Better results with rhenium-186 radiosynoviorthesis than with cortivazol in rheumatoid arthritis (RA): A two-year follow-up randomized controlled multicentre study

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Abstract

Objective

The aim of this international multicentric randomized phase 3 clinical trial was to compare prospectively radiosynoviorthesis (RSO) with rhenium-186-sulfide ([186]Re) to intra-articular corticotherapy in patients with clinically controlled rheumatoid arthritis (RA), but in whom one or a few medium-sized joints remained painful or swollen.

Methods

One hundred and twenty-nine joints in 81 RA patients [stratified into 2 groups: wrists (group 1, n = 78) and all the other joints (group 2, n = 51, including 18 elbows, 21 shoulders and 12 ankles)] were randomized to receive intra-articular injections of either [186]Re-sulfide (64 ± 4 MBq), or cortivazol (Altim®) 3.75 mg. Clinical assessment was performed before and then at 3, 6, 12, 18 and 24 months after local therapy, using a 4-step verbal rating scale (VRS) and a 100 mm visual analog scale for pain, a 4-step VRS for joint swelling and mobility and a 2-step VRS for the radiological stage. The Mantel-Haenszel test was used for qualitative variables, analysis of variance (ANOVA) for quantitative pain analysis and Kaplan-Meyer survival test for relapse analysis.

Results

[186]Re was observed to be statistically superior to cortivazol at 18 and 24 months while no statistical difference was seen for any criterion at 3, 6 and 12 months post injection. At 24 months, the difference in favor of [186]Re was significant for pain (p = 0.024), joint swelling (p = 0.01), mobility (p = 0.05, non-wrists only), pain and swelling (p = 0.03) and pain or swelling (p = 0.02). "Survival" studies (Kaplan-Meyer) demonstrated a greater relative risk of relapse in corticoid treated joints, but only from the second year of follow-up. No serious side effect was observed in any patient, with only light and transient local pain and/or swelling occurring in 24% of cases, regardless of the treatment used.

Conclusion

[186]Re-sulfide and cortivazol had similar efficacy up to 12 months post-injection, but [186]Re became clearly more effective at 18 and 24 months, for all criteria monitored and for RA outcome. Therefore, [186]Re RSO can be recommended for routine clinical use.

Key words

Radiosynoviorthesis, Rhenium-186, rheumatoid arthritis, corticosteroid, intra-articular.

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Received on January 26, 2004; accepted in revised form on June 9, 2004.

Introduction

Pharmacological synovectomy is indicated to reduce synovial inflammation in rheumatoid arthritis (RA) when the disease is, with the exception of a limited number of joints, largely well controlled by systemic treatment. Such treatment may involve either intra-articular corticosteroid injections or the more expensive radiosynoviorthesis (RSO or radiation synovectomy). RSO acts by destruction of the synovial tissue through the use of a beta emitter radiopharmaceutical [mainly yttrium-90 citrate or silicate (^{90}Y) for large joints, rhenium-186 sulfide (^{186}Re) for medium-sized joints and erbium-169 citrate (^{169}Er) for small joints] instead of a corticosteroid agent.

^{186}Re is best suited for medium-sized joints, mainly because of its emission properties [maximum and mean beta energies: 0.98 and 0.30 MeV; mean range of beta rays: 1.2 mm, to be compared with ^{169}Er (0.3 mm) and ^{90}Y (3.6 mm)] (1-5). ^{186}Re-sulfide has been widely used in the clinical practice for 25 years in Europe, and its efficacy is well accepted in RA, while adverse effects are minor and infrequent. Results from open clinical trials involving large cohorts of patients have been published and have repeatedly confirmed the efficacy of rhenium-186 in the treatment of medium-sized joints, with one-year success rates in the range 50-80% (2-9). However, in contrast to the situation with erbium-169 and yttrium-90 there were, until recently, no controlled clinical studies demonstrating the therapeutic efficacy of rhenium-186.

