Scientific Committee on Health, Environmental and Emerging Risks

SCHEER

Hearing on the SCHEER preliminary Opinion on the safety of breast implants in relation to anaplastic large cell lymphoma (BIA-ALCL)

16 November 2020

SUMMARY RECORDS

European Commission:

DG SANTE C2: Health information and integration in all policies
DG SANTE B6: Medical Devices, Health Technology Assessment

Experts from the SCHEER Working Group:

Scientific Committee on Health, Environmental and Emerging Risks - SCHEER members:

Wim H. de Jong	(Chair)
Demosthenes Panagiotakos	(Rapporteur)
Theo Vermeire	(Chair of the SCHEER)
Anna Proykova	
Theo Samaras	

External experts:

Mark Clemens (The University of Texas MD Anderson Cancer Center, Houston, USA)
Hinne Rakhorst (Medisch Spectrum Twente, Enschede, The Netherlands)
Fabio Santanelli di Pompeo (Sapienza University of Rome, Rome, Italy)
Suzanne Turner (University of Cambridge, UK)

Registered participants:
28 participants from 26 organisations participated in the hearing.

1. WELCOME AND OPENING (DG SANTE)

Philippe Roux, Head of Health information and integration in all policies Unit from the European Commission's Directorate General for Health and Food Safety (DG SANTE), welcomed the participants and briefly explained the role of the SCHEER Committee as an

independent advisory body on scientific matters. Mr Roux also introduced the agenda and explained that the purpose of the Hearing was to present the SCHEER preliminary Opinion on the safety of BIA-ALCL and to provide an opportunity to stakeholders to take part in an open scientific discussion with the scientists involved in producing the Opinion. He reminded the participants that the Hearing does not replace the public consultation, which is opened until 7 December 2020, and that only the comments submitted in writing (via the public consultation link on the website) would be taken into account by the SCHEER in the finalisation of the Opinion.

2. PRESENTATION OF THE MANDATE (DG GROW) - EU POLICY

Paul Piscoi from the European Commission, DG SANTE, Unit Medical Devices, Health Technology Assessment, introduced the request to the SCHEER for a scientific opinion on the safety of breast implants in relation to ALCL.

Mr Piscoi recalled that the SCHEER issued an advice in October 2017, stating that there was insufficient scientific information available to establish a methodologically robust risk assessment to investigate a possible association of breast implants with ALCL development. However, it was recommended that a more in-depth evaluation be conducted on the possible association of breast implants with the development of ALCL. A significant body of scientific information was published in the meantime and, therefore, the request for a new Opinion has been made. In the request, the DG SANTE asked to involve a wide range of experts and stakeholders.

In particular, the SCHEER has been asked:

1. To briefly describe the specific clinical indications and uses for various types of breast implants.
2. To briefly describe what BIA-ALCL is, the specific diagnostic criteria, the state of the art treatment, and the prognosis of the disease. In relation to ALCL, the good clinical practices for the follow-up of women with breast implants should also be described.
3. To indicate what knowledge is in terms of incidence of BIA-ALCL.
4. 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?).
5. To indicate whether a causal relationship between breast implants and ALCL can be established based on the evidence available to date. To discuss what may be the potential and if possible, the most plausible pathogenesis mechanisms. To evaluate the available information on incubation time, and in relation to this, discuss the importance of knowledge on previous implants history of women developing BIA-ALCL. To evaluate if preventive explantation is warranted in case reasons for concern related to breast implants or specific subcategories of breast implants are identified.
6. To describe the factors that may determine the risk of BIA-ALCL. To identify criteria regarding the characterisation of breast implants in relation to ALCL and control measures to reduce the identified risk.
7. In the context of ALCL to briefly describe alternatives to breast implants.
8. Where relevant to identify needs for further research and the best ways to collect the missing data regarding breast implants and ALCL.

The considerations should cover both reconstructive and augmentation use of breast implants.

3. PRESENTATION OF THE SCHEER PRELIMINARY OPINION ON THE SAFETY OF BREAST IMPLANTS IN RELATION TO ANAPLASTIC LARGE CELL LYMPHOMA (BIA-ALCL)

Wim de Jong, the Chair and the rapporteur of the responsible SCHEER working group (WG), gave an overview of the composition of the experts of the SCHEER working group and provided a summary of the content of the SCHEER preliminary Opinion on BIA-ALCL and summarised the SCHEER conclusions:

- Specific clinical use implants: reconstructive or aesthetic,
- BIA-ALCL: T cell lymphoma near BI as seroma and/or solid mass,
- Incidence BIA-ALCL: low but at risk ca 1/3000,
- Shell: characterisation according to ISO 14607:2018,
- Causal relationship: moderate evidence with textured implant (lack of knowledge on pathogenesis),
- Factors: Genetic alterations, Bacterial contamination / chronic inflammation, Shell shedding microparticles, Shell surface characteristics, Implant associated reactive compounds,
- Alternatives: autologous tissue or fat transfer.

