Review

Radiosynoviorthesis of medium-sized joints with rhenium-186-sulphide colloid: a review of the literature

R. Klett, U. Lange¹, H. Haas², M. Voth³ and J. Pinkert⁴

Hypertrophy and inflammation of the synovium with various underlying pathologies—such as rheumatoid arthritis, osteoarthritis, haemophilia and spondyloarthropathy—can be treated successfully by radiosynoviorthesis (RSO). For medium-sized joints (shoulder, elbow, wrist, hip and ankle), the radionuclide of choice is rhenium-186. We review the evidence for the efficacy of this local, relatively non-invasive therapy and evaluate its benefits and risks. We conclude good evidence of rhenium-186 RSO in rheumatoid arthritis and haemophilic arthropathy. In the remaining pathologies, up to now, the therapeutic efficacy has not been confirmed by today’s most stringent criteria for clinical studies. The available data support rhenium-186 RSO as a suitable second-line treatment for patients in whom other therapies (including locally injected corticoids) have failed, as long as proper attention is paid to correct administration—including post-treatment immobilization and the co-administration of corticoids.

Key words: Radiosynoviorthesis, Rhenium-186, Rheumatoid arthritis, Osteoarthritis, Haemophilia, Spondyloarthropathy.

Introduction

Rheumatic conditions are among the most common diseases encountered today, with a prevalence of about 2% in industrialized countries. They can be divided into those that are primarily inflammatory and those that are primarily non-inflammatory. Among the former, rheumatoid arthritis (RA) is the most common, affecting 1% of the population in the industrialized world [1]. The latter include haemophilic arthropathy, for example. First-line treatment of RA is systemic, i.e. symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAIDs), accompanied by glucocorticoids and disease-modifying antirheumatic drugs (DMARDs) for ‘modification’ of the underlying immuno-inflammatory events and delay of joint destruction (for reviews of anti-rheumatic systemic therapies see [2–4]). Especially, DMARDs are the subject of intensive development activity from pharmaceutical companies [1].

Local treatment, e.g. inflammation control with topical analgesics or glucocorticoids, is likewise often unsatisfactory in the long term and can, moreover, produce severe side effects. The next step is ablation of the diseased, hypertrophied synovium. Surgical resection of the synovium by open synovectomy is no longer generally practised; today, ‘keyhole’ arthroscopic synovectomy is standard [5]. However, this often fails to remove the entire diseased tissue, and effusion then recurs [6, 7]. Alternative methods to destroy the hypertrophied synovial tissue in situ have included the application of chemical agents such as osmic acid and of radioisotopes. The principle is to apply a substance that causes destruction of the diseased tissue and, ideally, allows restoration of the synovial membrane (synoviorthesis). Such therapy is today considered an appropriate second-line treatment for patients who have failed to respond to other systemic or topical treatments.

Radiosynoviorthesis (RSO) has been in use for several decades, the first report of its clinical use appeared in 1952 [8]. After injection, the radiopharmaceutical is phagocytized by the superficial synovial cells. The radiation halts the inflammatory activity, including the proliferative and destructive processes, resulting in alleviation of the pain and effusion [9, 10].

The choice of the nuclide for RSO is based upon the tissue penetration depth of the emitted radiation and upon the half-life of the radioisotope used. The penetration depth should be equal to the thickness of the synovium in the joint to be treated, balancing the inferior effect of too shallow penetration against the potential hazard of too deep penetration. The half-life should be long enough to allow good distribution within the synovium and adequate exposure, while being short enough to avoid excessive irradiation and significant leakage from the joint. These criteria have led to the current use of three isotopes for RSO in Europe [11]:

(i) Yttrium-90 (90Y; t½ 2.7 days; therapeutic penetration depth 2.8 mm) for the knee.
(ii) Erbium-169 (169Er; t½ 9.4 days; 0.3 mm) for the fingers and toes.
(iii) Rhenium-186 (186Re; t½ 3.7 days; 1.0 mm) for medium-sized joints: the hip, shoulder, elbow, wrist, ankle and subtalar joint.

A further criterion for successful RSO is the time of retention of the nuclide within the synovial capsule. This should ideally be longer than the decay time of the nuclide. Adequately long retention times are obtained by using colloids of an insoluble derivative, with an appropriate particle size. For rhenium, the sulphide has been found to be the best in this respect and is the only form used.