Open studies undertaken by Menkes *et al*. (5,6), have shown a greater improvement rate for pain and for swelling in 73% of wrists (n = 324), compared with 50% in shoulders (n = 215), 55% in elbows (n = 176) and 56% in ankles (n = 114). Studies in hips showed results at one year with rhenium-186 or osmium tetraoxyde to be comparable and clearly correlated with the Steinbrocker radiologic stage (10), with 63% success at stages I and II (n= 41), and only 19% at stage III (n = 19) (11). At 3 years, the results at stages I-II were still close to 45%.

A correlation with the radiologic stage has initially been reported in elbows (12): good or very good results accounted for 89% at radiologic stage I, but only 76% at stage II and 56% at stage III. In a meta-analysis including 2190 treated joints (different sizes and different isotopes), these primary results were extensively confirmed: RSO had a mean success rate of 72.8 ± 12.3% (Steinbrocker I), 64 ± 17.3% (Steinbrocker II) and 52.4 ± 23.6% (Steinbrocker III and IV) (9).

Similar results were reported for wrists by Gamp (4) in a series of 73 cases (67% of good or very good results at 6 months, 66% at one year and 63% at 2 years). In cases of relapse, a second rhenium injection continued to give a favorable response in 54% of patients at 6 months and in 38% at 1 year.

These results are in agreement with another study that has also demonstrated the influence of the radiological stage to be less prominent in the wrist [74-78% of good results at stages I-II-III (n = 302) than in other joints, except at stage IV(41%, n = 22)] (6).

Radiosynoviorthesis has been compared with corticosteroids in a retrospective study published by Grégoir and Menkes (12). This study demonstrated that, whilst corticosteroids gave better results at 6 months (81% of good results versus 66%), this effect was reversed at 12 months (61% versus 83%) and at 24 months (58% versus 65%). These results could also be modified by the synovial swelling or the immobilization of the treated joints (13). However, no controlled randomized study investigating the therapeutic effect of rhenium-186 sulfide in clinical practice was available until the recent publication of two controlled studies. The first of these studies investigated both rhenium and erbium (14), while the second had a similar design to the present study (15) with the exception that the possibility of RA flares, which is frequent in clinical practice, was not taken into consideration.

In the present study, we have demonstrated the efficacy of rhenium radiosynoviorthesis over the long-term regardless of the RAflare condition.

Materials and methods

Radiopharmaceuticals

Rhenium-186–sulfide (^{186}Re, half-life 3.77 days) disintegrates by beta$^-$ emission (maximum and average beta energies: 0.98 and 0.30 MeV) and electron capture, with two gamma emissions at 137 keV (9.5%) and 123 keV (0.6%). The mean and maximum ranges of beta particles in cartilage and soft tissues are about 1.2 mm and 3.7 mm, respectively. ^{186}Re-sulfide radiocolloid (Schering - CIS bio international, Gif-sur-Yvette, France) has a radioactive concentration ranging from 37 to 370 MBq/ml.

^{186}Re-sulfide was compared to cortivazol (Co) (Altim®, Roussel labs, 3.75 mg for 1.5 ml, i.e. 2.5 mg/ml). A complete vial of 1.5 ml was injected into each joint. Cortivazol was selected as the comparator because of the risk of temporary unavailability of triamcinolone hexacetonide when we started this study and because its high intra-articular efficacy (1.5 ml corresponds to 62.5 mg of prednisone, 6 weeks estimated half life) and its convenience of use (ready-to-use syringes) compared with triamcinolone hexacetonide.

Patients and joints

Patients over 18 years of age and fulfilling the American Rheumatism Association criteria for rheumatoid arthritis (16) were enrolled after they had signed informed consent. On entry, the disease activity had to have been satisfactorily controlled for at least 3 months, with the exception of joints that required only local treatment. Concomitant analgesic drugs, nonsteroidal anti-inflammatory drugs (NSAID), oral corticosteroids (up to 10 mg prednisone per day) and disease-modifying anti-rheumatic drugs (DMARDs) (mainly methotrexate) were permitted and, as far as possible, maintained unmodified during the observation period. However, apart from the assigned treatment and a drop of contrast medium (Hexabrix®, Guerbet, France), no other intra-articularly administered drugs were permitted during the 24-month trial period. Exclusion criteria included pregnancy, breast-feeding, previous surgery in any target joint, any intra-articular injection in the target joints during the last 6 months, and concomitant major anti-coagulants (heparin derivatives, anti-vitamin K). The patients' main characteristics are summarized in Table I. The occurrence of RA flares as judged by each investigator and/or necessitating a significant modification in the background treatment was recorded at each center and their influence on the treated joints was analyzed.

