



Transfer of yttrium-90 to breast milk during radiosynoviorthesis of the knee joint

Gilbert Pigrée¹ · Johann Césini² · Séverine Cruet-Hennequart¹ · Damien Peyronnet³ · Jonathan Vigne³ · Christian Marcelli² · Denis Agostini³ · Pierre Barbey¹

Received: 15 March 2019 / Accepted: 11 April 2019 / Published online: 8 May 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Dear Sir,

Radiosynoviorthesis (RSO) (or radiation synovectomy), which involves intra-articular injection of small radioactive particles, is a well-established therapy in arthritis to treat villonodular synovitis, rheumatoid arthritis and related indications [1–4]. RSO should only be used when all methods of conservative therapy have failed [5].

Various radioisotopes have been used for RSO, including gold-198, yttrium-90, erbium-169, rhenium-186 and phosphorus-32, but the silicate colloid of yttrium-90 (⁹⁰Y) is currently preferred [6]. ⁹⁰Y is a pure beta emitter with a mean/maximum tissue penetration depth of 3.6/11 mm, minimizing the radiation absorbed dose to the non-target tissue. It has a mean half-life of 2.7 days.

After direct injection into the articular cavity, the ⁹⁰Y colloid particles are phagocytized by macrophages and other inflammatory cells [7]. However, the lymphatic circulation may result in leakage of radionuclides to the locoregional lymph nodes and, afterwards, to non-regional lymph nodes. Spooren et al. noted that they could not find any radioactivity over the regional lymph nodes after 24 and 48 h [8]. Using a sodium iodide crystal, Boerbooms et al. [9] reported that the activity measured above the inguinal lymph nodes, liver and heart varied from 0.2 to 1.2% of the rate count measured above the knee joint. With proper joint immobilization, radioisotope leakage to the systemic circulation does not exceed 2% of the injected dose [10]. A comparison of extra-articular leakage

values of radiopharmaceuticals used for RSO was evaluated by Gedik et al. [11] using a gamma camera. The median leakage values calculated for ⁹⁰Y-citrate, ⁹⁰Y-silicate and ¹⁸⁶Re-sulfide were found to be 1.9, 2.4 and 2.7%, respectively. Using the same tool (gamma camera) applied to 69 patients, Jahangier et al. [12] observed that ⁹⁰Y leakage was found only in the liver and spleen (mean leakage 0.4 and 1.1%, respectively) 24 h after RSO. In order to assess the radioisotope distribution in the joint space and to find possible leakage of radioisotope outside the joint, a novel hybrid imaging method (single photon emission computed tomography and CT, SPECT/CT examination) was performed in 14 patients by Bielińska et al. [13]. This study demonstrated that the majority of ⁹⁰Y was located in the three compartments of the knee.

Taking into account the widely accepted view in the literature that injection of ⁹⁰Y colloid particles into the knee for RSO leads to very low leakage (2% or less), and that the main target tissues are bones, spleen, liver and kidneys, it was of interest to study a possible transfer of the radioisotope into breast milk that would justify the recommendation of breast-feeding contraindication.

Here, we present the first study demonstrating a transfer of ⁹⁰Y to breast milk just following RSO for the treatment of villonodular synovitis of the knee.

A 30-year-old female patient presenting with a recurrence of villonodular synovitis of the left knee was referred to the Rheumatology Department in January 2018 for radiosynoviorthesis. This patient, without a particular antecedent, had first undergone surgical synovectomy under arthroscopy in 2009 and then a second arthroscopic procedure in 2010 for an early recurrence. She presented with a new episode of left knee monoarthritis in August 2017, justifying the completion of an MRI that highlighted a new recurrence of her villonodular synovitis. A new surgical synovectomy was recommended and carried out in early December 2017. Radiosynoviorthesis with ⁹⁰Y was indicated in order to avoid further recurrence. This was carried out under fluoroscopic