A meta-analysis by Kresnik et al. [12] reflects extensive clinical experience with RSO. This study contains data on 2190 joints, of which according to our calculation 115 were treated with 186Re sulphide colloid. The authors defined four groups of diseases, in which the use of RSO was assessed as ‘appropriate’, ‘acceptable’, ‘helpful’ or ‘not indicated’. They concluded that, apart from the underlying disease, the pre-existing morphological damage to the joint is decisive for the therapeutic outcome.

A recently published systematic review on radiosynoviorthesis (RSO using Yttrium-90 colloid [13] underlines its clinical value for the knee joint but the benefit for medium-sized joints remains undiscovered.
The purpose of the present review is to survey the current status of RSO with \(^{186}\)Re and to assess its benefit–risk ratio in the light of all available data. Most studies of this treatment—going back nearly three decades—would not have fulfilled today’s rigorous present-day criteria for clinical research. However, these criteria) varied from 42 to 92% in the prospective and 61–80% in the retrospective trials; a closer comparison across trials cannot meaningfully be made as different success criteria and different follow-up periods were used.

As mentioned above, most of these studies—going back eight (Table 1) and nearly 30 yrs (Table 2), respectively—do not fulfill rigorous present-day criteria for clinical research. However, these studies, especially those conducted prospectively, do provide substantial evidence in favour of the efficacy of the treatment.

Efficacy of treatment with \(^{186}\)Re-rhenium sulphide

Rheumatoid arthritis (RA)

In Tables 1 and 2, we present a summary of the results of prospective and retrospective trials on the use of \(^{186}\)Re RSO in RA with a follow-up examination after at least 6 months. The clinical efficacy found (percentage of patients fulfilling the success criteria) varied from 42 to 92% in the prospective and 61–80% in the retrospective trials; a closer comparison across trials cannot meaningfully be made as different success criteria and different follow-up periods were used.

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### Table 1. Prospective studies on the efficacy of \(^{186}\)Re colloid in treating rheumatoid arthritis

<table>
<thead>
<tr>
<th>Study design</th>
<th>Intra-articular corticoid failure?</th>
<th>No. of joints (N)</th>
<th>Activity (MBq)</th>
<th>Assessment criteria</th>
<th>Follow-up duration (months)</th>
<th>Success rate: (% of joints)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open, uncontrolled</td>
<td>Yes</td>
<td>73</td>
<td>Shoulder, elbow, hip, ankle: 185</td>
<td>Effective treatment</td>
<td>12</td>
<td>75%</td>
<td>Jahangier et al. [45]</td>
</tr>
<tr>
<td>Multicenter, single-blind, randomized ((^{186})Re vs cortivazol 3.75 mg)</td>
<td>No</td>
<td>129</td>
<td>Shoulder, elbow, wrist, ankle: 63.5 ± 3.8</td>
<td>Decr. in pain / decr. in swelling / decr. in both</td>
<td>3 to 24</td>
<td>See Table 3</td>
<td>Tebib et al. [20]</td>
</tr>
<tr>
<td>Randomized ((^{186})Re vs triam vs both)</td>
<td>No</td>
<td>50</td>
<td>Hip, shoulder: 111</td>
<td>% TDOR</td>
<td>36</td>
<td>34%, 82%, 42%</td>
<td>Gobem et al. [46]</td>
</tr>
<tr>
<td>Randomized, placebo-controlled, double-blind, single center</td>
<td>Yes</td>
<td>27</td>
<td>Shoulder: 110</td>
<td>Change composite index (CCI)</td>
<td>6 and 12</td>
<td>74% / 81% vs 18% / 22%</td>
<td>van der Zant et al. [48]</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>No</td>
<td>23</td>
<td>Elbow, wrist, ankle: 74</td>
<td>Modified Richi score (pain, synovitis, joint function)</td>
<td>5</td>
<td>88%</td>
<td>Gratz et al. [37]</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>No</td>
<td>28</td>
<td>Hip, shoulder: 110–185</td>
<td>Pain reduction (by VAS)</td>
<td>6</td>
<td>78%</td>
<td>Farahati et al. [16]</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>No</td>
<td>40</td>
<td>Elbow, wrist, ankle: 74</td>
<td>Moderate, good and very good results</td>
<td>6–26</td>
<td>80</td>
<td>Rozeboom et al. [49]</td>
</tr>
</tbody>
</table>

\(^{186}\)Re was observed to be statistically superior to RA, seronegative spondyloarthropathy, osteoarthritis (OA), haemophilic arthropathy, calcium pyrophosphate dihydrate arthropathy, undifferentiated arthritis and other inflammatory joint conditions, chronic joint effusions and pigmented villonodular synovitis. A survey between 1991 and 1993 [15] revealed that, at that time, some 71% of RSO procedures were for RA. Today, there is a trend towards increasing use of RSO in other indications such as OA [16, 17].