Table I. Patients and joints characteristics (n = 129). Comparison of the rhenium and cortivazol groups at inclusion.

	Rhenium (n = 65)	Cortivazol (n = 64)
Age (years ± SD)	54.3 ± 11.6	54.9 ± 12.4
Sex ratio (F/M)	40/25	38/26
RAduration (years ± SD)	8.8 ± 7.6	6.8 ± 5.2
Corticosteroids (5-10 mg/d)	39/65 (60%)	37/64 (58%)
Methotrexate (7.5-15 mg/w)	40/65 (62%)	43/64 (67%)
Other DMARDs*	9/65 (14%)	6/64 (9%)
NSAID	39/65 (60%)	31/64 (48%)
Analgesics	29/65 (45%)	31/64 (48%)
Rheumatoid factor positive	57/65 (88%)	58/62 (94%)
Steinbrocker I-II	47/62 (76%)	44/53 (83%)
Steinbrocker III-IV	15/62 (24%)	9/53 (17%)
Number of target joints with previous local RSO	11/64 (17%)	9/64 (14%)

129 joints in 76 patients were interpretable (Some parameters were not available for all joints and/or patients; sum < 129). No significant differences were observed between the rhenium group (n = 65) and the cortivazol group (n = 64). DMARD: Disease Modifying Antirheumatic Drug. Other DMARDs include: Salazopyrine (n = 11), D-penicillamine (n = 2), Gold salt (n =1), Azathioprine (n = 1). NSAID : non steroid anti-inflammatory drugs. No significant difference was observed between the two groups for any of these parameters. RSO : radiosynoviorthesis.

The joints admitted into the trial were wrists, elbows, shoulders, hips and ankles. The joints were stratified into wrists or non-wrists (W or NW), and by centers (n = 3) and randomized to receive ^{186}Re-sulfide or cortivazol (6 random lists). The stratification between wrists or non-wrists was based on the results of Menkes *et al.* (5, 6), according which wrists, the most frequently affected medium-sized joints in RA, usually give better results at one year (70% of improvement) than elbows, shoulders, hips and ankles (50-55%).

Clinical follow-up was performed at 3, 6, 12, 18 and 24 months in each center by the same investigator and included global RA status and examination of the injected joint. The treatment was classified as a failure at each end-point if the treated joint required further management because of lack of significant improvement in respect of either a subsequent injection or surgery. A radiographic assessment of the treated joints was performed on entry and at 6 months of follow-up. The joints were classified according to the radiological stage [Steinbrocker index (10)] and stability or deterioration was assessed at 6 months. A total of 136 joints (in 81 patients) were included and randomized to receive either 63.5±3.8 MBq of ^{186}Re or 3.75 mg of cortivazol, with a maximum of 3 joints treated per patient. Of these joints, 131 were actually injected and 129 (65 of them received ^{186}Re and 64 cortivazol) were considered as interpretable at 6 months in the intend to treat analysis. More precisely, 120 (9 joint data are lacking at this time), 129, 87, 80 and 79 joints were interpretable at 3, 6, 12, 18 and 24 months, respectively. Patient attrition was primarily due to lack of efficacy and, to a lesser extent, loss of follow up (n = 12). Clinical efficacy analysis for each end point was performed on all assessable treated joints, whilst all 131 joints were included in the adverse events analysis and Kaplan-Meyer studies.

