0095	65	58	0.34	67	44	0.062
Decreased pain												
Qualitative evaluation, %	92	72	0.017	91	58	0.006	94	89	0.54	97	76	0.028
Quantitative evaluation, mm	32	25	0.1	31	18	0.03	34	35	NA	31	25	0.14

NA: not applicable because a unilateral test was used; Er: ^{169}Er-citrate; P: placebo; MCP: metacarpophalangeal joints; PIP: proximal interphalangeal joints.
*Data from one joint from the placebo group were not available at 6 months.

with recent (≤ 24 months) failure to respond to local injections of corticosteroids.

Our present findings support the efficacy of radiosynoviorthesis on the clinical signs of rheumatoid arthritis-affected finger joints randomly assigned to receive ^{169}Er-citrate or placebo (Table II). Indeed, based on our intent-to-treat analysis, decreased pain or swelling, decreased pain and swelling (principal criteria) were significantly decreased for 95 and 79% of them, and secondary criteria, decreased pain (92%), decreased swelling (82%) and increased mobility (64%), were also significantly attenuated or improved.

However, a striking result of this trial was the strong placebo effect on clinical signs. Indeed, decreased pain or swelling was reported for 79% of the placebo-treated joints. Other criteria were also considered to be greatly improved in the placebo group: decreased pain and swelling (47%), decreased pain (72%), decreased swelling (53%) and increased mobility (42%). This placebo effect is particularly pertinent because these patients had previously failed to respond to intra-articular corticosteroid injections. One can wonder why this placebo effect was not observed for corticosteroid injections. A recent review article of the placebo effect on pain concluded that it seems to be unusually high in nuclear medicine (13). The authors suggested that patients undergoing such treatments are greatly impressed by nuclear medicine devices and procedures, and are thus prepared to feel more relief.

An unexpected and still unexplained result of this study is the stronger placebo effect on PIP than MCP joints, which prevented ^{169}Er-citrate treatment to rise above the background noise of the placebo effect. Nevertheless, the magnitudes of symptom attenuation or improvement of ^{169}Er-citrate-treated PIP joints were similar to those of MCP joints.

The per-protocol population excluded those patients included in the intent-to-treat population who markedly changed their usual systemic treatment for rheumatoid arthritis. The results obtained were similar to those of the intent-to-treat analysis (Table II), with ^{169}Er-citrate injection being significantly more effective than placebo in terms of decreased pain and swelling and the qualitative evaluation of decreased pain. However, because fewer joints were analysed, decreased swelling and increased mobility only tended towards statistical significance. Analysis of MCP joints showed that ^{169}Er-citrate injection led to significantly decreased pain and swelling, decreased pain, decreased swelling and increased mobility.

Future studies should attempt to differentiate the different results obtained with the two composite criteria, namely decreased pain or swelling and decreased pain and swelling since the placebo effect on the former was very high making it more difficult to demonstrate as significant. In contrast, the more stringent criterion decreased pain and swelling was able to better distinguish between active treatment and placebo, and thus reach statistical significance.

Injections of ^{169}Er-citrate in joints were well tolerated and only rare local events occurred without differences between treated groups. However, there are some concerns about possible long term effects of radiation after radiosynovectomy on incidence of cancer and leukaemia due to potential leakage of radionuclid from joints. In a dosimetry study, we did not evidence increase of chromosomal aberrations in lymphocytes from patients undergoing ^{169}Er-citrate radiosynoviorthesis (8). Moreover, a recent retrospective study over 30 years after knee radiosynoviorthesis with ^{90}Yttrium – another β-ray emitter – did not evidence an increase of cancer (14). Since the maximum penetration range of ^{90}Yttrium in tissues is 11 mm – to be compared to only 1 mm for ^{169}Er – one can hypothesize that the incidence of cancer and leukaemia induced by ^{169}Er is not higher than for ^{90}Yttrium.

In conclusion, these results confirm the clinical efficacy of radiosynoviorthesis with ^{169}Er-citrate on rheumatoid-arthritis finger joints after failure of intra-articular corticotherapy.

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