The SCHEER has also listed a number of recommendations in the Opinion. On registries, the SCHEER recommends the following:

- Breast implant registries should be established and be mandatory, and include a minimum harmonised dataset of device characteristics, which is globally uniform, in order to optimise global post-market surveillance of breast implants. This should include the UDI (Unique Device Identification) or reference/serial number to provide structured denominator data for risk calculations.
- Funding of such registries should be independent from industry, and it is recommended that General Data Protection Regulation should provide a means to allow data connection between data sources.

It has been noted that a number of registries has been established already, e.g. ICOBRA (International Collaboration of Breast Registry Activities).

As regards epidemiology, the SCHEER recommends that the incidence of BIA-ALCL should be monitored with systematic data collection in registries (e.g. for breast surgery or pathology diagnosis) in preference to *ad hoc* case reporting and case findings.

4. QUESTION AND ANSWER SESSION

Nine presentations have been made during the Questions & Answers session:

1. EUSOMA (European Society of Breast Specialists, Spain): The EUSOMA perspective and proposed actions.
2. G.RE.TA (group of reconstruction and therapeutical advancement, Italy): Is Breast Implant Associated - Anaplastic Large Cell Lymphoma associated to textured implants?
3. Klinik für Senologie (Germany): Over 30 years personal experience with micro polyurethane surface (MPS) breast implants in aesthetic and reconstructive surgery

4. G&G Biotechnology Ltd. (Israel): Hypotheses and Evidence.
5. Italian Ministry of Health, Outcomes and knowledge gained from vigilance and surveillance activities on BIA-ALCL issue carried out by the competent authority: a 7-year report.
6. Plastic Surgery Department of Brussels University Hospital (VUB): Universitat Autonoma de Barcelona, Weighing risk versus benefit of Breast implants. Standards of Care is the Gold Standard.
7. Polytech Health & Aesthetics GmbH (Germany): Same surface, different risk - focusing on roughness is not the right approach.
8. LSCI (USA): Risks/Benefit Perspectives on Textured Breast Implants in Relation to BIA-ALCL.
9. GC Aesthetics (UK): How two breast implant manufacturers demonstrate the safety profile of breast implants.

1. EUSOMA presented experience of its members with working with breast cancer patients and with providing immediate breast reconstruction, and presented evidence gathered. In addition, EUSOMA has also offered a possible contribution as regards data on the type of reconstruction and details on implant type. Also, a contribution in spreading information on diverse EUSOMA initiatives as well as on establishment of a European database on breast reconstruction was offered. EUSOMA pointed out very clearly, as previously stated by the manuscript issued in 2019, that, except for Allergan implants already withdrawn from the market by the majority of countries in Europe, there is not enough evidence to take other actions against implants taking into account the risk/benefit and the lack of viable alternatives for breast cancer patients.

2. The representative of G.RE.TA (group of reconstruction and therapeutical advancement), presented a review of the available literature searching for primary studies on BIA-ALCL presenting an estimation of relative risk (odds ratio, relative risk, hazard ratio) and/or absolute risk of BIA-ALCL. The group has also performed a second review of available literature searching for all prospective cohorts including more than 10,000 breast implanted patients and papers reporting the results of FDA post-approval core-studies. The data presented by G.RE.TA showed cases with different types of implants: cases with smooth implants, cases with unknown prior history of implants, cases with history of at least one textured implant, cases with history of prior implants with unknown texture, cases with a history of one smooth implant and with no known textured implants. The presenter concluded that in order to carry out a balanced evaluation, there is a need to look at previous history of smooth implants for all patients developing BIA-ALCL on textured ones.

3. The presentation of the Klinik für Senologie focused on its experience in the field of plastic and reconstructive surgery with the use of micropolyurethane covered (MPS) implants in aesthetic and reconstructive breast surgery. According to the presenter, a strictly sterile "no touch" regimen during implantation and the characteristic properties of MPS covered breast implants with active ingrowth of new tissue during implantation, would avoid seroma formation and secondary infection. He stressed the importance of distinguishing between a textured surface and the coverage of the breast implant with MPS; MPS allows the ingrowth of tissue into the foam which is volcanized on the silicone surface. A textured implant allows no ingrowth, only a superficial tissue coverage which can convert into a linear second capsule.

4. The presentation of G&G Biotechnology focused on three issues: A) Analysis of available reliable data shows that ~85% of BIA-ALCL cases associated with silicone implants are attributed specifically to Allergan textured rather than to texture in general. For Polyurethane covered implants, ~90% are associated with Silimed specifically. Furthermore, when removing Allergan cases, the distribution of smooth and textured cases is similar to the market presence. B) Attempts at surface characterization should use the proper parameters, be relevant to the type of surface (e.g. 2D surface vs. 3D topology) and have clinical relevance. Current grading systems are oversimplifying. C) The presenter suggested collecting exhaustive epidemiological information, with thorough investigation on all reported cases to date (case by case) and through globally networked local registries, as well as systematic collection and analysis of tissues and implants of BIA-ALCL patients. Continuous efforts to increase awareness among patients, surgeons and health care providers has also been stressed.

