Rheumatol Int (1997) 17: 105–108

ORIGINAL ARTICLE

D. Göbel · S. Gratz · T. von Rothkirch · W. Becker
H.-G. Willert

Radiosynoviorthesis with rhenium-186 in rheumatoid arthritis: a prospective study of three treatment regimens

Received: 29 October 1996 / Accepted: 10 June 1997

Abstract The aim of this study was to evaluate the efficiency of radiation synovectomy with rhenium-186 in rheumatoid arthritis. In this prospective, randomized trial we compared three different treatment regimens for shoulder, elbow, wrist, hip and ankle joints: group 1, injection of rhenium-186; group 2, injection of rhenium-186 in combination with triamcinolone hexacetonide; group 3, injection of triamcinolone hexacetonide alone. Each treatment group included 50 joints. Patients included in the study had to fulfil the following criteria: (1) they had to have a diagnosis of rheumatoid arthritis (ARA criteria 1988), (2) their disease-modifying drug had to be methotrexate, started at least 6 months prior to injection therapy and given for the entire study time, (3) their nonsteroidal anti-inflammatory drug had to be diclofenac given at a dose of 150 mg/day or less and (4) they were also given prednisolone at a dose of 7.5 mg/day or less. After 3 years of follow-up, 79 joints met these criteria, i. e. 71 joints were excluded from the study: 26 joints because the patients changed the disease-modifying drug (12 joints from group 1, 4 joints from group 2 and 10 joints from group 3); 45 joints because of recurrent synovitis and second-stage treatment (21 joints from group 1, 5 joints from group 2 and 19 joints from group 3). During the follow-up period, joints were assessed for pain, synovitis, joint motion and stage of radiological destruction. Best clinical results and slowest progression in radiological destruction were achieved with the combined injection of rhenium-186 and triamcinolone hexacetonide. Therefore, we recommend this treatment for articulosynovitis with the exception of severe forms, the latter because of the effective penetration range of rhenium-186.

Key words Articulosynovitis · Minimal invasive therapy · Radiosynoviorthesis · Rheumatoid arthritis

D. Göbel (✉)· T. von Rothkirch · H.-G. Willert
Department of Orthopaedic Surgery,
University Hospital of Goettingen,
Robert-Koch-Str. 40,
37075 Goettingen, Germany
Tel.: *49-551-392782
e-mail: goebel-dr-dietmar@t-online.de

S. Gratz · W. Becker
Department of Nuclear Medicine,
University Hospital of Goettingen,
Robert-Koch-Str. 40,
37075 Goettingen, Germany

Introduction

Patients with rheumatoid arthritis quite frequently suffer from persistent synovitis of some joints, while other patients are successfully treated by the use of disease-modifying drugs. In persistent cases or in joints where surgery, i. e. mostly synovectomy, is difficult to perform, minimal invasive treatment by the method of injection therapy seems to be the best alternative. In the literature there are controversial reports about the success rate of radiosynoviorthesis [1 – 7]. With respect to rhenium-186 (Re-186), our medline inquiries revealed only a few reports and none answered the question of long-term outcome. No study compared Re-186 with the results of other forms of injection therapy. Therefore, we compared three different treatment protocols during a follow-up period of 3 years.

Materials and methods

Injection therapy was performed under aseptic conditions on 150 joints (shoulder, elbow, wrist, hip and ankle) randomized into three groups with 50 joints in each group. We included in our study only patients with rheumatoid arthritis diagnosed according to the criteria of the American Rheumatism Association (ARA) of 1988. Patients with another underlying inflammatory disease, such as ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis, etc., were not included in our study.

The medical management of the patients was standardized to minimize a possible infuence of drug therapy on the results of our study:

1. All patients received the disease-modifying drug, methotrexate, which was given intramuscularly or orally and was started at least 6 month prior to injection therapy.

Table 1 Doses of rhenium-186 and triamcinolone hexacetonide (Lederlon) used for injection therapy

Joint	Rhenium-186 (MBq)	Triamcinolone-hexacetonide (Lederlon) (mg)
Shoulder	111	20
Elbow	74	10
Wrist	74	10
Hip	111	20
Tibiotalar	74	10
Talocrural	74	10

2. All patients received the nonsteroidal anti-inflammatory drug, diclofenac, at a dose of 150 mg/day or less.
3. All patients received hydrocortisone in the form of 7.5 mg prednisolone equivalent or less per day.