According to current best practice [18, 19]:

(i) RSO should only be used as second-line treatment, when all methods of conservative therapy have failed, including intra-articular injections of long-acting corticosteroids.

(ii) The recommended activity range for RSO with \(^{186}\)Re sulphide colloid is as follows: for the hip, 74–185 MBq; shoulder, 74–185 MBq; elbow, 74–111 MBq; wrist, 37–74 MBq; ankle, 74 MBq; subtalar joint, 37–74 MBq.

(iii) When several joints are being treated in a single session, the total activity administered should not exceed 370 MBq.

(iv) The administration of glucocorticoids at the same time as RSO is recommended; apart from their short-term add-on therapeutic effect, they promote healing of the injection puncture and thus help to prevent unwanted radiation-induced necrosis.

(v) Absolute contra-indications to any RSO are pregnancy, breast-feeding, local skin infection and ruptured cysts communicating with the treated joint. Relative contra-indications are extensive joint instability with bone destruction, evidence of significant cartilage loss within the joint and, for patients <20 yrs of age, an unfavourable hazard–benefit ratio.

### Indications and standard activity range for \(^{186}\)Re RSO

The indication for RSO is, fundamentally, inflammatory hypertrophy of the synovium and thus includes RA, seronegative spondyloarthropathy, osteoarthritis (OA), haemophilic arthropathy, calcium pyrophosphate dihydrate arthropathy, undifferentiated arthritis and other inflammatory joint conditions, chronic joint effusions and pigmented villonodular synovitis. A survey between 1991 and 1993 [15] revealed that, at that time, some 71% of RSO procedures were for RA. Today, there is a trend towards increasing use of RSO in other indications such as OA [16, 17].

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difference in favour of $^{186}$Re was significant for pain, swelling, mobility, ‘pain and swelling’ and ‘pain or swelling’. A greater relative risk of relapse in corticoid-treated joints was demonstrated, but only from the second year of follow-up. The study concluded that $^{186}$Re and cortivazol had similar efficacy up to 12 months after injection, but that thereafter $^{186}$Re became more effective.

It was also noted that the Steinbrocker radiological stage at inclusion was not a predictive factor of efficacy. $^{186}$Re appeared equally effective in terms of long-term (12–24 months) improvement in pain and swelling, whatever the initial radiological stage. However, during the first 6 months, significantly more rapid improvement was noted in stages I–II than in stages III–IV. This is in line with other observations that the earlier stages of disease are more amenable to treatment by RSO [21–24].

Seronegative spondyloarthropathy

The term seronegative spondyloarthropathy covers a number of pathological conditions, for example ankylosing spondylitis, Reiter’s syndrome, psoriatic arthropathy and reactive arthritis. In many respects, their therapy resembles the therapy of RA and follows the principles of treatment of rheumatic diseases. Since here too, the underlying pathology is inflammatory alteration of the synovial membrane, the effectiveness of RSO in this group of diseases does not differ essentially from its effectiveness in RA. Therefore, the two conditions are frequently considered and assessed together [17].

Various authors have reported results of RSO with $^{186}$Re in patient groups that also included patients with seronegative arthropathy. In these publications, ‘very good’ and ‘good’ results were reported in around 50% of patients. Kampen et al. [25] conducted a retrospective study on 25 patients with inflammatory joint diseases (other than RA) who received RSO. $^{186}$Re sulphide colloid had been administered in one subtalar joint, four wrists, six ankles and one shoulder 6 to 18 months earlier. A questionnaire was sent to the patients during follow-up. Radiation synovectomy did not show significant clinical success (‘good’ and ‘very good’ results with respect to joint effusion and restriction of joint movement were obtained in 6/12 joints); however, no aggravation of symptoms was seen in any of the patients. Menkes et al. [26] reported retrospectively the results of RSO with $^{186}$Re in 357 wrists (including 28 cases of seronegative spondyloarthropathy). Among these joints, only 16 joints with psoriatic arthropathy were followed during 6 months. The results obtained in these 16 joints were very good or good in half of the cases (50%). Similar results were observed after between 1 and 2 yrs in a small population. Rampon et al. [27] described good and very good results in seven of eight treated joints after 6 months. Thus, the few results available document a good response in this indication.