Injection protocol

Rhenium-186 (70 MBq) was used in

the treatment of wrists, elbows, shoulders and ankles but, although eligible, no hips were recruited into the study. Cortivazol by syringe was preferred for its convenience given the size of injected joints (3.75 mg of cortivazol in 1.5 ml, 62.5 mg prednisone equivalent). In order to preserve blinding at each of the centers, a second physician, who was not involved in the clinical follow-up, performed intra-articular injections under radiographic control; the same physician administered all injections at each center. Patients were blinded for the treatment. After administration of a minimal amount (1 drop) of contrast medium, a drop of air (between 0.1 and 0.5 ml, according to each joint), which had been previously introduced into the syringe above the liquid surface, was used to completely void the syringe. When a three-way tap was employed (in all but 4 cases), the tap and needle were rinsed with a minimal volume of contrast medium. Following injection, all joints were immobilized in a splint for 48h. A quality control of the ^{186}Re injection procedure was performed in 37 patients; this involved a radioactivity count determination of syringes, needles and taps before and after injection, and demonstrated that a mean of 86% ± 7% of the ^{186}Re activity introduced into the syringe had actually been injected.

The scheduled (actual ± SD) time course between injection and the next visits were 3 months (2.5± 0.5; n = 120 joints), 6 months (5.8± 0.8; n = 129 joints), 12 months (11.8± 1.1 months; n = 87 joints), 18 months (17.7 ± 0.9; n = 80 joints) and 24 months (23.7 ± 1.4 months; n = 79 joints).

Adverse events were systematically recorded on the case report form at each visit.

Statistical methods

A 4-point scale was used for the qualitative parameters, (0: normal; 1: slightly abnormal; 2: moderately abnormal; 3: strongly abnormal), consequently a higher score corresponds to a more severe clinical status. For each parameter, the clinical course was assessed by subtracting the score at each time from the initial score. For radiological assessment, however, only two possibilities were considered (no change and worsening). The Mantel-Haenszel test was used instead of the simple χ^2 to take account of the stratification (weighting), together with a logistic model with 6 strata (3 centers, 2 types of joints). The exact Fisher test was used when necessitated by the small number of assessable joints (χ^2 test with or without Yates correction not applicable).

In addition, the relapse-free interval was calculated according to the Kaplan-Meyer method; the "relapse" of joints corresponds to a local failure as defined previously.

Results

Clinical efficacy

The number of assessable joints (W and NW) at 6 months was 129 (78 W and 51 NW) and 79 at 24 months of follow-up (45 W and 34 NW). The global results of the analysis are presented in Figure 1 . At 3, 6 and 12 months, the global success rates were identical for both treatments: about 70% for pain, 53% for swelling and 42% for mobility. Similarly, no differences were observed between either treatment arms in the W group. However, in the NW group, swelling was slightly improved when using ^{186}Re rather than cortivazol. This difference was, however, only slightly significant at 3 months (p = 0.04) and not significant at 6 months, consequently any definitive advantage for rhenium in the NW group during the initial 12 months remains debatable. However at 12 months, a trend in favor of ^{186}Re is apparent for all criteria (p > 0.05 but <0.20) and at 18 months, ^{186}Re was significantly better for all criteria, except mobility; these differences were similar in the W and NW subgroups (data not shown). Swelling displayed the greatest difference between both types of treatments (p<0.008) and combined criteria (pain and/or swelling) followed the same profile. At 24 months, the advantage of ^{186}Re over cortivazol increased for all parameters in the whole series.

The stability of RAat each evaluation

Joints were divided into two groups corresponding to patients with either stable (n = 67 at 18 months and 68 at 24 months) or flaring RA(n = 12 at 18 and 24 months). No difference between local treatments was observed between these two groups in terms of recurrence of local pain, swelling or loss of mobility (data not shown). Thus, RAflare did not clinically significantly affect the injected joints whatever local treatment was used.

The age at diagnosis and the DMARD prescription influence

In spite of some methodological limitations (age was not stratified), DMARD prescription and age were both analyzed as confounding factors. At 24 months, the difference ^{186}Re/cortivazol was not significant for patients aged less than 60 years at diagnosis but was significant for older patients (> 60 years, p<0.03) (Table II). Since general treatments differed as a function of age [more MTX in patients aged less than 60 years and significantly more corticosteroids in older patients (data not shown)], we also investigated the influence of the presence of MTX and/or corticosteroids on the efficacy of the intra-articular treatments (Table III): advantage of rhenium over cortivazol was statistically greater in the presence of systemic corticotherapy and/or methotrexate. However, in the absence of these general treatments, local injections gave similar clinical efficacy whatever the treatment used.