Exclusion criteria to and during the study were:

1. Patient's age less than 40 years [3, 6, 7, 20–22]
2. Previous surgery or radio- or chemical synovectomy on this/these joint/s
3. Change in disease-modifying drug during the study
4. Surgery or injection therapy during the follow-up time

Injection therapy was carried out using the doses of Re-186 and triamcinolone hexacetonide outlined in Table 1. Patients in group 1 underwent radiosynoviorthesis with Re-186, while in group 2, injection therapy was performed using a combination of Re-186 and triamcinolone hexacetonide. Patients in group 3 underwent injection of triamcinolone hexacetonide alone in the doses, outlined in Table 1, which are those recommended by the producer. Immediately after injection the joints were immobilized for 48 h to minimize early transport of the radionuclide via the perivascular lymphatic vessels.

During the follow-up period of 3 years, pain and synovitis were assessed on a semiquantitative scale from 0 (= no pain/synovitis) to 4 (= severe pain/synovitis). Total range of motion was measured in degrees, while radiological assessment followed the standard reference films of Larsen et al. [8]. Follow-up dates were: prior to injection, and 8 weeks, 3 and 6 months, and 1, 2 and 3 years post treatment.

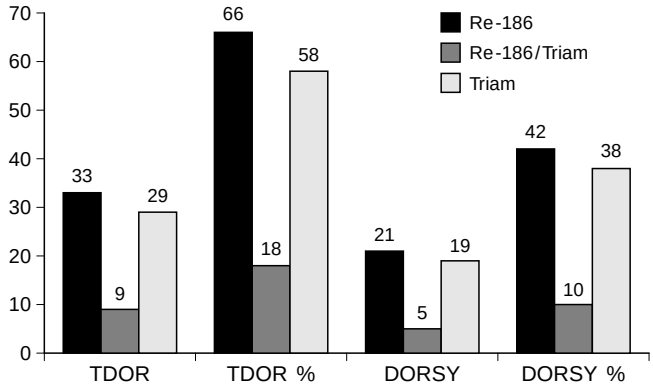

Fig. 1 Drop-out rate for each treatment group during follow-up; group 1, Re-186; group 2, Re-186/Triam; group 3, Triam (*Triam* triamcinolone, *Re* rhenium, *TDOR* total drop out, *DORSY* drop out due to recurrent articulosynovitis with second-stage treatment)

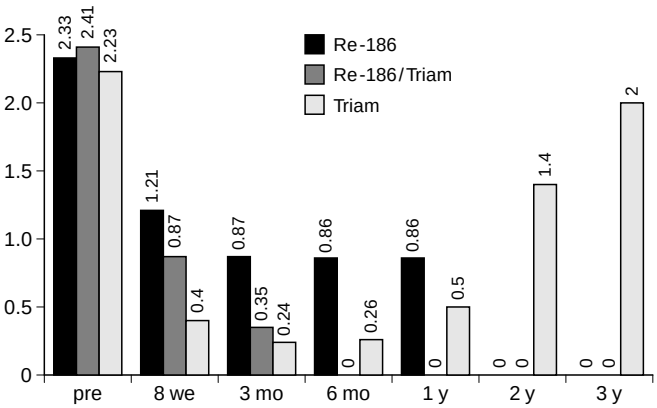

Fig. 2 Degree of pain during follow-up period; 0 = no pain, 1 = slight, 2 = moderate, 3 = intense, 4 = severe (*pre* pretreatment, *we* week *mo* month, *y* year)

Results

During the follow-up time, the drop-out rate was 47.3%, i. e. 71 joints were excluded from the study. Twenty-six joints were excluded because the patients changed their disease-modifying drug (12 joints from group 1, 4 joints from group 2 and 10 joints from group 3). Because of recurrent synovitis, 45 joints underwent surgery or injection therapy for a second time and had to be excluded (21 joints from group 1, 5 joints from group 2 and 19 joints from group 3; Fig. 1). After 3 years of follow-up, 79 joints were evaluated: 17 joints from group 1, 41 joints from group 2 and 21 joints from group 3.

There was a marked improvement in pain following triamcinolone hexacetonide injection (group 3) during the 1st year, while in groups 1 and 2 the decrease in pain was slower (Fig. 2). After 2 years, pain in group 3 increased above the levels of groups 1 and 2. The best results were seen in group 2, i. e. patients treated by the combined therapy.

