Regulatory Toxicology and Pharmacology 125 (2021) 104982

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Commentary

Final opinion on the safety of breast implants in relation to anaplastic large cell lymphoma: Report of the scientific committee on health, emerging and environmental risks (SCHEER)

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ARTICLE INFO

Handling Editor: Dr. Lesa Aylward

Keywords
Breast implants
Anaplastic large cell lymphoma
Cancer
BIA-ALCL

ABSTRACT

The Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) was requested by the European Commission (EC) to provide a scientific opinion on the safety of breast implants in relation to anaplastic large cell lymphoma (ALCL). There are several types of textured breast implants; surface textures of breast implants are not all manufactured in the same way, and breast implants with diverse surface textures may also present different benefits. The magnitude of the risk per type of textured implant is difficult to establish due to the low incidence of the breast implants associated anaplastic large cell lymphoma (BIA-ALCL). Therefore, risk assessments per implant type are needed.

Overall SCHEER considers that there is a moderate weight of evidence for a causal relationship between textured breast implants and BIA-ALCL, particularly in relation to implants with an intermediate to high surface roughness.The pathogenic mechanisms are not fully elucidated; current hypotheses include genetic drivers, chronic inflammation resulting either from bacterial contamination, shell shedding of particulates, or shell surface characteristics leading to friction, or by implant associated reactive compounds. Reporting of new BIA-ALCL cases by the national clinical registries is critically important to obtain a better estimate of the risk of BIA-ALCL for patients with a breast implant.

1. Introduction

At the request of the European Commission the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) drafted the Opinion on the safety of breast implants in relation to the occurrence of Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) (SCHEER, 2021). Specifically, the SCHEER was requested to describe the specific clinical indications for the use of breast implants, the various aspects of BIA-ALCL, including diagnostic criteria and disease prognosis, and good clinical practice for the follow-up of women with breast implants, and the incidence and current knowledge of BIA-ALCL. In addition, SCHEER was requested to identify whether a causal relationship between breast implants and BIA-ALCL can be established based on the evidence available to date, to describe the state-of-the-art knowledge regarding the characterisation and classification of textures of the breast implant shells (e.g., is classification possible?), to describe the factors that may determine the risk of BIA-ALCL, to identify criteria regarding the characterisation of breast implants in relation to BIA-ALCL and

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https://doi.org/10.1016/j.yrtph.2021.104982
Received 17 June 2021; Accepted 24 June 2021
Available online 30 June 2021

control measures to reduce the identified risk. Lastly, it was requested to describe alternatives to breast implants and to identify needs for further research and the best ways to collect the missing data regarding breast implants and BIA-ALCL.

1.1. Clinical use of breast implants

The specific clinical indications and uses of various types of breast implants are either reconstructive, primarily for the loss of breast volume or secondary to a surgical procedure, or aesthetic for the correction of breast anomalies or a volume increase and shape improvement. Clinical indications for the use of a specific type of breast implant should depend on a consultation between clinician and patient to allow informed decision making to take place with regards to the choice of an appropriate breast implant. For breast reconstruction, a shared consultation with a multidisciplinary healthcare team including an oncologist, surgeon, breast care nurse, etc, should be held with the patient to allow informed decision making to take place with regards to the breast reconstruction procedure, as well as the choice of implant. For both aesthetic and reconstructive surgery all aspects of breast implants should be evaluated and discussed with the patient, expressly covering advantages, disadvantages, follow-up procedures and risk factors.

1.2. Basic information of Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

BIA-ALCL is the occurrence of a lymphoid malignancy adjacent to a breast implant. It often occurs within the scar capsule surrounding the implant and can manifest as a spectrum of presentation of one disease, from a primary fluid effusion containing tumor cells within the implant capsule, to a solid tumor mass with or without lymph node and/or organ metastasis. Diagnosis of BIA-ALCL is achieved by analysis of seroma fluid or if a mass, core needle, incisional or excisional tissue biopsy. Radical *en bloc* surgical resection (i.e., implant including seroma, intact capsule, and associated masses) with disease-free margins, including healthy tissue, is recommended as the standard of care treatment, with a very good prognosis. (Clemens, 2016, 2019).

1.3. Reported cases of BIA-ALCL

At the EU level, the EU Taskforce on BIA-ALCL composed of competent authorities received 398 BIA-ALCL reports (probable cases; some of these were unconfirmed cases due to the absence of testing), of which 345 (86.7%) were confirmed BIA-ALCL cases of from various European countries. The FDA released an updated report on BIA-ALCL incidence on August 20, 2020 and conveyed that they had received reports of "*733 unique cases of BIA-ALCL and 36 patient deaths globally*" as of January 2020 (SCHEER, 2021).

Regarding the epidemiology of BIA-ALCL the incidence is considered low, varies by implant type, and is mainly associated with macro-textured implants. It is difficult to provide accurate estimates of the incidence by country and by manufacturer since there are significant limitations related to the frequent use of *ad hoc* reporting of cases compared with systematic reporting, the progressive nature of an emerging disease, and the use of sales data provided by manufacturers (Santanelli di Pompeo, 2020).