Osteoarthritis

Osteoarthritis OA develops from degenerative joint disease; the inflammatory alteration of the synovial membrane is the result of articular degeneration, and the clinical symptoms are a combination of those of the degenerative joint disease and of the synovitis. The proportion of RSO treatments performed for OA is a little above 7% and is rising [15–17]. The response to RSO depends on the extent of involvement of degenerative disease and synovitis, and in the two largest studies with $^{186}$Re, it was 78% and 69% (Table 4); the other studies were too small to allow appropriate assessment.

Haemarthrosis (haemophilic arthropathy)

Haemophilia is a hereditary blood coagulation disorder that can occur in various forms. Haemorrhagic arthropathy occurs as a result of bleeding into the joint. Recurrent bleeding into a joint causes a gradual destruction of bone and cartilage, which can lead to the development of various joint alterations and eventually to ankylosis. RSO is indicated when a chronic state of synovitis has developed as a result of repeated articular haemorrhages and when haematological therapy has failed [28].

**Table 2. Retrospective studies on the efficacy of $^{186}$Re colloid in treating rheumatoid arthritis**

<table>
<thead>
<tr>
<th>Study design</th>
<th>Intrarticular corticoid failure?</th>
<th>No. of joints (N)</th>
<th>Activity (MBq)</th>
<th>Assessment criteria</th>
<th>Follow-up duration (months)</th>
<th>Success rate: (% of joints)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncontrolled; use of questionnaire</td>
<td>No</td>
<td>125</td>
<td>Subtalar joint: 40; elbow, wrist, ankle: 70; shoulder: 110</td>
<td>Good and very good results</td>
<td>6–18</td>
<td>71</td>
<td>[25]</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>No</td>
<td>324</td>
<td>Wrist: 74</td>
<td>Good and very good results</td>
<td>6–12–24</td>
<td>73</td>
<td>[26]</td>
</tr>
<tr>
<td>Uncontrolled (some treated with $^{186}$Re, some with $^{186}$Er)</td>
<td>No</td>
<td>390</td>
<td>Hip: 111–148; shoulder: 74–111; elbow, wrist, ankle: 55.5–74</td>
<td>Good and very good results</td>
<td>6</td>
<td>80 (overall, both nuclides)</td>
<td>[27]</td>
</tr>
<tr>
<td>Uncontrolled, multicenter</td>
<td>Not stated</td>
<td>62</td>
<td>Elbow</td>
<td>Good and very good results</td>
<td></td>
<td>66 vs 81</td>
<td>[50]</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>Most</td>
<td>193</td>
<td>Wrist: 55–74</td>
<td>‘Good’ or ‘satisfying’ results</td>
<td>24</td>
<td>61 seropos, pats Gamp [51] 68 seroneg. pats</td>
<td></td>
</tr>
</tbody>
</table>

Results calculated by the authors from data in the publications cited.

Triam, triamcinolone hexacetonide; vs, versus; CS, corticosterone.