The time elapsed since the onset of the disease

When patients were grouped into those diagnosed for greater than 5 years and those for less than 5 years, no discriminating effect was found.

Influence of the radiological stage

Steinbrocker radiological stage, measured at 0 and 6 months, was not discriminating as such and did not show any significant joint impairment whatever the treatment.

However, when the influence of the initial Steinbrocker stage (at the time of injection) on the other clinical parameters was analyzed [lower stages I-II (n = 101) versus severe stages III–IV (n = 28)], rhenium appeared equally effec-

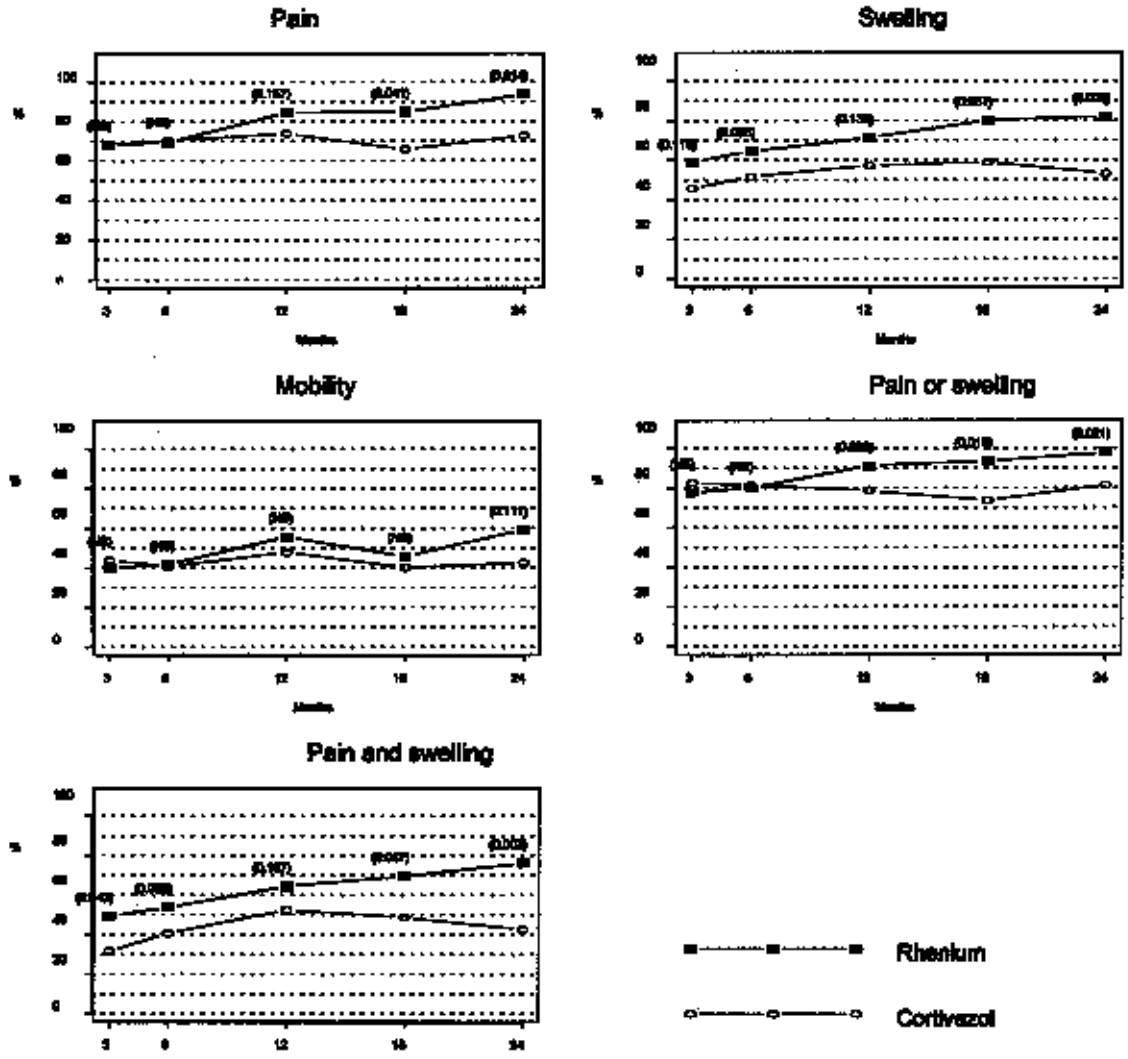


Fig. 1. Comparison of pain, swelling, mobility and combined pain and/or swelling during the 24-month follow-up (all joints). The percentage of improvement (y axis) for pain, swelling, mobility and combined criteria (pain or swelling and pain and swelling) were assessed in both the [186]Re sulfide (Re) and cortivazol (Co) groups at 3, 6, 12, 18 and 24months and compared by the $\chi 2$ test. A trend in favor of Re treatment appeared at 18 months for some parameters and was confirmed at 24 months for every measurement except mobility (numbers in brackets: p: $\chi 2$ test, unweighted. NS means $p > 0.2$).

tive in terms of long-term (12-24 months) pain and swelling improvement, whatever the initial radiological stage, but during the first 6 months, a more rapid improvement was noted in stages I-II than in stages III-IV ($p < 0.04$ for swelling, non-significant trend for pain and mobility).

The situation was different in the corticoid-treated group, where a non-significant trend appeared, the joints with severe initial Steinbrocker stages (III-IV) giving long-term poorer clinical results than those with an initial lower rating ($0.05 < p < 0.08$, at 24 months).

The relapse-free interval

The relapse-free interval curves (Kaplan-Meyer method) (Fig. 2) indicate that the relapse rates remained similar in both groups until one year. Subsequently, rhenium-treated joints displayed approximately half the relapse rate of those seen for the corticoids treated joints. The relative risk to relapse for cortivazol was 1.58 (unweighted RR; $p < 0.05$) or 1.92 (weighted RR; $p = 0.015$), as compared to [186]Re.

Adverse events