Regarding reduction of synovitis, the best short-term results were achieved by injection of triamcinolone hexacetonide, but after 1 year synovial swelling increased again, reaching nearly pretherapeutic levels in the 3rd year. In the other groups, joints remained free from signs of articulosynovitis (Fig. 3).

The increase in the range of motion correlated with the reduction in the levels of pain and synovitis, i. e. during the 1st year following injection the best results were achieved in group 3, while there was reduction in joint motion in group 3 in the 2nd and 3rd years. In groups 1 and 2, joint motion did not change during the follow-up period. This correlated with radiological assessment. The radiological progression of joint destruction – Larsen stage after 3 years minus Larsen stage prior to treatment – was as follows: group 1 = 1.0; group 2 = 0.62; group 3 = 1.7 (Fig. 4). Complications in the form of joint infection, radiation dermatitis or any periarticular soft tissue damage were not encountered.

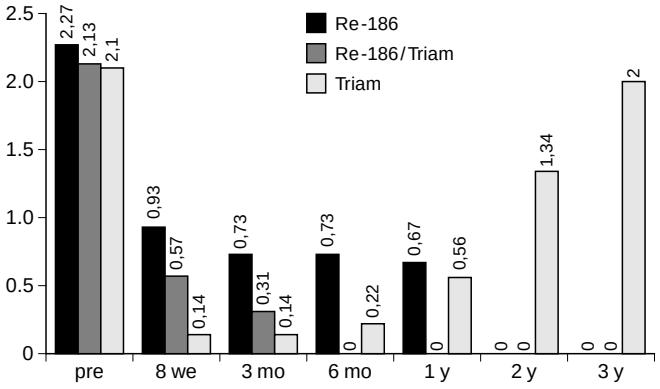

Fig. 3 Synovial swelling during follow-up period (0 = no synovitis, 1 = slight, 2 = moderate, 3 = intense, 4 = severe)

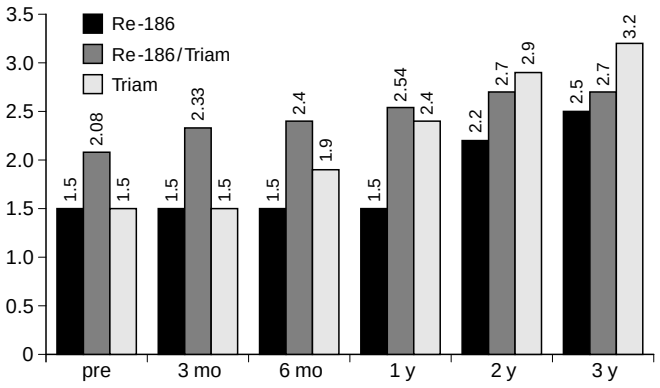

Fig. 4 Radiological stage of joint destruction according to standard reference films of Larsen et al. [8]

Discussion

Currently, radiation synovectomy seems to be the only established alternative to open or arthroscopic surgery. Depending on the size of the joint there are different radionuclides available: yttrium-90 for the knee joint [9–13], erbium-169 for finger joints [2, 4, 14, 15] and Re-186 for shoulder, elbow, wrist, hip and ankle joints [5, 6]. While gold-198 is not used any longer, dysprosium-165, mainly used for the knee joint [16], has some major disadvantages for general use in Germany: (1) it is not a registered drug in Germany, (2) it is around 10 times more expensive than yttrium and (3) the place of production and the place of application have to be close together [5]. Consistent with the report of Deutsch et al. [1], we observed that most reports in the literature present their experience with yttrium-90, while there are only a few reports of radiosynovectomy with Re-186 [17–19]. While Menkes [19] reports a 50–60% rate of good and excellent results, Gregoir [18] presents a success rate of 83% for the elbow joint 1 year after injection of rhenium. At 2 years follow-up, the success rate drops down to 65%. However, Gregoir reviewed only 40% of his patients, i. e. he did not know the outcome of the remaining 60%. Gumpels [2], who compared the injection of methylprednisolone with erbium-169 (follow-up = 1 year; review of 99.3% of all joints), has found a rate of improvement of 25% and no difference between the two therapies. Thus, our study seems to be the first randomized, prospective trial comparing steroid injection with rhenium radiosynoviorthesis and combined treatment, with a 3-year follow-up and 100% review of treated joints.

