

# Scientific Meeting Report

## Radiosynovectomy — radionuclide treatment of synovitis in the peripheral joints

On 25 February 2012, an interdisciplinary scientific meeting on the Radiosynovectomy of Peripheral Joints (RPJ) was held in a lecture hall of Nukleomed clinic in Warsaw. The meeting was participated by a number of orthopaedists, rheumatologists, general practitioners and nuclear medicine specialists, including Prof. Jarosław Czubak from the Prof. A. Gruca Independent Public Clinical (CMKP) Hospital in Otwock, Prof. Leszek Królicki from the Medical University of Warsaw and Prof. Manfred Fisher from the Medical University in Kassel (Germany), who apply or wish to initiate radionuclide treatment of synovitis for their patients. The meeting was opened and hosted by Dr Krzysztof Toth from Nukleomed clinic in Warsaw.

The inauguration lecture was given by Prof. Leszek Królicki (LK), National Consultant for Nuclear Medicine. First, Prof. Królicki referred to the enormous advancement in the development of new diagnostic methods in Europe, pointing out the advantages of hybrid methods, such as SPECT/CT, PET/CT and PET/MRI, over traditional imaging methods. He noted that today the percentage of scintigraphic tests is very high compared to other diagnostic methods used on an everyday basis in the European Union and that they will continue to be favoured in the future over traditional radiological procedures. Currently, about 50% of cardiological tests and 55% of skeletal system tests are scintigraphic procedures compared to other diagnostic imaging methods used in Europe. According to the projections based on the method of technopolis (aimed at forecasting the development of new technologies and their application in the future), there will be fewer tests based on traditional procedures and the percentage of diagnostic tests with the assistance of hybrid technologies will increase. The essential advantage of the latter is the capability of simultaneous imaging both the morphological structure and functioning of specific organs.

In the second part of his presentation Prof. Królicki presented a historical background and guidelines of the European Association of Nuclear Medicine (EANM) for radionuclide joint treatment.

He reminded that the essential objective of radionuclide treatment is to inhibit the growth of the synovial membrane by using the energy of beta radiation of intra-articularly administered radiocolloids. An isotope phagocytized by synoviocytes emits energy which causes the decay of over-reactive cells, thus preventing local effusions and inhibiting inflammatory factors in the joint, and finally alleviating pain and improving the joint kinetics. LK discussed in detail the properties of isotopes used for RPJ: yttrium-90, rhenium-186 and erbium-169, and emphasized the importance of their proper selection relative to the size of the joint and thickness of the synovial membrane.

The isotope-specific hardness of beta radiation determines its action within the joint. For this reason yttrium-90 isotopes with average radiation hardness of 3.6 mm in the soft tissue are used for treating knee joints, rhenium-186 isotopes with maximum radiation hardness of 1.1 mm are used for mid-size joints, such as brachioradial, cubital, iliofemoral, tarsal or shoulder joints and erbium-169 isotopes with radiation hardness of 0.3 mm are used for small-size joints of the hand and foot. In reference to factors underlying the efficacy of the treatment LK focused particular attention on proper qualification of patients based on close cooperation between nuclear medicine physicians and clinicians. According to the EANM guidelines, the treatment of joints using radionuclides involves is only a symptomatic treatment designed for patients whose level of pain or other problems within the joint have a significant adverse impact on their mobility or require taking analgesics on a permanent basis. RPJ may be used for the following nosological entities:

- rheumatoid arthritis (RA);
- psoriatic arthritis (PA);
- reactive spondyloarthropathies;
- other types of arthritis, e.g. Lyme disease;
- Behcet's disease;
- persistent joint effusions;
- haemophilia;

- calcium pyrophosphate dihydrate disease (CPPD);
- pigmented villonodular synovitis (PVNS);
- persistent joint effusions following prosthetic surgery;
- non-classified inflammatory conditions, if the major symptoms include inflammation, synovial thickening and effusion.

If different forms of therapy are applied, the radionuclide treatment should not be used until 6 weeks after joint implementation and 2 weeks after joint biopsy. If it is necessary to re-administer a radioactive isotope, there should be a minimum time interval of 6 months. Absolute contraindications to RPJ include pregnancy and breast feeding, local skin infections and Baker's cyst rupture. Although a significant degree of joint instability and/or significant damage to joint cartilage are only relative contraindications to RPJ in accordance with the EANM guidelines, the treatment is practically not used in the case of patients with such problems on account of no analgesic effect and high risk of complications. The radionuclide treatment may be used for children and persons under the age of 20 after careful consideration of potential benefits and risks of possible complications.

