GENERAL REVIEW

The latest information on Macrolane™: Its indications and restrictions

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Macrolane™; Breast augmentation; Hyaluronic acid; Injectable; NASHA

Summary

Introduction. — Hyaluronic acid has come to represent the most widely used injectable cosmetic product in the world. Brought into being by the Swedish company Q-Med, in 2007 Macrolane™ was authorized for use in France, and the year after, it received official European approval as a means of breast augmentation. Since then, however, numerous controversies pertaining to its side effects have led to its withdrawal from the worldwide breast augmentation market. The objective of this article is to carry out a review of the literature providing updated information on Macrolane™ and its recent indications.

Materials and methods. — We carried out a review of the literature on the PubMed and PubMed Central data bases through use of the keywords "Macrolane™", "NASHA", "hyaluronic acid" and "soft filler", and subsequently analyzed the levels of evidence and possible biases of the different publications. The official sites of the French, English, Spanish and American scholarly organizations of plastic surgery were likewise consulted. Perusal of the notifications and recommendations for use brought out by the Q-Med company completed our study.

Results. — A large majority of the available clinical series on Macrolane™ with regard to not only breast augmentation, but also its other indications, offer an insufficient level of evidence and present a number of conflicts of interest. Since April 2012 Macrolane™ has been temporarily withdrawn by its distributors from the worldwide breast augmentation market. In point of fact, Macrolane™ injections have been found to interfere with breast imaging and screening for breast cancer. As regards the latest indications for this controversial product, it is not yet possible to step back and take stock.

Conclusions. — Present-day scientific data fail to justify the market reappearance of Macrolane™ breast augmentation products. Q-Med has shown full awareness of the problem by
Introduction

As attractive alternatives to surgery, injectable filling products for esthetic purposes have acquired worldwide popularity. In France, they are not considered as drugs, which means that their commercialization is not contingent on the marketing authorization (AMM) awarded by the French ANSM (health product safety agency). While only six injectable products have been authorized in the United States, where the Food and Drug Administration compels “fillers” to go through the same procedures as medicines prior to being placed on the market, no less than 160 such products are allowable in France.

The most widely marketed gels contain hyaluronic acid and have been highly successful as skin care products used millions of times, particularly in fighting aging. For this type of indication, words of warning have been issued, and numerous adverse effects ranging from infection to cutaneous necrosis and even arterial embolism have been shown to occur [1,2]. One of the non-animal stabilized hyaluronic acid (NASHA) gels, Macrolane™, which is distributed by the Swedish company Q-Med, has been on the market in Europe since 2006. As is the case with the other fillers, its commercialization was legitimized on 15 June 1998 by the European Union directive 93/42/EC pertaining to class III implantable medical devices (IMD). The official EC seal of approval enables them to be legally distributed as IMDs. In 2008, Macrolane™ was authorized for use in France as a means of breast augmentation. However, it does not fulfill the criteria for scientific validation of a drug, and its marketing in North America has consequently never been sanctioned by either the FDA or the Public Health Agency of Canada.

In August 2011, the French AFFSAPS (now known as ANSM) decided to withdraw the authorization previously given to MacrolaneTM as a means of breast augmentation. And in April 2012, as doubts mushroomed, breast augmentation indications were temporarily suspended by Q-Med.

We propose an exhaustive review of the literature on Macrolane™ with regard not only to breast augmentation, but also to the product’s other recently reported uses.

Materials and methods

We carried out a review of the literature on the PubMed and PubMed Central databases through use of the keywords “Macrolane™”, “NASHA”, “hyaluronic acid” and “soft filler”, and subsequently proceeded to analyze the levels of evidence and possible biases of the publications.

The official sites of the French, English, Spanish and American scholarly organizations of plastic surgery were likewise consulted. Perusal of the notifications and recommendations for use of the Q-Med company completed our study. We compiled a list of the complications and adverse effects described in the literature on Macrolane™. Our contentions were supported and illustrated by photographs along with mammographic, ultrasound and MRI images.

Results

On the PubMed data base, 22 articles on Macrolane™ were found. On PubMed Central, one article has been included in our study; updating occurred following the 2011 publication of a text of ours in the Annales de chirurgie plastique esthétique [3].