One systemic adverse event was noted in a single patient (facial rash), lasting 12 hours after having received both cortivazol and [186]Re in two different joints. Minor local events were observed in 32 cases (out of 131 injections, i.e. 24%) and consisted of light (n = 23), moderate (n = 6) or severe pain (n = 2), generally lasting a few minutes and not necessitating any treatment. In 5 cases, a slight (n = 3) or moderate (n = 2) transient swelling was also observed. These adverse events appeared equally distributed between the two local treatments (n = 16 for each product for pain; n= 3 for [186]Re and n = 2 for cortivazol for swelling).

Discussion

Compared to local corticoid treatment rhenium-186 sulfide provided significantly greater clinical improvement over the long term. This advantage became apparent from the second year after injection regardless of the RAstage. While during the first 12 months of follow-up, cortivazol and rhenium gave

Table II. Joint improvement (number and percentage of treated joints) at 24 months as a function of the age of diagnosis of rheumatoid arthritis.

	≤ 60 years		> 60 years	
	Improvement with rhenium	Improvement with cortivazol	Improvement with rhenium	Improvement with cortivazol
Pain (qualitative)	32/34 (94%)	19/22 (86%)	11/12 (92%)	5/11 (45)%
	p = NS		p < 0.03	
Swelling	27/33 (82%)	14/22 (64%)	9/11 (82%)	3/10 (30%)
	p < 0.13 (trend)		p < 0.03	

No significant difference between Rhenium and Cortivazol could be observed for pain and swelling in patients with RAonset before or at 60 years, while a significant difference in favor of rhenium appears for pain and swelling in patients with onset of RAafter 60 years of age. Mobility was not discriminating. p: Fisher test.

similar efficacy, with only slight differences depending on the criteria considered, from the 18th month, the difference in favor of rhenium became increasingly obvious for all clinical parameters, including the rate and the time interval before local relapse occurs (Fig. 2). Furthermore, combined criteria, pain and swelling and pain or swelling gave similar results to the individual criteria (Fig. 1). Pain and swelling was the most discriminating parameter to demonstrate the improved efficacy of rhenium at 24 months; this is of prime clinical importance because these represent the two main local symptoms of RA.