LK recommended ultrasound scanning and dynamic bone scintigraphy among the tests which should be carried out as part of the qualification process for RPJ. Ultrasound scanning makes it possible to accurately determine the synovial membrane thickness and presence of effusions as well as to examine ligament structures of the joint, while scintigraphy makes it possible to determine physical functions of the joint synovial fluid. Greater uptake of the osteotropic marker in the vascular and parenchymatous phase supports the idea of high metabolic activity of the synovium and makes a good eligibility index.

Of significant importance here is close cooperation between clinicians and nuclear medicine specialists because treatment effects depend to a great extent on the time of application the radionuclide method from among a range of treatment forms. It is important to carry out RPJ at an early stage of the degenerative disease and at active stages of autoimmune or reactive diseases. One of the newest methods used for evaluating the activity of the inflammatory process is scintigraphy with specific markers. LK referred to the studies of Martins et al. concerning the application of labelled anti-CD3 monoclonal antibodies and of Rogier et al. concerning scintigraphy with labelled monocytes. At least two intra-articular haemorrhages in the course of a disease are considered a clinical indication for the application of RPJ in the treatment of arthropathy in the course of haemophilia. On the other hand, Kat and Shabat recommend comprehensive treatment — surgery followed by adjuvant radionuclide therapy — for patients with pigmented villonodular synovitis. Radionuclide therapy should be held in a nuclear medicine institute which has appropriate technical rooms and qualified personnel. Accurate application of radiopharmaceutical to the articular cavity should be absolutely carried out under aseptic conditions. It is recommended that punctures should be made in the X-ray or USG visual track as homogenous distribution of radiocolloid in the joint is necessary for the therapy to be effective. Patients should be informed about possible intermittent intensification of pain in the 1<sup>st</sup> – 2<sup>nd</sup> week of treatment. Restrictive joint immobilisation for 48 hours minimises the risk of complications, such as isotope moving back to the puncture channel and skin necrosis. Currently, a single intra-articular application of steroids (e.g. Triamcinolone

40 mg/1 ml in the case of large and mid-size joints, 20 mg/0.5 mL in the case of small-size joints) is recommended.

When discussing the efficacy of isotope-based radiosynovectomy, LK emphasized that it is a symptomatic treatment, and treatment effects in the form of improved articular mobility, reduced pain and swelling, and general improvement of the quality of life are delayed. The first follow-up visit should be arranged after 6–8 weeks. LK pointed out that the lack of clinical improvement after approximately 6 weeks from the isotope application shows that the results of therapy are uncertain. In some patients, a second isotope dose turns out to be effective. The therapy should not be re-applied until at least 6 months from the date of the first application.

When discussing the efficacy of radiosynovectomy, LK pointed out that the his own materials and literature review showed that better response to the treatment is achieved in the case of autoimmune (RZS, ŁZS) and reactive (chlamydiosis, Lyme disease) diseases compared to degenerative arthropathies. LK referred for example to the study of Rau et al. („Multicenter study of radiosynoviorthesis" 2004) which aimed to evaluate the impact of RPJ to the clinical condition and quality of life in 691 patients. The therapy has been observed to be most effective in patients diagnosed with 1<sup>st</sup>- and 2<sup>nd</sup>-stage RZS (78–80%). In the case of patients diagnosed with other diseases or more advanced stages of RA clinical improvement was observed in only 56%, and improved quality of life in 59% of them. LK referred also to the study of Markau et al. (2009) who published the results of 6-month yttrium-90 treatment for 76 patients with intense knee pain in the course of degenerative joint disease. Pain was resolved in as many as 89% of the patients, and improved articular mobility was achieved in 65%. The authors established that the efficacy of isotope-based therapy of knee joint synovitis depends on the duration of the disease, stage of progress and patient's age. Better response was achieved in the case of younger patients with less intense articular lesions. Similar conclusions were published by Kresnik et al. (2002), while according to Farahati et al. (2002) the duration of arthritis does not affect the efficacy of RPJ. Significant pain relief was reported for 78% of the patients at various intervals from the onset of pain. Finally, LK pointed out that despite the application of radioactive substances, isotope treatment of joints is fully safe in terms of exposure to ionizing radiation. Professor referred to the study of Vuoreli et al. in which indicators of carcinogenesis were evaluated for patients who underwent RPJ of knee joints. The authors demonstrated that intra-articular application of yttrium-90 does not contribute to the development of neoplastic diseases of other organs, and the indicator of cancer development for post-RPJ patients was twice as low compared to the control group. LK recapitulated that the potential of radionuclide therapy, which continues to be unappreciated in Poland and applied to a much more limited number of cases than in other European countries, and often enough can provide an important additional therapeutic option for orthopaedists, can only be fully realised by clinicians and nuclear medicine specialist working closely together.