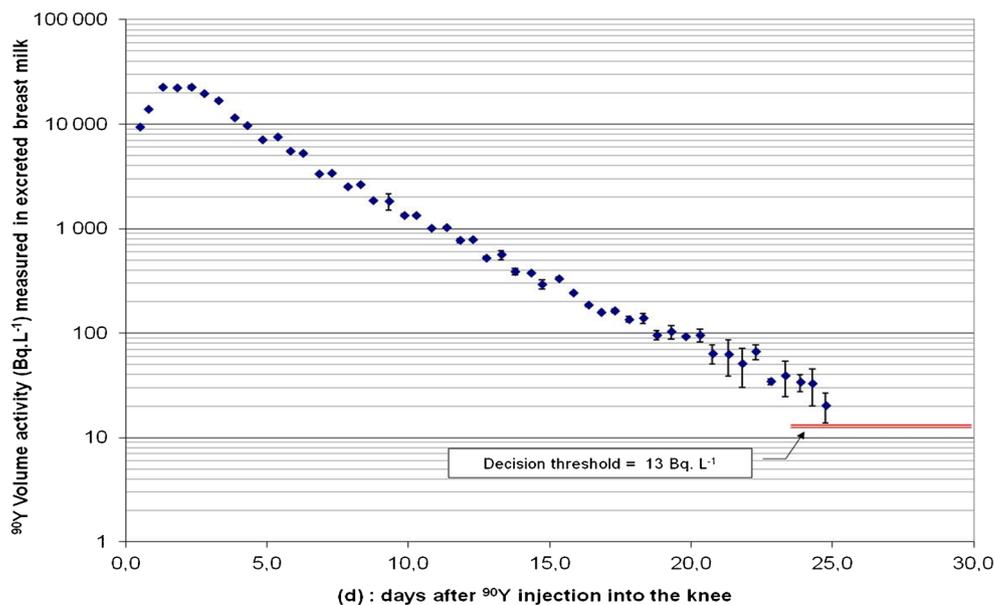
✉ Pierre Barbey
pierre.barbey@unicaen.fr

¹ IMOGERE Laboratory, University of Caen Normandy, CS-14032, Esplanade de la Paix, F-14032 Caen, France

² Rheumatology Department, University Hospital Center, Avenue de la Côte de Nacre, CS-30001, F-14033 Caen, France

³ Nuclear Medicine Department, University Hospital Center, Avenue de la Côte de Nacre, CS-30001, F-14033 Caen, France

Fig. 1 Biokinetic transfer of ^{90}Y to the breast milk of a 30-year-old breast-feeding mother up to 26 days after injection. The graph represents the volume activity ($\text{Bq}\cdot\text{L}^{-1}$) measured in excreted breast milk according to the day after ^{90}Y injection into the knee by RSO. Volume activity was measured in breast milk 5 mL test samples. Each point corresponds to the mean (\pm standard deviation) of two test samples



guidance on January 25, 2018. Since the patient wished to continue breastfeeding her 20-month-old child, we proposed a regular measure of radioactivity in breast milk, after the infiltration of yttrium (^{90}Y -citrate, Cis bio international), to determine when it was safe to resume breastfeeding. A control MRI was performed at the beginning of December 2018, and it did not show any recurrence of the villonodular synovitis.

In agreement with the 2003 European Association of Nuclear Medicine (EANM) recommendations, the total injected activity into the left knee was 185 MBq. Breast milk was collected 12 h after the administration of the radiopharmaceutical, and daily follow-up continued for 26 days. Two 5-mL test samples were collected and 15 mL of liquid scintillator (LS) added before analysis in a liquid scintillation counter (Tri-Carb 2100; PerkinElmer) using high-sensitivity count mode.

As seen in Fig. 1, biokinetic transfer of ^{90}Y to breast milk occurs rapidly, since a concentration of $9.400 \text{ Bq}\cdot\text{L}^{-1}$ was measured within 12 h of radiopharmaceutical injection to the knee. The volume activity increased to reach a short plateau phase from 32 to 56 h, where a concentration of $22.500 \text{ Bq}\cdot\text{L}^{-1}$ was observed. The volume activity then decreased slowly until the 26th day, where the activity was very low, around $20 \text{ Bq}\cdot\text{L}^{-1}$. During the final control carried out on the 38th day, radioactivity remained below the decision threshold of $13 \text{ Bq}\cdot\text{L}^{-1}$.

The EANM has written and approved Procedure Guidelines for Radiosynovectomy [14]. These generic recommendations—not to be rigidly applied to all patients in all practice settings—propose an absolute contraindication for breast-feeding.

A French toxicology center had previously reported the absence of data in the literature and suggested a period of abstinence corresponding to five physical half-lives (13.3 days). According to our present results, and considering

maximum recommended activity of 220 MBq for knee RSO, we recommend, in all circumstances, a ban of breastfeeding for a period of not less than 1 month.