**Table 3. Comparative efficacy of $^{186}$Re and cortivazol at different times**

<table>
<thead>
<tr>
<th>Time after treatment</th>
<th>Treatment</th>
<th>Pain</th>
<th>Swelling</th>
<th>Mobility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$^{186}$Re</td>
<td>36/43</td>
<td>68%&lt;sup&gt;ns&lt;/sup&gt;</td>
<td>37/63</td>
</tr>
<tr>
<td>6 months</td>
<td>Cortivazol</td>
<td>39/57</td>
<td>68%&lt;sup&gt;ns&lt;/sup&gt;</td>
<td>26/57</td>
</tr>
<tr>
<td></td>
<td>$^{186}$Re</td>
<td>45/65</td>
<td>69%&lt;sup&gt;ns&lt;/sup&gt;</td>
<td>42/65</td>
</tr>
<tr>
<td>12 months</td>
<td>Cortivazol</td>
<td>45/84</td>
<td>69%&lt;sup&gt;ns&lt;/sup&gt;</td>
<td>33/64</td>
</tr>
<tr>
<td></td>
<td>$^{186}$Re</td>
<td>45/64</td>
<td>70%&lt;sup&gt;ns&lt;/sup&gt;</td>
<td>33/64</td>
</tr>
<tr>
<td>18 months</td>
<td>Cortivazol</td>
<td>38/45</td>
<td>84%&lt;sup&gt;ns&lt;/sup&gt;</td>
<td>32/45</td>
</tr>
<tr>
<td></td>
<td>$^{186}$Re</td>
<td>31/42</td>
<td>74%&lt;sup&gt;ns&lt;/sup&gt;</td>
<td>24/42</td>
</tr>
<tr>
<td>24 months</td>
<td>Cortivazol</td>
<td>39/46</td>
<td>85%&lt;sup&gt;ns&lt;/sup&gt;</td>
<td>38/45</td>
</tr>
<tr>
<td></td>
<td>$^{186}$Re</td>
<td>39/46</td>
<td>84%&lt;sup&gt;ns&lt;/sup&gt;</td>
<td>36/44</td>
</tr>
<tr>
<td></td>
<td>Cortivazol</td>
<td>23/35</td>
<td>66%&lt;sup&gt;ns&lt;/sup&gt;</td>
<td>20/34</td>
</tr>
<tr>
<td></td>
<td>$^{186}$Re</td>
<td>43/46</td>
<td>94%&lt;sup&gt;ns&lt;/sup&gt;</td>
<td>36/44</td>
</tr>
<tr>
<td></td>
<td>Cortivazol</td>
<td>24/33</td>
<td>73%&lt;sup&gt;ns&lt;/sup&gt;</td>
<td>17/32</td>
</tr>
</tbody>
</table>

Results are expressed in numbers and proportions of joints clinically improved at the different times.<sup>ns</sup>, not significant; *, $P < 0.1$; **, $P < 0.05$. 

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Articular haemorrhages lead, via various mechanisms, to synovitis, which in turn increases the tendency toward further bleeding into the joint. RSO interrupts this progressive vicious circle by inducing fibrosis of the inflamed synovial membrane.

It has been demonstrated in a number of studies that after RSO the frequency of bleeding is reduced. Molho et al. [29] compared the results of RSO with those of osmic acid administered intra-articularly. They treated 107 patients (206 joints) including 48 medium-sized joints to which $^{186}\text{Re}$ was administered. Six months after treatment, 81% of the joints treated with isotopes showed good results, in contrast to only 44% of those treated with osmic acid. This was confirmed up to 4 yrs after treatment in 28 joints followed-up, of which 17/20 joints treated with $^{186}\text{Re}$ showed improvement compared with only 4/8 joints treated with osmic acid. Similar results (up to 88% success) were obtained by Fernandez-Palazzi and Caviglia [30], with a reduction in haemarthrosis in 14–28% of cases and no more haemarthrosis followed-up, of which 17/20 joints treated with $^{186}\text{Re}$ showed improvement compared with only 4/8 joints treated with osmic acid. A study by Fernandez-Palazzi et al. [31] showed that, the RSO treatment will often be more unacceptable, especially to a child, than surgery or repeated injections of glucocorticoid. Nonetheless, published data on this are scarce, and in view of the (at least theoretical) risk of radiation-induced malignancy the decision to use RSO must be backed up by a detailed individual case assessment and a scrupulous risk–benefit consideration.

Another potentially important application of $^{186}\text{Re}$-RSO is expected to be in the developing countries. Here, the health-care services often lack the means to detect, and the resources to treat, haemophilia. Consequently, this disorder is less well controlled than in the industrialized countries, and secondary disorders such as haemarthrosis develop more frequently. Especially, in haemarthrosis RSO can also be performed without proved synovitis. Therefore, in this special field no expensive diagnostic procedure like MRI or bone scintigraphy is needed, and joint-bleeding can be prevented with low cost using RSO.

### Other indications

These include the following diseases, where RSO offers a way of treating the inflammatory alterations of the synovial membrane when other conventional therapeutic procedures have failed or are inherently inadequate:

(a) Crystal arthropathy with calcium pyrophosphate crystals: only one publication was found [32]. Twelve shoulders treated with $^{186}\text{Re}$ were included among 32 joints in all. RSO was found to be effective: after an average of 3.3 yrs, the treatment, although lacking a definite analgesic effect, frequently led to lasting cessation of the haemarthrosis.

(b) Undifferentiated arthritis (characterized by synovitis, synovial membrane swelling or effusion) and other inflammatory joint diseases (e.g. borreliosis, Behçet’s disease): different authors [27, 33] reported results of RSO with $^{186}\text{Re}$ in groups that comprised some patients with the aforementioned indications, reporting good results overall. There is no evidence that these patients responded differently to those treated because of RA.