The second part of the meeting featured presentations of radionuclide treatment results for chronic peripheral arthritis by physicians with extensive experience in this area.

The first presentation was held by Dr Maria Płazińska (MP), nuclear medicine specialist who described her own practice in the Nuclear Medicine Laboratory of the University Hospital in Warsaw.

RPJ procedure was applied in a group of 555 patients composed of 460 women and 95 men, where 243 patients were treated for chronic articular discomfort in the course of rheumatoid arthritis, 291 — in the course of osteoarthropathy (OA), and 21 patients suffered from psoriatic arthritis (PA). RPJ therapy was applied to all types of joints, mostly knee joints, shoulder joints, brachioacarpal joints and small-size joints of the hand. The isotope was administered twice to about 2/3 of the patients. MP detailed the methodology of RPJ and showed a range of photographs made during the procedures. The efficacy evaluation of radionuclide treatment included the change in the synovial membrane thickness and the amount of effusion within the joints subject to ultrasound scanning, joint swelling according to the circumference of the joint in cm, pain level, joint mobility and daily amount of analgesics. MP presented the results of knee joint treatment based on yttrium-90 for 40 patients as evaluated after 6 and 12 months from the date of procedure. She pointed out that the proper effects of radionuclide therapy should be subject to evaluation on a delayed basis. According to the statistical analysis, the percentage of patients for whom clinical improvement was achieved totalled approximately 75% at a 6-month interval and approximately 80% at a 24-month interval following the treatment.

Afterwards radionuclide treatment results for chronic synovitis in knee joints were presented by Dr Bogusław Musiał (BM), orthopaedist, who spoke on his own and Dr Tomasz Gołąb's behalf. As a preliminary point BM said that the literature contains few reports of radionuclide joint treatment results for diseases other than RA and haemophilia. In the Clinica Medica Nuclear Medicine Institute in Tychy, RPJ therapy was applied in 90 out of 124 patients who underwent qualification for the procedure. The number of radiosynovectomy procedures based on yttrium-90 was 89 in the case of OA patients and 12 in the case of RA patients. The efficacy evaluation of the treatment was carried out according to the criteria published by Blachut et al. which take into account the subjective impression of improvement, better joint mobility and recurrence of joint discomfort. Very good and good results were obtained for 52% of the patients suffering with degenerative joint disease, satisfactory results for 37%, while no effects were observed for 11%. The best treatment results (efficacy at approx. 80%) were demonstrated in the presented material for patients diagnosed with psoriatic arthritis, in the course of arthritis urica (efficacy at approx. 80%) and RA (efficacy at approx. 60%). BM pointed out that the literature contains a large number of studies concerning radionuclide peripheral joint treatment in RA and PA, however, there are no reports of treatment results for degenerative joint disease, and this was a prevailing disease among the patients included in the presented study. BM referred to the report of Deutsch et al. who analysed RPJ results from 72 German centres for patients who underwent the treatment because of pain in the course of RA in the years 1975–1992. Very good and good therapy results were achieved for 60–80% of the patients treated with synoviorthesis after an observation interval of one year or longer.

The next presentation titled "Radiosynovectomy in orthopaedic practice — 3 years of experience" was held by Dr Piotr Godek (PG). Firstly, PG extended a thank you to Dr Toth for showing interest in RPJ and initiating this specific procedure into the scope of practice in the Nuclear Medicine Laboratory at the Nukleomed clinic.