We excluded articles dealing with the use of hyaluronic acid for the face, the reason being that hyaluronic acid is intended for facial cosmetics, as in Restylane™, a product marketed by Q-Med, it does not present the same characteristics. It is less cross-linked, and is consequently subject to more rapid degradation. Moreover, the quantities injected are ten times less sizable than those of Macrolane™, and the complications it may bring about, such as cutaneous necrosis, are markedly different [1,2,4]. Numerous published articles have been devoted to this type of product, which is manifestly of proven use. For all these reasons, the problems pertaining to Macrolane™ are product-specific. Finally, we have excluded articles dealing with non-cosmetic use of hyaluronic acid, particularly in the treatment of fecal incontinence, ureteral-vesical reflux and arthralgias.

Macrolane™ and breast augmentation

In May 2008, AFFSAPS authorized the use of Macrolane™ in breast augmentation. In February 2010, however, the French health and safety commission for medical devices decided to limit manipulation of the product to a surgical setting in which its use could be adequately monitored [5]. This decision was in agreement with a report issued in December 2008 by the French Direction Générale de la Santé (DGS), which stipulates that invasive procedures involving the breach of an aponeurosis shall be carried out by surgeons alone [6].

In April 2011, we took note of the many uncertainties surrounding Macrolane™ and its presumed innocuousness in breast augmentation [3]. The rare prospective studies on the subject had been carried out by Q-Med consultants and/or involved only a limited number of patients. The degradation mechanisms proper to Macrolane™ and the consequences of repeated injections remained largely unknown [3]. Table 1 summarizes the studies performed on Macrolane™ in breast augmentation.

In a recent study authored by Inglefield and published in 2011, from November 2007 to August 2009 a series of 194 patients were administered under local anesthesia a mean quantity of 136 ml of Macrolane™ by breast. Close to 9% reported adverse effects including infection, capsular contracture and early resorption. Carried out by a Q-Med consultant and characterized by insistence on product efficacy, safety and patient satisfaction, this type of work
### Table 1 Summary of the studies on Macrolane™ in breast augmentation.