5. The Italian Ministry of Health (IMoH) has been promoting physicians' and patients' awareness since 2014 and many actions have been undertaken to achieve the correct BIA-ALCL diagnosis. Among others, it has centralized the recovery and collection of data for each BIA-ALCL patients and has issued a complete registry of the Italian cases, including sales data per year from breast implants distributors. Guidelines on the management and treatment of BIA-ALCL patients have been established and issued at national level. Retrospective and prospective studies have been performed in order to share the increased acknowledge on this matter with the scientific community. However, this scientific evidence has regrettably not been considered and added among the references in the SCHEER Opinion. The presenter raised several comments to the SCHEER preliminary Opinion: 1) Clinical indication for the use of one type of breast implant versus another depends on the preoperative clinical condition for both aesthetic and reconstructive purposes; 2) Anatomical shaped/textured breast implants cannot be always replaced by other procedures in aesthetic surgery; 3) AFT as an alternative to breast implant augmentation is often not possible as it depends on the amount of fat tissue available for multiple surgical sessions; 4) Autologous reconstruction requires a great surgical expertise and physicians are not always able to perform it. There is the high risk that many patients do not receive reconstruction. The IMoH highlights that many limitations in the BIA-ALCL research still exist and severe data gap have been largely declared worldwide. One of the main limitations regards the implant history of the patients, a fundamental information to understand which was the device implanted at the onset of the first symptoms and this is unfortunately often unknown in the reported literature. To date, all types of breast implants have to be monitored, mandatory breast implants registries must be supported and promoted in order to achieve a more reliable estimation of BIA-ALCL incidence. Pre-market studies have to be enhanced and the classification of breast implant surfaces has to be improved. The IMoH believes that, to date, corrective action against textured breast implants are not supported by scientific evidences.

6. The presentation of the Plastic Surgery Department of Brussels University Hospital focused on the necessity to clarify the classification of implant surfaces. In April 2018, the new edition of the approved ISO standard was published. Appendix H of these new ISO guidelines provides precise definitions for the surfaces of mammary implants, which, according to the presenter, is inconsistent.

NOTE of the secretariat: ISO has started a new work item on revision of the standard describing breast implant surfaces.

7. Polytech Health & Aesthetics GmbH stressed in the presentation that the discussion on the possible causes of BIA-ALCL almost always focused on the surface of the implants

and that the degree of surface roughness being "the" trigger. However, the tissue interaction with a 2D silicone surface is radically different than with a 3D polyurethane matrix. The company presented data according to which there has been a statistically significant difference in the occurrence of BIA-ALCL in breast implants with the same surface type which refutes the theory that surface/roughness is *per se* a decisive trigger for BIA-ALCL.

8. The presentation of LSCI focused on two particular topics 1) the quantifiable specific benefits (along with risks) of particular types of texture, considered in the context of quantifiable risks (including mortality) of aesthetic breast surgery reoperations; and 2) shortcomings of proposed breast implant surface classification systems including their lack of clinical validation.

9. GC Aesthetics focused in its presentation on the breast implant classification system which does not provide consistent data on product classification. According to the presenter, textured implants are needed to prevent sub-optimal patient outcomes in certain conditions and exposure to risks associated with re-operations and increased morbidities. There is an array of clinical evidence available demonstrating the benefits of macro textured devices in comparison to micro textured implants.

Presentations given during the hearing will be published on the scientific committees' website in agreement with the respective speakers:

https://ec.europa.eu/health/scientific_committees/events/ev_20201116_en

Additional comments raised by the participants during the hearing:

- There is a need to create a meaningful classification for the breast implants. Average roughness actually has no clinical relevance for the biological scale; the only reason it is used is because it is easy to measure.
- The risk of systemic ALCL has been shown to be higher in studies that looked at cancer registries such as the De Boer and Prantl studies.
- There is a role of industry in providing valuable data on various breast implants, e.g. on sales.
- There is need to get a full picture on the individual cases; it is important not only to look at the implant at the time of the diagnosis of ALCL, but also to know the whole history of the individual patient's implants.
- There is no evidence of a causal relationship between textured and BIA-ALCL as suggested in the preliminary report.
- Inconsistent analysis of data: FDA and other data available clarifies the history of previous implants in cases of smooth diagnosed patients but does not provide the history (and whether there is a smooth implant in it) in textured diagnosed cases.
- Registries face issues with GDPR when reviewing the "old" cases.

5. CLOSING

The Chair thanked participants for their contributions and reiterated that the deadline for submitting written contributions and supporting evidence through the public consultation would be on 7 December 2020:
https://ec.europa.eu/health/scientific_committees/consultations/public_consultations/scheer_consultation_09_en

The Chair also recalled that the contributions to the consultation process should not be about policy or risk management issues, but should aim at improving the scientific basis of the Opinion. Only submissions directly referring to the content of the preliminary Opinion and relating to the issues that the document addresses would be considered by the SCHEER.

The SCHEER will consider all the relevant submissions related to the scope of the public consultation and will decide if and to what extent each of the contributions should be taken into account in the formulation of the final Opinion.