During the three years of cooperation with Dr Krzysztof Toth at the Nukleomed clinic in Warsaw 333 radiosynovectomy procedures were performed in the years 2009–2011, where 290 procedures were carried out on knee joints, 11 — on brachioacarpal joints, 10 — on small-size joints of the hand, 9 — on shoulder joints, 8 — on tarsal joints, and 3 — on cubital joints. Prepatellar bursa treatment was attempted in two cases. Among the patients included in the study a prevailing group of 171 patients suffered from intense degenerative lesions, 27 patients treated because of intensified articular discomfort in the course of RA, 4 — in the course of AS, and 1 patient with juvenile idiopathic arthritis (JIA). Radionuclide was injected twice in the case of 30 patients, and RPJ procedure was performed three times in the case of 9 patients. All patients had an ultrasound scan of the joint, including an evaluation of the synovial membrane thickness and the amount of effusion, prior to the treatment. In some patients the evaluation of joint synovitis was based on the three-phase dynamic bone scintigraphy results. Positive qualification criteria included increased accumulation of the marker (HMDP-Tc99m) within the joint in the parenchymatous phases of scintigraphy scanning and/or synovial hypertrophy diagnosed based on ultrasound results. Similarly as Dr Płazińska, PK illustrated his presentation with photographs taken during the procedures. In each case ultrasound monitoring was applied at the time of radionuclide administration. Administration of an appropriate radionuclide to the articular cavity was followed by injection of glucocorticosteroid (Betametazone 7 mg/mL). Following the procedure the joints were immobilized with orthoses as already mentioned proper immobilization of the treated joint is a necessary prerequisite for correct distribution of the marker in the articular cavity and prevents radioactive colloid from moving back to the puncture channel. All patients received thromboprophylactic treatment. To evaluate the efficacy of RPJ PG used so-called subjective assessment of patient's satisfaction which includes pain level, joint range of motion, daily activity. This method was used for evaluating the improvement of the quality of life on a scale from 0 to 100% in the case of 178 patients. Based on his own observations and literature data, PG determined that the highest efficacy of treatment was achieved in the case of JIA patients (improvement at 80%), and the lowest efficacy in the case of patients with degenerative lesions in the most advanced stage of the disease who had a disorder of the joint axis of symmetry (25%). A high level of satisfaction from the treatment was reported for patients with RA (70%) and reactive arthritis (60%). Based on an analysis of his own results, PG hypothesized that the change in the synovium membrane thickness during the therapy is one of the major predictive factors of patient's satisfaction. According to his observations, patients for whom the greatest reduction in the synovium thickness occurred reported the best improvement in pain level and joint mobility. It is also important to apply the treatment only to joints with preserved correct alignment. During his presentation PG also discussed thoroughly the complications observed in his patients. There was one serious complication in the form of skin necrosis at the isotope application site during the three-year observation period. When analyzing this case, PG pointed out that it was one of the first female patients to receive the treatment. Skin necrosis occurred in the prepatellar region, most likely on account of the defective barrier in the form of the bursa wall (as opposed to the barrier in the form of the joint capsule), despite

the explicit synovial hypertrophy. Therefore, according to PG, the relatively high risk of similar complications following the application of an isotope outweighs any possible benefits derivable from the treatment of synovial bursitis. The other complications included minor lesions, such as 3 superficial burns, 6 point discolorations at the radiopharmaceutical application site, 4 cases of transient pain intensification within the treated joint and 1 purulent arthritis. PG emphasized the importance of very restrictive immobilisation of the treated joints. He noted that since the implementation of the rule that patients who underwent RPJ of the knee joint have their lower limb fully immobilized and are wheeled to the exit (and do not leave on their own) neither point skin discolorations at the application site nor other complications have been observed. When discussing these complications, PG noted the importance of interdisciplinary meetings and exchange of experience between medical centres and physicians with different specializations. PG is convinced that only direct contact between orthopaedists and nuclear medicine specialists could allow clarifying indications for RPJ, and thus optimizing the group of patients who could most benefit from the treatment. Taking advantage of the fact that interdisciplinary meetings offer an opportunity to discuss specific clinical problems, PG requested the participants to initiate a discussion with a view to clarifying the following issues:

1. if total uncovering of the subchondral layer contributes to bone necrosis;
2. if the lack of non-defective joint capsule precludes the possibility of the RPJ procedure as the determination of the condition of the synovial bursa, e.g. in the shoulder joint, is a difficult task;
3. if the RPJ procedure should be applied in the treatment of popliteal cyst;
4. if the RPJ procedure should be applied in the treatment of prepatellar bursa.