Taking in mind the total drop-out rate (TDOR), as well as the drop out because of recurrent synovitis (DORSY) in groups 1 (TDOR = 66%, DORSY = 42%) and 3 (TDOR = 58%, DORSY = 38%), there was no significant difference between rhenium and steroid injection alone, which is in keeping with the results of Gumpel [2]. On the other hand, high levels of synovitis and pain at 3 years follow-up, as well as the radiological progression of joint destruction, favoured radiosynoviorthesis over steroid injection.

The long-term success rate of 34% for the rhenium injection was far below the values of Menkes and Gregoir [18, 19], while for the combined treatment the success rate of 82% was promising. The additional injection of triamcinolone hexacetonide seemed to prevent at least part of the transient local reaction and therefore reduced pain faster than was observed following the injection of the radionuclide alone. This seemed to have beneficial effects on the progression of radiological destruction. Therefore, our theory is that the long-term success of radiosynoviorthesis depends on the control of synovitis during the first 8 weeks after injection therapy. If transient local synovitis caused by the radionuclide injection results in a build up of a synovial layer that is thicker than the effective penetration range of Re-186, this will lead to fibrosis in the superficial layer of the synovium, while deeper structures are still able to perpetuate an exudative synovitis [24–27].

The effective penetration range is, according to Johnson and Yanch [23], ". . . the distance from the source at which 90% of the absorbed dose is deposit . . .", which for rhenium is 0.9 mm. In other publications [5, 7] we found a mean range of 1.2 mm. Therefore, in future a synovitis of much more than 1–1.5 mm could be considered a contraindication to radiosynoviorthesis with Re-186. However, this theory has to be proved in future studies, e. g. evaluating synovial thickness by ultrasound scan prior to injection therapy.

In conclusion, we believe that, in patients over 40 years of age who have undergone 6 months of an overall successful treatment with a disease-modifying drug, radiosynoviorthesis is indicated in joints with remaining synovitis. We also believe that radiosynoviorthesis is indicated in patients who are unable to undergo surgery. We prefer to give the radionuclide in combination with triamcinolone hexacetonide and to immobilize the joint for 48 h to minimize radionuclide leakage from the joint. In marked synovitis, i. e. synovial swelling above the effective range of Re-186, we

recommend surgery because lower layers of the synovium are not reached by radiosynoviorthesis and the destructive process will continue. In patients who do not respond to radiosynoviorthesis, we do not recommend that therapy be repeated because of the unacceptably high failure rate [28]. In the case of additional tenosynovitis or bursitis, we favour surgical treatment by teno- and articulosynovectomy to prevent further damage to tendons and soft tissues [29]. With these exceptions in mind, we believe that radiosynoviorthesis with Re-186 has proved it's efficacy in the long-term and can be considered as an alternative to surgery.