<table>
<thead>
<tr>
<th>Author et al., Year Review</th>
<th>Type of study</th>
<th>Population</th>
<th>Objectives</th>
<th>Product Quantity of product injected</th>
<th>Level of evidence</th>
<th>Bias</th>
<th>Follow-up duration</th>
<th>Adverse effects</th>
<th>Means of monitoring</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inami et al., 2006 JJPS</td>
<td>Prospective Monocentric Independent author</td>
<td>1100 women</td>
<td>Effectiveness Feasibility Detection of adverse effects</td>
<td>NASHA gel 35 ml/breast</td>
<td>C (low)</td>
<td>Not referenced PubMed No follow-up duration No clear means of monitoring</td>
<td>NC</td>
<td>0.18% infections Frequent: pain, swelling</td>
<td>Clinical</td>
<td>Easy to administer Few adverse effects An interesting alternative to implants</td>
</tr>
<tr>
<td>Tengvar et al., 2008 Poster IMCAS</td>
<td>Prospective study Monocentric</td>
<td>19 women (31 years mean age)</td>
<td>To assess breast imaging after injection</td>
<td>Macrolane™ 80 to 100 ml/breast</td>
<td>C (low)</td>
<td>Q-Med consultant Conflicts of interest</td>
<td>24 months</td>
<td>The hyaluronic acid gel augments radiotransparency of the breast Mammography at 12 months Ultrasound and MRI at 3, 12 and 24 months.</td>
<td>Mammaryography clear and easy to read MRD not indispensable to follow-up</td>
<td></td>
</tr>
<tr>
<td>McCleave et al., 2010 JPRAS</td>
<td>Clinical series retrospective</td>
<td>3 women (32 years mean age)</td>
<td>To report on complications</td>
<td>Macrolane™ 110 ml/breast</td>
<td>C (low)</td>
<td>Low power</td>
<td>One week to 4 months</td>
<td>Secondary infection and capsular contracture developed around injection points</td>
<td>Clinical Surgical</td>
<td>Frequency of complications +++ Insufficient level of scientific evidence Difficulty in radiological follow-up</td>
</tr>
<tr>
<td>Inglefield et al., 2011 PRS</td>
<td>Prospective study Monocentric</td>
<td>194 women</td>
<td>Effectiveness Safety</td>
<td>Macrolane™ 136 mL/breast</td>
<td>C (low)</td>
<td>Q-Med consultant Conflicts of interest</td>
<td>12 months</td>
<td>8.7% adverse effects: infection, capsular contracture, early resorption</td>
<td>Clinical/ultrasound/mammography at 1 month, 2 months, 3, 6 and 12 months</td>
<td>Effectiveness in breast augmentation/high satisfaction/few adverse effects</td>
</tr>
<tr>
<td>Per heden et al., 2011 PRS</td>
<td>Prospective Multicentric</td>
<td>20 women (37 years mean age)</td>
<td>To develop a reproducible injection technique</td>
<td>Macrolane™ 97.8 ml/breast</td>
<td>C (low)</td>
<td>Q-Med consultant Conflicts of interest</td>
<td>12 months</td>
<td>25% capsular contracture 13% nodule 25% pain on palpation</td>
<td>Clinical MRI D1, D5, 3 months, 6 months, 12 months</td>
<td>Reproducible injection technique A new alternative to surgery</td>
</tr>
<tr>
<td>Author, Year, Review</td>
<td>Type of study</td>
<td>Population</td>
<td>Objectives</td>
<td>Product Quantity of product injected</td>
<td>Level of evidence</td>
<td>Bias</td>
<td>Follow-up duration</td>
<td>Adverse effects</td>
<td>Means of monitoring</td>
<td>Conclusions</td>
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<td>Pienaar et al., 2011</td>
<td>Radiological retrospective study</td>
<td>19 women</td>
<td>To assess the impact of Macrolane™ injections on breast imaging</td>
<td>C (low)</td>
<td>Small population</td>
<td>NA</td>
<td>False positives on mammography / infiltration of the pectoralis major 5/19 / cyst-like anechoic aspect on ultrasound or solidification / persistence of Macrolane™ at 24 months</td>
<td>Mammmography, ultrasound and MRI</td>
<td>Possible confusion at clinic and in images with breast tumors / migration of Macrolane™ / persistence at 24 months / images difficult to interpret</td>
<td></td>
</tr>
<tr>
<td>Crawford 2011 JPRAS</td>
<td>Clinical case</td>
<td>1 women</td>
<td>Late breast cancer diagnosis</td>
<td>100 mL/breast</td>
<td>C (low)</td>
<td>1 case</td>
<td>NA</td>
<td>Late diagnosis of infiltrating lobular carcinoma / problematic treatment</td>
<td>Clinical mammography, ultrasound and MRI</td>
<td>Difficulties in screening / diagnosis / surgical breast cancer treatment</td>
</tr>
<tr>
<td>Becchere et al., 2012</td>
<td>Clinical study Retrospective Monocentric</td>
<td>7 women</td>
<td>To report on complications</td>
<td>Macrolane™ 60 to 80 mL/breast</td>
<td>C (low)</td>
<td>Small population</td>
<td>Selection bias</td>
<td>NA</td>
<td>Nodules painful on palpation (7/7) / infiltration of the muscles (2/7) / parasternal infiltration (1/7)</td>
<td>Clinical, mammography and ultrasound</td>
</tr>
<tr>
<td>Yamaguchi et al., 2013</td>
<td>Prospective study Monocentric</td>
<td>98 women</td>
<td>Effectiveness Safety</td>
<td>Macrolane™ 86 and 90 mL/breast</td>
<td>C (low)</td>
<td>Financed by Q-Med Conflicts of interest</td>
<td>1 month, 6 months, 12 months</td>
<td>46.9% capsular contracture, Baker grades II to IV, 2% hematoma, 4.1% pain, 4.1% early resorption</td>
<td>Clinical (satisfaction, examination) / mammography and ultrasound at 12 months</td>
<td>Attractive alternative to breast implants Effectiveness and good product tolerance</td>
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</table>
is invariably more difficult to interpret than a study devoid of conflicts of interest. In addition, mean follow-up of only 12 months and a single injection session do not suffice to justify dispel misgivings with regard to long-term use of Macrolane™ or concern over the complications possibly entailed by repeated injections [7].

A similar study, which was conducted by Yamaguchi et al., financed to some extent by Q-Med (since 2011 a division of Galderma) and published in 2013, had as its objective to study the efficacy and safety of Macrolane™ VRF30 in a cohort of Japanese women [8]. In this research, 98 patients were treated with a mean quantity of 86 to 90 ml of Macrolane™ by breast and subsequently monitored for 12 months. Ultrasound control revealed fortuitous intramammary or retropectoral placement in seven patients. Nearly half of the subjects, that is to say 46, were shown to have developed capsular retraction. Moreover, 12% of the patients presented with Baker grade III or grade IV capsular retraction. As regards cosmetic improvement, at 12 months 48% of the breasts were considered by the patients to be satisfactory.