This conclusion is in agreement with two recently conducted randomized prospective studies with rhenium-186 (and erbium-169) in rheumatoid arthritis patients (14, 15). One of these studies (15) evaluated the efficacy of rhenium alone, triamcinolone hexacetonide alone, and a combination of both (50 joints per group) over a period of 3 years: clinical results with rhenium were significantly better than for the corticoid during the second and the third year of follow up. However, the corticoid appeared better at 6 months and both products were equivalent at 12 months. While these results are broadly in agreement with ours, some differences in design ought to be highlighted.

Firstly, cortivazol instead of triamcinolone hexacetonide was used in our study, primarily because of the temporary unavailability of triamcinolone hexacetonide. A syringe of cortivazol contains the equivalent of prednisone 62.5 mg, whereas the triamcinolone hexacetonide 10 to 20 mg injected by Göbel *et al*. (15) corresponds to only prednisone 12.5 to 25 mg. In our study, the advantage of rhenium over this more competitive challenger is thus all the more significant. Secondly, the study by Göbel *et al*. excluded patients experiencing a flare of RA during the follow-up period, which reduced the power of the study (25% drop-out rate), particularly since no relapse-free interval analysis was performed. Our study differs in that we analyzed all assessable joints in every patient, even when RA flares occurred. It might be anticipated that the occurrence of flares could have significantly affected our results, since diffusion of the inflammatory process following RA flare could lead to a possible advantage for the treated joint in comparison with other joints. However, this was not a significant problem because the number of flares was relatively low as the inclusion criteria required stable RA activity on entry. Nevertheless, the observed effect of treatment may have

Table III. Efficacy of intra-articular rhenium and cortivazol at 24 months when systemic treatment contains methotrexate (MTX) and/or corticosteroids.

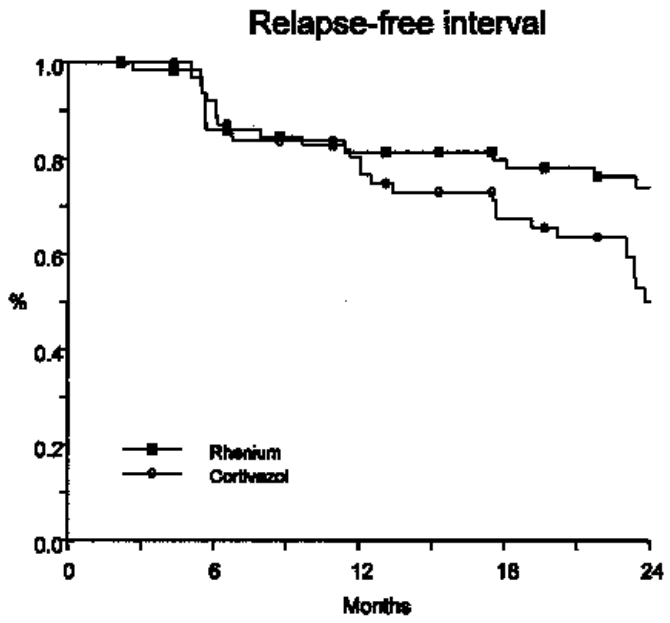
A

Pain	Corticosteroids				MTX			
	No (n = 37)		Yes (n = 42)		No (n = 18)		Yes (n = 61)	
	stable/worse	improved	stable/worse	improved	stable/worse	improved	stable/worse	improved
Co	3	12	6	12	2	4	7	20
Re	2	20	1	23	2	10	1	33
	p = 0.38 (Fisher)		p = 0.036 (Fisher)		p = 0.57 (Fisher)		p = 0.024 (Fisher)	

B

Swelling	Corticosteroids				MTX			
	No (n = 34)		Yes (n = 42)		No (n = 17)		Yes (n = 59)	
	stable/worse	improved	stable/worse	improved	stable/worse	improved	stable/worse	improved
Co	5	9	10	8	4	2	11	15
Re	5	15	3	21	2	9	6	27
	p = 0.77 (Fisher)		p = 0.003 (Fisher)		p = 0.11 (Fisher)		p = 0.04 (Fisher)	

Results of local treatment at 24 months for pain (A) and swelling (B) were analyzed in conjunction with the use of systemic corticosteroids (5-10 mg/j) and/or methotrexate. When neither treatment was prescribed, no difference was observed between the success rates of either local treatment, whereas significant improvement was obtained with rhenium ($p \leq 0.04$) when at least one of these systemic treatments was prescribed.