(c) Chronic articular effusion: this term is encountered especially in the older literature, where there are no exact data that would allow a differentiation of the origin of the effusion [34]. The pathophysiological picture resembles OA when other mechanical causes have been excluded.

(d) Pigmented villonodular synovitis (PVNS) is a rare benign disease of the synovial membrane that is treated primarily by

### Table 4. Efficacy of $^{186}\text{Re}$ colloids in treating osteoarthritis

<table>
<thead>
<tr>
<th>Study design</th>
<th>Intra-articular corticoid failure?</th>
<th>No. of joints (N)</th>
<th>Activity (MBq)</th>
<th>Assessment criteria</th>
<th>Follow-up duration (months)</th>
<th>Success rate: (% of joints)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncontrolled use of questionnaire</td>
<td>No</td>
<td>12</td>
<td>Subtalar joint: 40, Wrist, ankle: 70</td>
<td>'Excellent' or 'good' clinical result for pain</td>
<td>6–18</td>
<td>58%</td>
<td>Kampen et al. [25]</td>
</tr>
<tr>
<td>Prospective, uncontrolled use of questionnaire</td>
<td>No</td>
<td>9</td>
<td>Shoulder: 110, lower ankle: 40</td>
<td>Subjective improvement</td>
<td>6–18</td>
<td>40%</td>
<td>Kronger et al. [33]</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>No</td>
<td>5</td>
<td>Hip: 111–148, Shoulder: 74–111, Elbow, wrist, ankle: 55–74</td>
<td>Very good result</td>
<td>6</td>
<td>2/5</td>
<td>Rampon et al. [27]</td>
</tr>
<tr>
<td>Multicenter, retrospective, uncontrolled</td>
<td>Not stated</td>
<td>91b</td>
<td>Hip: 150, Shoulder: 70, Elbow: 75, Wrist, ankle: 40–70</td>
<td>'Excellent' or 'good' clinical results</td>
<td>≥ 6</td>
<td>69%</td>
<td>Rau et al. [17]</td>
</tr>
</tbody>
</table>

Percentages calculated by the present authors from data in the publications.

*aOverall patient results for all joints with inflammatory OA, not only $^{186}\text{Re}$

*b13% of joints were not treated for OA.

Ref. reference.
Synovectomy. Very limited data are available on $^{186}$Re in PVNS [35]; three patients with PVNS of the hip were treated surgically and with $^{186}$Re with clinically good results. Kresnik et al. [12] regarded PVNS as ‘appropriate’ for RSO. As above, RSO may usefully follow surgical synovectomy.

**Safety of RSO with $^{186}$Re-rhenium sulphide**

As with any nuclide therapy, safety issues with the $^{186}$Re sulphide colloid comprise those associated with radioactivity and those caused by the mechanical or surgical procedures involved or the nuclide’s chemical vehicle. The effects of radioactivity may be due to direct radiation from the site of application of the radiopharmaceutical, or to leakage of radioactive material from this site and resulting systemic effects. These safety factors are considered in turn.

**Radiation from the application site**

The $\beta$-radiation, because of its short penetration distance, reaches only structures in the immediate vicinity of the joint cavity, while the 137-keV $\gamma$-ray co-emitted by $^{186}$Re, and secondarily generated bremsstrahlung can reach more remote organs. In this connection, the radiation dose to the gonads is the main topic. The highest dose results from a RSO of the hip. For a RSO of other joints, the dose to the gonads is clearly smaller because of the greater distance to the gonads and a lower activity injected. For an activity of 150 MBq of $^{186}$Re administered to the hip, the maximal $\gamma$-radiation dose to the gonads was estimated at 3.5 mSv, with a further <10% due to bremsstrahlung [36].

**Leakage from the application site**

There are limited clinical data on leakage of colloidal $^{186}$Re sulphide out of treated joints, based upon $\gamma$-imaging. Gratz et al. [37] conducted whole-body imaging and when the treated joint was immobilized, activity in the lymph nodes was undetectable; without immobilization of the joint, leakage of 40% was observed.