The problems presented by Macrolane™ in breast augmentation

Clinical and imagery-related

In January 2013, Becchere et al. reported on a series of seven patients presenting with mastodynia secondary to the use of Macrolane™ in breast augmentation. In every case, painful mammary gland nodules were discovered on physical examination [9]. The most commonly mentioned adverse effect of Macrolane™ was encapsulation or capsular contracture [8,10–13]. Unfortunately, attempts at aspiration under ultrasound guidance often fail and appear to be a source of anxiety for the patients [14]. Use of a hyaluronidase to dissolve the lumps caused by hyaluronic acid fillers [2] and to correct irregularities has yet to yield conclusive results, and to date, no study has provided sufficient insight.

From a mammographic standpoint, the density of Macrolane™, 98% of which consists in water, approximates that of the densest breast tissues. The modifications ensuing secondarily to Macrolane™ injections result in a non-specific augmentation of mammary gland density that is less typical than in prosthetic silicone implants. In ultrasound, Macrolane™ inclusions form seemingly benign cyst-like images [3]. The indurations and irregularities perceived during clinical breast examinations are particularly worrisome when translated into mammography as capsular contractures or lumps, which occur in 25% to 52% of the patients in the different series [5,8,10]. They can be difficult to distinguish from a malignant pathology and frequently necessitate a third, MRI-type examination in order to establish a diagnosis. They may also lead to calcifications entailing false positives for mammary neoplasia and consequently necessitating biopsies to provide histological certainty.

Pienaar et al. have noted that a large majority of patients presents dense lesions that are clearly circumscribed in mammographic images (Fig. 1) [14]. In more than 25% of the cases, Macrolane™ deposits have likewise been shown to appear in the pectoralis major muscle [3,9] (Fig. 2), and there also occurred a case of parasternal infiltration that necessitated surgical treatment [9]. As of now, however, the long-term effects of intramuscular—or deeper—placement have yet to be determined [15,16]. With ultrasound, Pienaar et al.—and our team, as well—have depicted the typical aspect of Macrolane™ deposits [3,14] (Fig. 3). A so-called “Sparkly Lake” consists in multiple anechogenic collections filled with echoes that vary in size and echogenicity. In fact, ultrasonography appears particularly useful and of valuable specificity in patients having undergone Macrolane™ treatment. That said, in over one fifth of the patients, Macrolane™ infiltrations are liable to take on a more solidified appearance, thereby necessitating ultrasound-guided biopsies in view of eliminating cases of breast cancer [14]. On MRI, the deposits appear as echo gradients hypoT1 and hyperT2 [14]. And finally, contrarily to the time limits announced by Q-Med and the company’s consultants, Pienaar
et al. showed by means of IRM that Macrolane™ could persist for more than 24 months following the breast augmentation procedure.

As is the case with adipose tissue transfer (ATT), a Macrolane™ injection can consequently complicate the interpretation of mammary imaging [17,18].

Difficulties in screening for breast cancer

Becchere et al. have noted that the hypoechochogenic images observed before Macrolane™ injection could be masked by the product itself [9]. It is easy to imagine that after Macrolane™ injection, mammography and echography interpretation becomes pronouncedly more complex and can devolve into a source of diagnostic errors [19]. Crawford reported on a case of delayed breast cancer diagnosis in a patient having received Macrolane™ injections for breast augmentation [20]. He went on to explain the risk of failing to recognize a tumor by means of self-palpation, clinical examination or standardized complementary screening. In actuality, Macrolane™ creates subcutaneous stone-like curvatures that can take on the appearance of malignant tumors. In addition, during surgical treatment, extensive Macrolane™ infiltration rendered it impossible to macroscopically locate the cancer and to immediately reconstruct the breast.

Oncogenesis?
Given the relative absence of clinical studies and long-term follow-up, the impact of Macrolane™ on breast cancer is not presently known. While data in the literature on the role of

Figure 2  Breast MRI (sagittal section in MIP reconstruction). Retropectoral and axillary diffusion after retroglanular injection.