Both orthopaedists and nuclear medicine specialists were of the opinion that:

Re 1. RPJ is a symptomatic treatment which can only be applied to the joints with synovial hypertrophy and preserved cartilage layer which protects the periosteum against the energy of ionising radiation. Therefore it is necessary at all times to accurately evaluate the synovial membrane thickness and select pharmaceutical with an appropriate range of beta radiation in the soft tissue. Prof. Fisher reminded that this range was strictly specified in scientific terms and is 3.6 mm for yttrium-90, 1.1 mm for rhenium-186 and 0.3 mm for erbium-169.

Re 2. RPJ should only be applied to stable joints with preserved joint capsule.

Re 3. Results of popliteal cyst treatment are questionable. Despite the reports in the literature (mainly Modder et al., 1995) concerning the efficacy of this treatment following the injection of an isotope to the Baker's cyst, PG does not recommend application of RPJ in this group of patients. On the other hand, Prof. Fisher pointed out that good effects can be achieved in the case of patients with preserved check-valve mechanism which can be verified by holding down the cyst with the ultrasound head and observing the flow of fluid.

Re 4. Based on his own experience and on account of the high risk of complications, PG does not recommend radiosynoviorthesis for treatment of bursas.

The safety of radionuclide joint treatment was the central topic of the guest lecture "60 years of intra-articular radionuclide therapy radiosynovectomy — a safe procedure?" by Prof. Manfred Fisher (MF) of the Medical University in Kassel (Germany). Based on several dozen years of experience in radiosynovectomy in Germany, MF stressed that the essential prerequisite for successful and safe radionuclide joint treatment is proper qualification of patients. It should always be remembered that it is a symptomatic treatment aimed at destroying the hypertrophic synovium membrane stimulated due to the inflammation, with the preservation of the other structural components. Intra-articular administration of radionuclides should not be applied in the case of patients for whom there is a possibility of contact between radiocolloid with the bone tissue, thus it is always necessary to perform a functional assessment, and additionally to determine the morphological condition of the joint. Damaged cartilage, accompanied by uncovering of the bone tissue in the joint is an absolute contraindication for radionuclide treatment on account of the high risk of local bone necrosis. It should be remembered here that bone necrosis is caused by a number of other factors, such as: trauma, hemoglobinopathies, caisson disease, metabolic disorders (hypercortisolaemia, hyperlipidaemia), acute and chronic renal failure, post-burn conditions and others (Mirzai et al., 1999). MF pointed out that if radiopharmaceutical is properly selected, there is no possibility of damaging the bone layer as the range of beta radiation within the soft tissue is strictly specified for each radionuclide, and the absorbed dose of radiation on the bone surface is smaller than that absorbed during frequently applied radiotherapy procedures. Professor referred to the experimental studies of Makel et al. concerning histological examination of lesions with the chondrocytes sampled from the articular surface in rabbits following intra-articular injection of holmium-166 solution. Over the several dozen years of application of this method in Germany and Europe the best effects of treatment were achieved in the case of patients with early-stage reactions within the joints. Therefore, RPJ is now applied in Germany only to Class I and II patients according to the Steinbrocker functional classification of joints in RA and/or according to the criteria of the American Rheumatism Association. From among the diagnostic methods used for evaluation of the intensity of inflammatory processes within joints in patients scheduled for radionuclide treatment, MF recommended three-phase bone scintigraphy, radiological examination and ultrasound scanning. MF referred to the studies of Avral (2005) and Conaghan (2010) to point out that the recurrence of articular effusion is the most important indicator among a range of predictors of adverse development of inflammatory lesions within the knee joint which make it necessary to implant an articular prosthesis. When discussing the safety of radionuclide synovectomy, Prof. Fisher presented the results from the registration of adverse effects of preparations used for radiosynovectomy in the years 1990–2010. Only 28 serious adverse events (SAE) and 40 complications described as non-serious cases were reported for about 831 000 radiosynovectomy procedures. These SAEs included 17 cases of acute articular infections which depend on the injection method, and not on the administration of a radioactive isotope. According to MF, there are few medical procedures with such positive safety profile.