Van der Zant et al. [38] injected $^{186}$Re into 54 ankle joints of 40 patients. Glucocorticoids were co-administered and the joints were immobilized for 3 days. Twenty-four hours after injection, $\gamma$-camera imaging was performed. The mean activity fractions were: for the lymph nodes, 2.4% of the injected activity (range: 0.9-6.6%); for the liver, 0.8% (0-5.5%); for total leakage, 3.2% (0-9.6%). A limitation of the study was the rather short time between injection and observation. Nevertheless, the data are relevant because of the large number of patients and in view of the fact that all today’s recommendations were adhered to: choice of the ankle joint for the $^{186}$Re preparation, co-administration of corticoids and immobilization.

The authors compare the risk of $^{186}$Re RSO of the ankle with that of other activities and conclude, for example, that the risk of radiation-induced death in this procedure is 1/25 of the risk of a computer-tomographic chest examination.

**Estimation of organ exposure to radiation**

It is possible to estimate the radiation dose due to leakage, if certain assumptions are made. These are: (i) The fraction of activity leaking out is 10% of the total activity (this is about three times the most reliable value found to date [38]). (ii) All of this radioactivity is taken up by the reticulo-endothelial system (RES). (iii) The locoregional nodes are a transitory station for the activity coming out of the treated joint and thus contain a constant fraction of the leaked-out activity [39]. (iv) The fraction of the activity in the lymph nodes is about 3% of the injected activity [38]. Together, these assumptions lead to an overestimate (some of the activity is counted both in the RES and the lymph nodes). Finally (v), the distribution of colloid particles is taken to correspond to that given for small colloids [40]; liver 70%, red bone marrow 15%, spleen 10%, remaining tissues 5%. On the basis of these assumptions, the radiation exposure due to uptake by the RES was calculated to be 925 $\mu$Gy/MBq for the liver, 1370 $\mu$Gy/MBq for the spleen and 102 $\mu$Sv/MBq for the effective whole body dose [36]. In a RSO with 75-MBq $^{186}$Re these values lead to a radiation dose of 69 mGy to the liver, 103 mGy to the spleen and 7.7 mSv to the whole body.

Up to now, only a small number of studies have calculated the radiation dose by measuring the real leakage using whole body scintigraphy or by measuring blood activity. For an injected activity of 75 MBq, the radiation dose to the whole body, the liver, the spleen and lymph nodes was calculated to be between 2 and 53 mGy, 7.5 and 100 mGy, 26 and 203 mGy and 15 and 35 Gy, respectively [37–39, 41]. (The whole body dose of 0.15 mSv, reported by van der Zant et al. [38], could not be considered because of the described calculation method, this value must result from a calculation error.) The dose to the red marrow was only calculated in one study, which reported a dose of 3 mGy [41]. In a RSO of the hip or shoulder with a maximum activity of 185 MBq the doses are about 2.5 times greater.

For assessment of the benefit-risk ratio of RSO with $^{186}$Re, these radiation-absorbed doses should be seen in comparison with the radiation doses incurred by other diagnostic and therapeutic medical measures.

The lower value (2 mGy) of the whole body dose range is exceeded by a great number of very frequently performed diagnostic procedures in nuclear medicine and radiology. Some medical measures such as interventional fluoroscopic procedures (25 mSv) and myocardial perfusion scintigraphy with $^{201}$TL (26 mSv) reach values similar to the upper range of the estimated doses. In the radionuclide therapy of benign thyroid diseases with $^{131}$I, typical effective doses are about 41 to 46 mSv (excluding the dose to the target tissue thyroid). In the case of treatment of thyroid carcinoma with $^{131}$I, a typical effective dose is 287 mSv. In view of the fact that RSO with $^{186}$Re is—after failure of intra-articular cortisone administration—the last non-surgical option in patients with painful inflammatory joint diseases, doses in the estimated order of magnitude appear acceptable.

**Biological dosimetry—chromosome aberrations**

Hitherto, data on chromosome aberrations are also few and far between. One study reported the results of only two patients [42] and one of the patients was treated with both $^{186}$Re and $^{90}$Y at the same time. Therefore, these data are not helpful. Manil et al. [39] reported biological dosimetry results in 24 patients who received $^{186}$Re RSO in up to three joints at the same time (maximal injected activity = 210 MBq). The number of dicentrics increased from Day 0 to Day 7. However, a baseline was not measured for all patients and the patients without baselines account for one-third of the incremental dicentrics observed. Because of this, the result of the study is not meaningful.