2. Summary of the SCHEER opinion on BIA-ALCL

In a previous report in October 2017, the SCHEER advised the EC that there was insufficient scientific information available to establish a methodologically robust risk assessment regarding a possible association between breast implants and ALCL development (SCHEER, 2017). However, the 2017 Advice recommended that a more in-depth evaluation be conducted on the possible association of breast implants with the development of BIA-ALCL.

Since 2017, a significant body of scientific information has been published which offers the possibility of a more in-depth analysis of BIA-ALCL. The final evaluation of the possible relationship between breast implants and the occurrence of BIA-ALCL was recently finalised by SCHEER and presented in public (SCHEER, 2021). The views expressed in the Opinion represent the opinion of the SCHEER committee and is based on the current literature and a public consultation with experts in the field including clinicians, scientists and producers, and do not necessarily represent officials views or positions of the European Commission that requested the Opinion.

2.1. Literature search

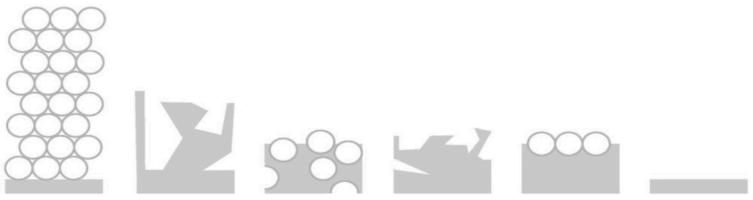
A systematic literature search was conducted using PubMed and Find-eR, covering the period from September 1st, 2016, to April 30th, 2020. The literature review was conducted by WG SCHEER members who first evaluated the papers independently and then discussed them as a group before reaching their conclusions. In addition, other relevant official sources, and literature beyond that period, e.g., the previous SCHEER opinion (2017), were considered. After excluding all irrelevant and duplicate papers, a total of 605 papers remained from the literature search and were evaluated in this Opinion.

2.2. Factors associated with BIA-ALCL

The common factor underlying the occurrence of BIA-ALCL is the presence of a textured breast implant. This suggests that a feature of these devices play a key role, directly or indirectly. A second key aspect is the T cell origin of BIA-ALCL, cells that play a central role in the adaptive immune response, inflammatory response and defense against pathogens that are normally detected and removed from the body. These factors highlight potential mechanisms of disease aetiology and pathogenesis, as a result of cellular mutations, chromosomal alterations, and a common pathogenic mechanism of chronic inflammation (Turner, 2020). There are five proposed hypotheses regarding the pathogenesis of BIA-ALCL: genetic predisposition, bacterial contamination resulting in chronic inflammation, shell shedding of particulates resulting in chronic inflammation, shell surface characteristics leading to friction resulting in chronic inflammation, and potential exposure to implant-associated reactive compounds. None of the proposed hypotheses are necessarily mutually exclusive whereby chronic inflammation, no matter what causes it, might drive lymphomagenesis by multiple pathways. In this manner, the chronically stimulated T cells would be assumed to acquire malignancy-promoting mutations. However, there is insufficient scientific evidence available to rule out any of these potential mechanisms of disease pathogenesis. Based on the underlying prominence of chronic inflammation, it is highly likely that this process plays a central role in the development of BIA-ALCL.

A full implant history can be difficult to obtain in patients who have had multiple implants. However, when the breast implant surface was identified in BIA-ALCL cases, they were in almost all cases identified as textured. There has only been 1 suggested case of BIA-ALCL in a patient with a known implant history in which only smooth implants were used. As far as the manufacturer for textured implants was known most cases (approximately 91%) were found for the *Allergan Biocell* implant (textured by salt loss technique), while for PU coated breast implants BIA-ALCL cases were mainly associated with the *Silimed* implant. Occurrences with implants from other manufacturers were much lower.

Based on these data SCHEER considers that there is a moderate weight of evidence for a causal relationship between textured breast implants and BIA-ALCL, particularly in relation to implants with an intermediate to high surface roughness. The association between BIA-ALCL and textured implants is now established due to consistency in epidemiologic studies. The weight of evidence is considered "moderate" for causation as the pathogenic mechanisms have not been fully characterized such as elucidation of the complete etio-pathology,



Manufacturing Process	Polyurethane foam	Salt loss	Vulcanisation	Salt loss	Imprinting	Smooth/Nano
Surface Area	High	Intermediate	Intermediate	Low	Low	Minimal
Roughness	High	Intermediate	Low	Low	Low	Minimal

Fig. 1. Implant surface texturing as it relates to the manufacturing method, surface area and surface roughness (based on Jones et al., 2018).

demonstration of oncogenicity of textured implants within an animal model, and/or meta-analyses of high quality prospective randomized controlled trials of smooth and textured surface implant patients.