Figure 3  Typical aspect of Macrolane in mammary ultrasonography.
hyaluronic acid in tumor development have remained mutually contradictory, interactions of hyaluronic acid with mammary parenchyma likewise have occasioned debate [12,21,22]. Even though it has not been proven that hyaluronic acid could constitute a factor triggering the tumor process, it may be present in the process of tumoral neoangiogenesis and would thereby diminish the efficacy of chemotherapy [23–25]. Some authors go so far as to consider the level of hyaluronic acid in breast tumors as a factor of poor prognosis for patient survival [26]. That said, the problem resides not only in cancers induced by hyaluronic acid, but also in the cross-linking agents such as BDDE that are associated with the gel. Finally, the recommended injection mode constitutes a traumatizing procedure; nowadays, we are aware of the existence of local secretion of a growth factor generated by surgical procedures; in this operative context, the trauma is induced by the comings and goings of a cannula.

Recent utilization of Macrolane™

According to the Q-Med Internet site, Macrolane™ is on the market in Austria, Belgium, Denmark, Finland, Germany, Hong Kong, Italy, the Netherlands, Norway, Poland, Portugal, Singapore, Spain and Sweden (Table 2). Q-Med now proposes Macrolane™ as a means of augmenting the curves of the buttocks and the calves and of remediing the defects connected with liposuction. Following withdrawal of the breast augmentation product, the range of uses for Macrolane™ has widened.

In 2012, Sinna proposed Macrolane™ as a means of treating moderately severe pectus excavatum. He described the feasibility of the technique without detailing any results that had been achieved. It would be of pronounced interest to compare from a distance this procedure with the reference treatment for pectus excavatum through placement of a silicone endoprosthesis or ATT [27,28].

In April 2013, Per Heden and Magnus Tengvar, both of them serving as Q-Med consultants, published a preliminary study on remodeling of the buttocks [16]. Eight subjects received 162.5 ml of Macrolane™ VRF30 on the average in each buttock. MRI monitoring took place at 12 and at 24 months. In more than 60% of the patients, a large portion of the Macrolane™ gel was found in their subcutaneous fat tissue, while the rest of it was located in intramuscular areas, specifically in the gluteus maximus. This somewhat ambiguous result could be explained by the clinical difficulty of correctly pinpointing the injection site, which is also a difficulty encountered in retroglular breast injection. In addition, it was shown by Heden and Tengvar that the location of the gel changes over time. In six months, the gel had locally migrated in 62.5% of the subjects but without any supplementary displacement at 12 and 24 months. All told, at least up to 24 months after the injection 60% of the patients were convinced that their buttocks had improved.

As an alternative to ATT, remodeling through injection of 10 to 30 ml of Macrolane™ in the superficial irregularities secondary to liposuction has been proposed by Cerqua [29]. In 11 out of the 12 patients included in the study, correction ranging from 60 to 70% remained present at 8 months. In this indication, small quantities of Macrolane™ injections appear not to have entailed adverse effects, but their interest is relative and their effectiveness of a transitory nature [29].

In 2013 Sito et al., who are likewise employed as Q-Med consultants, conducted a retrospective study on Macrolane™ injection as opposed to ATT in penis enlargement [30]. Fifty-six patients participated in a Macrolane™ injection session and 27 in an ATT session. Mean volumes of 30 to 40 ml were injected. Unlike the aftermath of ATT, subsequent to the Macrolane™ injections no adverse effects (hematoma, seroma, calcification, cutaneous necrosis, infection…) were noted. The authors insisted on the fact that for Macrolane™, as opposed to TTA lipofilling, which is unpredictable, resorption speed was constant, with a gradient of 50% at one year.

As regards use of the gel in modeling of the calf, only one article has been published, in our unit; dating back to 2011, it reports on severe cellulitis in a patient having received an injection of Macrolane™ in her calf (Figs. 4 and 5) [31]. The action had been carried out by a dermatologist in a non-hospital practice and eloquently illustrates the need to limit injections to a surgical environment [6].