Vargas and Fernandez-Palazzi [43] assessed chromosomal structural changes (CSCs) in haemophiliacs who did ($n = 31$) or did not ($n = 31$) receive $^{186}$Re, and in non-haemophilic controls ($n = 110$). Pre-malignant CSCs were not found in any of these groups. Non-specific CSCs were found 6 months after RSO with $^{186}$Re in 1.25% of the metaphases, but were not found another 6 months later. In the group of haemophiliacs who did not receive radioactive treatment, non-specific CSCs were found in 0.79% of metaphases. In the control group, no non-specific CSCs were found.

Fernandez-Palazzi and Caviglia [30] reported results on the safety of RSO with $^{186}$Re in haemophilic patients (age range 6-40 yrs; 65% of the patients were <12 yrs-old). They performed chromosomal studies before RSO in 11 patients and after RSO in seven of these. No pre-malignant chromosomal abnormalities were found (markers, segregations, triradicates,
dicentrics or others). Non-specific CSCs were observed in 4.7% of the metaphases before RSO and in 11.94% 6 months after RSO. The results confirmed that changes potentially linked to the radiation appeared equally frequently in irradiated and non-irradiated patients, and that the changes due to the radiation disappear with time, never reaching the dangerous level of 2% of structural changes.

Thus, the sparse data currently available suggest that $^{186}$Re RSO does not engender dangerous levels of chromosomal aberrations, but well-designed studies using state-of-the-art methodology, as described by Voth et al. [44], are needed to further disclose a substantial radiation exposure to the patient.

Other adverse effects

None of the publications of studies with $^{186}$Re cited in this article describe adverse side effects of the RSO. Tebib et al. [20] report that no serious side effects were observed in any patient, with only light and transient local pain and/or swelling occurring in 24% of cases, regardless of the treatment used. Jahangier et al. [45] mention that no short-term adverse effects were seen, and Göbel et al. [46] state that no complications in the form of joint infection, radiation dermatitis or any periarticular soft-tissue damage were encountered. A nationwide survey in Germany with a standardized questionnaire has shown that only very few side effects are associated with RSO (the survey covered all nuclides currently used in RSO) [47].

Conclusion

RSO with a $^{186}$Re sulphide colloid offers a local, relatively non-invasive therapeutic method for the treatment of arthritic joint conditions of various origin in medium-sized joints such as the shoulder, elbow, wrist, hip and ankle. RSO can thus, in many cases, restore the patient’s ability to lead a fairly normal life. A good evidence for its therapeutic efficacy exists in RA and haemophilic arthropathy (Table 5). Although in the remaining indications the therapeutic efficacy has not been confirmed by today’s most stringent criteria for clinical studies (randomized, double-blind, controlled, correct dosing, sufficiently powered, etc.), the accumulated evidence of the numerous trials and surveys conducted to date indicates strongly that the method is effective. The available data support the efficacy of $^{186}$Re RSO as a second-line therapy for patients in whom injection of long-acting steroids has failed. The risk–benefit ratio of $^{186}$Re RSO, when it is correctly applied, also compares favourably with the alternatives available.

Practical details regarding the administration of $^{186}$Re and the avoidance of unwanted side effects can be found in the current European [18] and German [19] RSO guidelines designed to ensure the routine attainment of the full effectiveness of the method in a safe manner. Adherence to these guidelines—which are similar in all important points—will ensure that this is the case.

Conflicts of interest. R.K. has received study sponsoring, consultancy fees and speaker’s fees from Schering Germany and CIS Bio.M.V. is an employee of Bayer Schering Pharma, the former owner of CIS biointernational (supplier of Re-186 colloid). J.P. is an employee of Schering Germany, a subsidiary of Schering AG, the former owner of CIS biointernational (supplier of Re-186 colloid). The other authors have no conflicts of interest to declare.

References


| Table 5. Level of evidence (AHCPR [52]) of the different indications |
|---------------------|---------------------|
| Indication          | Level of evidence   | Reference                |
| Rheumatoid arthritis| I b                 | Tebib et al., Göbel et al., van der Zant and Jahangir [29, 46, 48] |
| Spondyloarthritis   | IV                  | all                      |
| Osteoarthritis      | IV                  | all                      |
| Hemophilic arthropathy | II a              | Molho et al. [29]        |
| Other               | IV                  | all                      |

Rheumatology key messages

Evidence for therapeutic efficacy of $^{186}$Re RSO is:

- Good for RA and haemophilic arthropathy
- Poor for other inflammatory joint diseases