At this point it should be noted that there are several types of textured implants, surface textures of breast implants are not all manufactured in the same way, and implants with diverse surface textures may also present different benefits. The magnitude of the risk per type of textured implant is difficult to establish due to the low incidence of the BIA-ALCL. Even with macro-textured implants, BIA-ALCL has a very low incidence. Therefore, risk assessments by manufacturer type are needed. Furthermore, the risk should be weighed against the benefits. There is also a need for an unambiguous, clinically validated classification system for breast implants including more parameters than just "*surface roughness*". A history of textured breast implants/expanders appears to be necessary but not sufficient for the development of BIA-ALCL. Contributing factors include, but are not limited to, a genetic predisposition to cancer and the presence of chronic inflammation, which may drive lymphomagenesis by multiple pathways. The most important criterion that is associated with the occurrence of BIA-ALCL is the type of surface characterising the implant. So far the only identified factor that determines the risk of BIA-ALCL is the presence of an implant with a textured or rough surface, i.e., not a smooth surface (*see* Fig. 1). In particular, a certain type of macrotextured or PU implant manufacturing process might also be a risk factor for BIA-ALCL. However, it is not yet possible to determine the relative risk for BIA-ALCL and various surface characteristics. Therefore, there is a need for an unambiguous, clinically validated classification system for breast implants including parameters beyond "*surface roughness*".

2.3. Treatment of BIA-ALCL

Disease latency varies between a few and up to 20 or more years. The previous implant history of those developing BIA-ALCL is of crucial importance in relation to the role of the surface texture of the implant. BIA-ALCL treatment exists on radical *en bloc* surgical resection (i.e., implant including seroma, intact capsule, and associated masses) with disease-free margins, including healthy tissue, is recommended as the standard of care treatment, with a very good prognosis. (Clemens, 2016, 2019). In the case of a unilaterally diagnosed BIA-ALCL patient, a contralateral prophylactic implant removal with total capsulectomy is recommended as there have been several cases of bilateral disease reported worldwide to date. In non-symptomatic patients with textured implants or implants with an unknown surface, implant removal with or without total capsulectomy for the single purpose of BIA-ALCL prophylaxis is not recommended due to the very low incidence of this disease. No risk reducing procedure has been demonstrated once a patient has been exposed to a textured implant, and disease development has been known to occur years after prior explantation and capsulectomy. However, some patients may request removal of the implant and capsule, particularly patients with manufacturer-recalled implants or the reported high-risk breast implants (e.g., certain polyurethane or salt-loss macrotextured implants etc.). Any surgery should follow an informed consent discussion on the related surgical risks and that a risk of BIA-ALCL may persist following surgery. In symptomatic patients with textured implants in place, diagnosis by liquid aspiration and CD30 immunohistochemistry is recommended with imaging performed prior to surgical intervention by implant removal with total capsulectomy with disease-free margins, including healthy tissue.

2.4. Alternatives to breast implants

There are several alternatives to breast implants that involve plastic surgery techniques, either using autologous flap tissue or autologous fat transfer. The latter may need multiple procedures before an acceptable result is obtained. However, patient characteristics may limit the application of these techniques which are less commonly used outside of reconstructive surgery practice.

2.5. Future directions

There is an imminent need for an in-depth understanding of the pathophysiology and the role of patient genetics as well as features of the implant devices themselves in the development of BIA-ALCL. Moreover, reporting of new BIA-ALCL cases by the national clinical implant registries is of major importance in order to produce a clear picture of the epidemiology of this disease with regards to the types of breast implants implicated in BIA-ALCL, the level of related and attributed risk, and the effectiveness of treatment procedures, particularly in advanced disease. In addition to reporting symptomatic cases, numerator data (e.g. sales data with number and types of implants sold periodically) should be collected and made available.

Breast implant registries should be established and be mandatory, and include a minimum harmonised dataset of device characteristics, which is globally uniform, to optimise global post-market surveillance of breast implants. The incidence of BIA-ALCL should be monitored with systematic data collection in those registries (e.g., for breast surgery or pathology diagnosis) in preference to *ad hoc* reporting of case findings (Hopper, 2018).

A universal grading system for implant surfaces and surface characterisation should be further explored. This should include research on the role of surface characteristics in relation to particle shedding, and surface characterisation related to chemical moieties for their carcinogenic potential. The role of implant qualities in inducing chronic inflammation should be investigated including the possible roles of particle shedding, bacterial contamination, and chemical moieties on the surface of breast implants. Further research should be conducted into the aetiology of BIA-ALCL regarding the potential contribution of genetic predisposition for mutations and chromosomal abnormalities.

3. Conclusion

SCHEER considers that there is a moderate weight of evidence for a

causal relationship between textured breast implants and BIA-ALCL. As BIA-ALCL is a low incidence disease, developing and maintaining global networks with cross-country communication is of major importance to better understand its pathogenesis and spread to the population. Also, current registries should collaborate and strengthen their networks as well as aim to inform. This should be encouraged and actively supported by providing funding and infrastructural support.

Funding body information

None.

CRediT authorship contribution statement

Wim H. De Jong: Supervision. **Demosthenes Panagiotakos:** Supervision. **Ana Proykova:** members of the working group. **Theodoros Samaras:** members of the working group. **Mark W. Clemens:** members of the working group. **Daphne De Jong:** members of the working group. **Ingrid Hopper:** members of the working group. **Hinne A. Rakhorst:** members of the working group. **Fabio Santanelli di Pompeo:** members of the working group. **Suzanne D. Turner:** members of the working group.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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