Discussion

On paper, Macrolane™ would appear to be particularly attractive; a slowly resorbed filler, it is easy to manipulate under local anesthesia, and can be indicated in many cases as a feasible alternative to surgery. Moreover, ATT in the breast has been and remains a subject of controversy and a source of polemics. And as regards the breast augmentation indication that created great expectations for Macrolane™, it has been repeatedly contested; over recent years, following the August 2011 withdrawal of its authorization in France, in April 2012 the Q-Med company discontinued its indication throughout the world (see Introduction) [32]. Since that date, Q-Med has likewise contraindicated Macrolane™ as a means of enlarging the penis or cosmetically enhancing the hands. The decision was taken subsequent to the observation, given as a customer warning, that “the benefit-risk balance has not been adequately investigated in prospective studies” [33].

Why, in August 2011, did AFSSAPS decide to so drastically restrict the use of injectable fillers such as Macrolane™ in breast augmentation prescribed for esthetic reasons [13]? In point of fact, the decision was engendered both by review of the relevant literature and by study of the safety data in a clinical trial that had been transmitted to the French watchdog in 2010 [3,12,14,20,34]. The restrictive measure was predicated on four main arguments. First, repeated product injection in the retro-glandular region creates a risk of inflammatory breast cancer. Second, the injected product can migrate and contribute to the formation of nodules. Third, the product may interfere with clinical and image-based examination and occasion delay in the screening and diagnosis of mammary pathologies. Finally, screening and early diagnosis of breast cancer are considered to be nationwide public health priorities. To sum matters up, Macrolane™ deposits in the breast are liable to mask breast cancer, delay diagnosis and complicate surgery.

As we previously indicated in October 2011 [35], on 17 April 2012 Q-Med announced in a press release its decision to discontinue worldwide use of Macrolane™ as a means of breast augmentation. According to the spokesperson for the
<table>
<thead>
<tr>
<th>Author Review Year</th>
<th>Type of study</th>
<th>Population</th>
<th>Objectives</th>
<th>Product Quantity of product injected</th>
<th>Level of evidence</th>
<th>Bias</th>
<th>Follow-up duration</th>
<th>Adverse effects</th>
<th>Means of monitoring</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaput B. Ann Chir Plast Esthet 2011</td>
<td>Clinical case</td>
<td>1 case</td>
<td>To report on complications</td>
<td>Macrolane® 150 mL</td>
<td>C (low)</td>
<td>Low power</td>
<td>NA</td>
<td>Cellulitis of the calf</td>
<td>Clinical</td>
<td>Usual caution, strict surgical environment</td>
</tr>
<tr>
<td>Sinna R. Ann Thorac Surg 2012</td>
<td>Feasibility study</td>
<td>Unknown</td>
<td>Feasibility, effectiveness of Macrolane® in correction of pectus excavatum</td>
<td>Macrolane® 40 to 80 mL</td>
<td>C (low)</td>
<td>Population Study design unknown Non-comparative</td>
<td>None</td>
<td>None</td>
<td>Unknown</td>
<td>Innovative method—alternative to historical Ravitch-type surgery</td>
</tr>
<tr>
<td>Sito G. Aesthetic Surgery Journal 2013</td>
<td>Clinical study Retrospective Monocentric Comparative</td>
<td>83 patients</td>
<td>Effectiveness and safety of Macrolane® in penis enlargement VS ATT</td>
<td>Macrolane® 30 to 40 mL</td>
<td>C (low)</td>
<td>Consultant Q-Med Conflict of interests</td>
<td>12 months</td>
<td>None</td>
<td>Measurement/clinical/satisfaction at 7 days—2 weeks, 1 month, 6 months, 1 year and 2 years</td>
<td>Rapidity, effectiveness, few complications, superiority to TTA</td>
</tr>
<tr>
<td>Cerqua S. Journal of Cosmetic and Laser Therapy 2013</td>
<td>Clinical study Prospective Monocentric</td>
<td>12 patients</td>
<td>Effectiveness, duration, safety of Macrolane® in correction of post-liposuction irregularities</td>
<td>Macrolane® 10 to 30 mL</td>
<td>C (low)</td>
<td>Low power</td>
<td>8 months</td>
<td>None</td>
<td>4, 6, 8 months satisfaction/results</td>
<td>Safety/lasting and predictable results/effectiveness</td>
</tr>
<tr>
<td>Camenisch C. PRS 2013</td>
<td>Pilot study prospective Monocentric</td>
<td>8 patients</td>
<td>MRI evaluation of Macrolane® in remodeling of buttocks</td>
<td>Macrolane® 162.5 mL by buttock</td>
<td>C (low)</td>
<td>Q-Med consultants Conflict of interests/low power</td>
<td>24 months</td>
<td>62.5% migration of gel—speed of degradation highly variable according to subjects &gt; 50% gel in intra-muscular (gluteus maximus)</td>
<td>Clinical/biological at 1—5 days, 6 months, 12 months and 24 months MRI</td>
<td>Feasibility, satisfaction, tolerance, user safety</td>
</tr>
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Swedish company, temporary market withdrawal is due to a lack of consensus on potentially malfunctioning breast examinations in women having undergone Macrolane™ treatment. [32]. On 20 April 2012, the British Association of Aesthetic Plastic Surgeons (BAAPS) approved the decision taken by Q-Med to take its breast enlargement product off the market. Moreover, the association deems it desirable that filling products be subjected to the same authorization procedures as medical products with regard to the FDA in the United States [36]. In June 2009, according to a poll, no less than 96% of the British plastic surgeons interrogated considered the European Union seal of approval to be insufficient [37], even though the so-called "lunchtime boob job" had involved thousands of patients in English-speaking countries. The Spanish health product safety agency (AEMPS) likewise announced, on 3 May 2012, its decision to ban the use of Macrolane™ in breast augmentation [38]. It would appear obvious that in its present-day form, the EU seal of approval is contingent neither on adequate scientific knowledge, nor on any stepping back and taking stock of the merits and demerits of a product to be placed at the disposal of one and all. Given on the one hand the lack of prerequisites for EU approval and on the other hand the cumberliness of the French AMM procedure in terms of cost and scientific bona fides, it might be imaginalbe that with regard to these products, independent university-based teams develop procedures that would constitute a happy medium. In this context, the intransigent, - take no prisoners - approach employed by the FDA and the difficulty of obtaining market authorization in the United States may at times seem tantamount to protectionism.