Acknowledgments The authors wish to thank the patient who agreed to provide two breast milk samples per day for 1 month and allowed the study to be carried out.

Compliance with ethical standards

Conflict of interest None.

Ethical approval The protocol was approved by the Ethics Committee for Health Research of the University Hospital of Caen Normandy, and the study was performed in accordance with the ethical standards required by the national and international institutions.

Informed consent Informed consent for the study to be carried out and the results to be published was obtained from the individual participant included in the study.

References

- Jacob R, Smith T, Prakasha B, Joannides T. Yttrium⁹⁰ synovectomy in the management of chronic knee arthritis: a single institution experience. *Rheumatol Int.* 2003;23:216–20.
- Kampen WU, Hellweg L, Massoudi-Nickel S, Czech N, Brenner W, Henze E. Clinical efficacy of radiation synovectomy in digital joint osteoarthritis. *Eur J Nucl Med Mol Imaging.* 2005;32:575–80.
- Van der Zant FM, Boer RO, Moolenburgh JD, Jahangier ZN, Bijlsma JWJ, Jacobs JWG. Radiation synovectomy with ^{90}Y trium, ^{186}Re henum and ^{169}Er biun: a systematic literature review with meta-analyses. *Clin Exp Rheumatol.* 2009;27:130–9.
- Zalewska J, Węgierska M, Barczyńska T, Waszczak M, Żuchowski P, Jeka S. Efficacy of radiation synovectomy (radiosynovectomy or radiosynoviorthesis) with yttrium-90 in exudative inflammation of

- synovial membrane of knee joints in patients with rheumatic diseases - preliminary report. *Reumatologia*. 2016;54(1):3–9.
5. Kampen WU, Voth M, Pinkert J, Krause A. Therapeutic status of radiosynoviorthesis of the knee with yttrium [⁹⁰Y] colloid in rheumatoid arthritis and related indications. *Rheumatology*. 2007;46:16–24.
 6. Heuft-Dorenbosch LL, de Vet HC, van der Linden S. Yttrium radiosynoviorthesis in the treatment of knee arthritis in rheumatoid arthritis: a systematic review. *Ann Rheum Dis*. 2000;59:583–6.
 7. Knut L. Radiosynovectomy in the therapeutic management of arthritis. *World J Nucl Med*. 2015;14(1):10–5.
 8. Spooren PFMJ, Rasker JJ, Arens RPJH. Synovectomy of the knee with ⁹⁰Y. *Eur J Nucl Med*. 1985;10:441–5.
 9. Boerbooms A, Buijs W. Efficacy and safety of radiation synovectomy with Yttrium-90: a retrospective long-term analysis of 164 applications in 82 patients. Letter to the editor. *Rheumatology*. 1993;32(12):1114–5.
 10. Klett R, Puille M, Matter HP, Steiner D, Stürz H, Bauer R. Activity leakage and radiation exposure in radiation synovectomy of the knee: influence of different therapeutic modalities. *Z Rheumatol*. 1999;58(4):207–12.
 11. Gedik GK, Uğur O, Atilla B, Pekmezci M, Yildirim M, Seven B, et al. Comparison of extraarticular leakage values of radiopharmaceuticals used for radionuclide synovectomy. *Ann Nucl Med*. 2006;20(3):183–8.
 12. Jahangier ZN, van der Zant FM, Jacobs JW, Riedstra HG, Gommans GM, Verzijlbergen JF, et al. The intra-articular distribution of ⁹⁰yttrium does not influence the clinical outcome of radiation synovectomy of the knee. *Ann Rheum Dis*. 2007;66(8):1110–2.
 13. Bielińska A, Korkosz M, Gąsowski J, Tomaszuk M, Staszczak-Sowa A, Kwaśny-Krochin B, et al. Yttrium-90 distribution following radiosynoviorthesis of the knee joint in rheumatoid arthritis patients: a SPECT/CT study. *Ann Nucl Med*. 2014;28(7):688–92.
 14. Clunie G, Fisher M, for the EANM Radionuclide Therapy Committee. EANM procedure guidelines for radiosynovectomy. *Eur J Nucl Med Mol Imaging*. 2003;30:BP12–6.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.