References

1. Deutsch E, Broddack JW, Deutsch KF (1993) Radiation synovectomy revised. Eur J Nucl Med 20: 1113 – 1127
2. Gumpel JM, Matthews SA, Fisher M (1979) Synoviorthesis with erbium-169: a double-blind controlled comparison of erbium-169 with corticosteroid. Ann Rheum Dis 38: 341 – 343
3. Lueders C, Feinendegen LE (1993) Die Radiosynoviorthese. Strahlenther Onkol 169: 383 – 386
4. Menkes CJ, Le-Go A, Verrier P, Aignan M, Delbarre F (1977) Double-blind study of erbium 169 injection (synoviorthesis) in rheumatoid digital joints. Ann Rheum Dis 36: 254 – 256
5. Mödder G (1995) Die Radiosynoviorthese – Nuklearmedizinische Gelenktherapie und -diagnostik in Rheumatologie und Orthopädie. Warlich Druck, Meckenheim
6. Müller-Brand J (1990) Grundlagen der Radiosynoviorthese. Schweiz Med Wochenschr 120: 676 – 679
7. Weber M (1993) Lokale Gelenkbehandlung bei chronischer Polyarthritis (cP): intraartikuläre Kortikosteroide und radioaktive Isotope. Schweiz Rundsch Med Prax 82: 353 – 358
8. Larsen A, Dale K, Eek M (1977) Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. Acta Radiol Diagn 18: 481 – 491
9. Bridgman JF, Bruckner F, Bleehen NM (1971) Radioactive yttrium in the treatment of rheumatoid knee effusions. Ann Rheum Dis 30: 180 – 182
10. Isomäki AM, Inoue H, Oka M (1972) Uptake of ^{90}Y resin colloid by synovial fluid cells and synovial membrane in rheumatoid arthritis. Scand J Rheumatol 1: 53 – 60
11. Jaworski R, McLean R, Choong K, Smart R, Edmonds J (1993) Re-evaluating the need for hospitalization following synovectomy using Yttrium-90 silicate. Br J Rheuamtol 32: 1012 – 1017
12. Webb FWS, Lowe J, Bluestone R (1969) Uptake of colloidal radioactive yttrium by synovial membrane. Ann Rheum Dis 28: 300 – 302
13. Will R, Laing B, Edelman J, Lovegrove F, Surveyor I (1992) Comparison of two yttrium-90 regimes in inflammatory and osteoarthopathies. Ann Rheum Dis 51: 262 – 265
14. Boussina I, Toussaint M, Ott H, Hermans P, Fallet GH (1979) A double-blind study of erbium-169 synoviorthesis in rheumatoid digital joints. Scand J Rheumatol 8: 71 – 74
15. Tubiana R, Menkes CJ, Galmiche B, Delbarre F (1979) Die intraartikuläre Injektion von β-Strahlern. Therapiewoche 29: 507 – 513
16. Zuckerman JD, Sledge CB, Shortkroff S, Venkatesan P (1987) Treatment of rheumatoid arthritis using radiopharmaceuticals. Nucl Med Biol 14: 211 – 217
17. Chinol M, Vallabhajosula S, Goldsmith J, et al. (1993) Chemistry and biological behavior of samarium-153 and rhenium-186-labeled hydroxyapatite particles: potential radiopharmaceuticals for radiation synovectomy. J Nucl Med 34: 1536 – 1542
18. Gregoir C, Menkes CJ (1991) Rheumatoid elbow: patterns of joint involvement and the outcome of synoviorthesis. Ann Hand Upper Limp Surg 3: 243 – 246
19. Menkes CJ (1979) Radioisotope synoviorthesis in rheumatoid arthritis. Rheumatol Rehabil 45 – 46
20. Edmonds J, Smart R, Laurent R, et al. (1994) A comparative study of the safety and efficacy of dysprosium-165 hydroxide macro-aggregate and yttrium-90 silicate colloid in radiation synovectomy – a multicentre double blind clinical trial. Br J Rheumatol 33: 947 – 953
21. Noble J, Jones AG, Davies MA, Sledge CB, Kramer RI, Livni E (1983) Leakage of radioactive particle systems from synovial joint fluid studied with a gamma camera. J Bone Joint Surg 65-A: 381 – 389
22. Stevenson AC, Bedfort J (1973) Cytogenetic and scanning study of patients receiving intra-articular injections of gold-198 and yttrium-90. Ann Rheum Dis 32: 112 – 132
23. Johnson LS, Yanch JC (1991) Absorbed dose profiles for radionuclides of frequent use in radiation synovectomy. Arthritis Rheum 34: 1521 – 1530
24. Combe B, Krause E, Sany J (1989) Treatment of chronic knee synovitis with arthroscopic synovectomy after failure of intra-articular injection of radionuclide. Arthritis Rheum 32: 10 – 14
25. Guaydier-Souquieres C, Beguin J, Ollivier D, Loyau G (1989) Knee arthroscopy after yttrium or osmic acid injection. Arthroscopy 5: 70 – 75
26. Mohr W, Mohing W, Hersener J (1977) Morphologische Veränderungen am Gelenkkapselgewebe nach vorausgegangener Synoviorthese. Z Rheumatol 36: 316 – 331
27. Yates DB (1973) Arthroscopy of the knee after the injection of ^{90}Y. Ann Rheum Dis 32 [Suppl]: 48 – 50
28. Stucki G, Bozzone P, Treuer E, Wassmer P, Felder M (1993) Efficacy and safety of radiation synovectomy with yttrium-90: a retrospective long-term analysis of 164 applications in 82 patients. Br J Rheumatol 32: 383 – 386
29. Peters W, Lee P (1994) Radiation necrosis overlying ankle joint after injection with yttrium-90. Ann Plast Surg 32: 542 – 543