Figs. 2. Relapse-free interval of joints treated by cortivazol or by rhenium-186 sulfide.
No significant difference in the relapse rate was observed between the two local treatments up to 12 months; however the difference became significant thereafter, favoring Re for all elementary or combined clinical parameters, except mobility. Unweighted and weighted (type of joints) relative risks (RR) for relapse at 24 months (Co/Re) are 1.58 ($p = 0.05$) and 192 ($p = 0.015$), respectively.

been influenced by the background therapy: in particular, steroids and methotrexate significantly increased the advantage of rhenium over cortivazol at 24 months (Table III).

Statistical analyses indicated that the radiologic stage (Steinbrocker index) at diagnosis poorly influenced the clinical outcome to both treatments. This is in line with what is generally observed in the literature. Nevertheless, rhenium remained equally effective in all stages studied (I and II versus III and IV) whereas cortivazol presented a non-significant trend for better efficacy in less degraded joints. This supports the use of Re in patients with poorer radiological stages, although these results need to be confirmed in an appropriate joint protective study.

The age of onset of RAdisease (i.e. the diagnosis date) appeared critical in the interpretation of our results, even though the duration of the disease was not discriminating. In patients younger than 60 at diagnosis, the response to intra-articular treatments was globally better than in patients becoming ill later in life; this difference was due to the relatively superior results with cortivazol in the younger patients, although any difference between [186]Re and cortivazol in this subgoup did not reach statistical significance (TableII). However, where RA onset occurred after 60 years of age, cortivazol results were less favorable and rhenium was significantly better for both pain ($p < 0.03$) and swelling ($p = 0.03$). As this advantage was not definitively significant, it might be concluded that radiopharmaceutical treatment is a valuable alternative to corticosteroids in rheumatoid arthritis with onset in the elderly. However, this interpretation has to be made with caution since general treatments, i.e. methotrexate in younger patients and steroids in older patients, play an important role in the success of local treatment, as previously mentioned. Thus, a further study to measure the respective influence of age onset and of general treatment is desirable. Such a study needs to keep under consideration that radiosynoviorthesis remains a local treatment.

Another consideration is that multiple injections in the same patient may interact with each other. In particular, systemically released cortivazol (62.5 mg of prednisone) could temporarily improve the general status of disease and hence indirectly the response of the other joints to local treatments, leading to reduced differences between the two arms of treatments and delaying occurrence of the advantage of rhenium over cortivazol. However, analysis of local clinical results of Re in the 55 patients who had more than one intra-articular injection (with at least one Co and one Re injection) did not significantly differ from the 26 patients who had only one Re injection (data not shown).

Overall, the results of this study demonstrate that rhenium-186 radiosynoviorthesis is more effective in the long term than an intra-articular corticosteroid, even when a relatively high dose of steroid is used. The comparative clinical design of this study confirms the advantage of radiosynoviorthesis over corticoid infiltration in joints remaining painful or swollen in otherwise well controlled RA patients and justifies the interest for the use of rhenium-186 radiosynoviorthesis in this group of patients, in spite of the higher cost of the radiopharmaceutical.

Acknowledgments

We would like to thank the staffs of all participating teams, and in particular Dr P Barbier (Nuclear Medicine Department, Centre Hospitalier Lyon-Sud), Claudine Gilder (Nuclear Medicine, Cochin Hospital), Jocelyne Redon (Rheumatology Department, Cochin Hospital) and Aline Rivory (Schering-CIS) for their skilled technical or administrative assistance and for helpful discussions.

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