Fig. 6 summarizes the history of Macrolane™ as concerns this indication.

With regard to the breast, the two studies carried out over the last couple of years with the support of Q-Med remain interesting even though the evident conflicts of interest somewhat undermine the level of evidence. Moreover, patient follow-up is still rather low. And finally, the life span of Macrolane™ is pronouncedly uncertain, and it is so strongly cross-linked that, in some instances, it devolves into an actual foreign body, a sort of long-term side effect necessitating surgical removal.

As concerns remodeling of the buttocks, in MRI at 24 months, from 16 to 45% of the product was still present [16]. The resorption rate is highly variable and can easily create a risk of late-onset inflammatory and immune-mediated adverse effects in some of the patients having received a Macrolane™ injection [2]. In addition, the substantial cost...
of the injections compared to ATT or to prosthesis installation is a factor to be taken into account. According to location or establishment, an injection of transient effectiveness may cost several thousand euros, which is why a comparative economic study would be of interest.

As pertains to the other indications such as modeling of the calves, correction of the pectus excavatum and repair of liposuction defects, the data in present-day literature are few and far between. The studies published offer a low level of evidence and are vitiated by various biases on account mainly of conflicts of interest and/or lack of power.

Lastly, as regards penis enlargement, the risk of erectile dysfunction connected with the injections has been a cause for controversy in Sweden. Since 2011, dozens of patients have complained of erectile dysfunction subsequent to modeling injections. An investigation conducted by the Swedish agency for medical products (Läkemedelsverket) led Q-Med to update restrictions on Macrolane™ use in April 2012. In its customer’s notice, the company mentions the absence of prospective clinical studies and consequently advises against use of Macrolane™ in penis enlargement [33]. Sito et al. explain the difficulties by citing the fact that Macrolane™ is injected not between the superficial and the deep fascia, but rather in the cavernous body [30].

Conclusion

In contemporary France, fillers are still insufficiently evaluated prior to their commercialization, and it is hardly surprising that with regard to Macrolane™, the national health authorities made an unusual U-turn. Even the distributor, Q-Med, came to the conclusion that a product with considerable marketing potential might not only open the way to misuse and yield adverse effects, but also hinder breast cancer screening and monitoring. We wish to praise Q-Med for running the risk of erring on the side of caution; we also wish to insist once again that before once again proposing Macrolane™ for the breast or other locations such as the penis or the hands, it will be necessary to mobilize larger cohorts of patients and to stand back and take stock. Has falling for Macrolane™ made some of us forget the most fundamental precautionary principles?

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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The latest information on Macrolane™: Its indications and restrictions


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