A wide range of practical aspects were discussed between the lectures.

Prof. Czubak pointed out that one of the serious orthopaedic problems is the recurrent effusion in the joints following arthroplasty and asked if the radionuclide method could be used in this group of patients. Both Prof. Królicki and Prof. Fisher emphasized that RPJ is very effective in such cases, but it is necessary to observe the rule that intra-articular administration of a radionuclide should not take place until 6 months from the date of orthopaedic surgery. Prof. Fisher stressed that in Germany the group of patients who underwent RPJ after total arthroplasty is very large, the effects are positive and orthopaedists readily work together nuclear medicine specialists in this respect as in these cases RPJ often helps to eliminate the need for a complicated and costly re-operation.

One of the practical questions addressed the issue who can administer radionuclides intra-articularly. LK explained that radionuclides should be administered by a physician having necessary skills and experience. Given the fact that a radioactive substance is administered and bearing in mind the possibility of more serious complications compared to intra-articular administration of steroids or other medications, a radionuclide should be injected after it is confirmed that the needle is inside the joint, preferably based on ultrasound scanning results. Radionuclide can be injected by an orthopaedist, rheumatologist or another physician and it is not required that the injection should be performed by a nuclear medicine specialist. On the other hand, the procedure should take place in a nuclear medicine institute or laboratory as only such units are adapted for proper handling of radioactive isotopes. It is also necessary to work together with a nuclear medicine specialist who is responsible for the selection of a radionuclide and dose and must be present during the injection, if it is performed by another physician.

Another issue discussed by the participants was the variety of nosological entities which lead to arthritis and their diverse clinical classifications. It was noted that neither pain nor the width of the hypertrophic synovial membrane should be used as guidelines for qualifying patients for RPJ. Prof. Czubak pointed out that patients should be qualified based on an accurate diagnosis of the aetiology of arthritis and criteria applicable to a given nosological entity. Dr Płazińska stressed that patients referred for RPJ by rheumatologists are only treated for the joints affected by acute-stage arthritis. Only patients for whom the inflammatory process within the soft tissue was confirmed by scintigraphy results are qualified for the RPJ therapy. On the other hand, Prof. Fisher again pointed

out the fact that in Germany, following a period of wide application of synoviorthesis in the case of all patients affected by pain and effusions in the course of osteoarthritis, currently only early-stage patients, i.e. patients with intense bone lesions (osteophytes, joint deformities) are qualified for the procedure.

As the joints are immobilised during the RPJ procedure, also thromboprophylactic measures were discussed. In some centres all patients, who undergo radionuclide treatment of the knee joints, receive low molecular weight heparin, while in other centres it is not used at all. According to both Prof. Fisher, Prof. Czubak and Prof. Królicki, there is no need for obligatory application of anticoagulants in all patients under treatment, while special attention should be paid to patients with a high risk of embolism. It was recommended to determine the risk of potential embolic complications as part of the qualification procedure and apply Fraxiparine in patients with metabolic disorders with a history of thromboembolic events or other risk factors. At the same time Prof. Fisher noted that total immobilisation is not recommended even during the treatment of the knee joints. On the contrary, patients are encouraged to use toilet on their own or move their toes, while the knee joint remains immobile.

The closing speech was given by Prof. Jarosław Czubak who represented orthopaedists and Prof. Leszek Królicki who represented nuclear medicine specialists. Both professors extended a hearty thank you to the organizer of the meeting, Dr Toth, for the opportunity to learn about the most recent achievements in radiosynovectomy of the peripheral joints and to exchange experience and information. Prof. Czubak noted that such meetings are of vital importance as the extensive development of radionuclide methods makes it necessary for different specialists to expand their knowledge of nuclear medicine. Radiosynovectomy shows that this method is a very valuable add-on treatment for traditional therapies and should be used on a wider basis. The most important factors underlying the efficacy of RPJ include proper qualification of patients based on the nosological entity and progress of the disease, treatment of early-stage joint lesions, selection of proper radiopharmaceuticals and their doses, treatment control based on uniform criteria. In order to achieve this, physicians dealing with joint diseases and nuclear medicine specialists should closely work together. As noted by Prof. Królicki, the number of scintigraphy examinations in Poland is 7 times as low compared to other European countries and therefore such meetings are highly called for and should also be organised in the future.

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