National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Summary International Expert Meeting on BIA-ALCL

RIVM

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On November 19th 2018, the Dutch National Institute for Public Health and the Environment (RIVM), supported by the Dutch Ministry of Health, Welfare and Sport (VWS) and the Dutch Health and Youth Care Inspectorate (IGJ), brought together in Amsterdam (the Netherlands) an international multidisciplinary group of regulators, public health authorities, medical specialists, epidemiologists, experts on implant registries, and breast implant manufacturers to discuss the problem of a very rare form of lymphoma seen in women with breast implants. This form of lymphoma is called breast implant-associated anaplastic large cell lymphoma (BIA-ALCL).

It is currently accepted that having breast implants is associated with an increased risk of developing the very rare disease ALCL. BIA-ALCL is considered at this point an emerging disease: the number of cases reported so far is still very low, however, it is increasing. It is not clear whether the observed increase in incidence is due to implant or patient risk factors that were not present before, or whether it is rather due to an increase in the number of women receiving breast implants, or to other factors. There is also an increased awareness about the disease among health care providers, and more attention for tissue sampling and pathological diagnosis. The key now is to understand the origin of the association between breast implants and BIA-ALCL. Knowing whether particular types of implants may be putting patients at risk or whether particular types of patients may be more susceptible to developing the disease can bring possibilities for implementing (regulatory) actions (e.g. changing implant materials, discouraging implant use for specific types of patients) aimed at providing safety for women having or considering to have breast implants. This meeting aimed at formulating research questions with high priority at this moment and exploring how to bring this research forward. Given the relatively low number of BIA-ALCL cases seen per country, performing individual research per country is likely going to be hampered by statistical limitations, and will probably not find answers to all relevant research questions. Therefore, an international approach is necessary.

Morning session

The meeting was opened by Annemiek van Bolhuis (RIVM) and chaired by Josée Hansen (former IGJ Chief Inspector). In the morning, seven presentations were given by keynote speakers from the Netherlands, Australia, and the US (see Annex I for the speakers' affiliations and Annex II for the presentations of those speakers who gave consent to have their presentation published). In the afternoon, the participants were distributed in three discussion groups. Two questions were to be answered regarding the way forward for future research on BIA-ALCL: what should be the focus of future research? And how to organize and fund future research?
The first keynote speaker, Dr. Wim de Jong (the Netherlands), presented the 2017 advice from SCHEER, a scientific committee installed by the European Commission, on the state of scientific knowledge regarding a possible

connection between breast implants and ALCL.[1] The SCHEER advice recommends a more in-depth evaluation of the possible association between breast implants and the development of ALCL, and calls for prospective studies in order to be able to perform such an evaluation.

Prof. Flora van Leeuwen (the Netherlands) followed with a presentation on the epidemiological challenges inherent to studying an association between an infrequent exposure (breast implants) and a very rare disease (ALCL in the breast). She elaborated on the advantages and disadvantages of cohort and case-control studies. While the former require large (historical) registries, the latter need a careful selection of cases and agreement on what the controls should be. The case-control study she co-authored, published in JAMA Oncology in 2018[2], found a high relative risk of BIA-ALCL in women with breast implants. Of note, the absolute risk remained small, with an incidence of 1 case of ALCL in 7000 women with breast implants at 75 years of age. She recommended future research on the influence of implant type (e.g. different textures, surface area), implantation factors (e.g. time of getting the first implant, years having an implant, number of implant revisions), and patient characteristics (e.g. genetics) on BIA-ALCL risk.

The third speaker, Dr. Mark Clemens (United States), shared the US experience with BIA-ALCL. In the safety communication released by the FDA in 2017[3], the FDA agreed with the World Health Organization provisional classification of BIA-ALCL as a newly recognized malignancy. The FDA currently supports what is known as NCCN guidelines (National Comprehensive Cancer Network guidelines) for the diagnosis and management of BIA-ALCL. The FDA also recommends reporting of confirmed cases to what is called the PROFILE registry (i.e. the American Society of Plastic Surgeons' prospective registry to study BIA-ALCL in collaboration with the FDA). According to Dr. Clemens, all BIA-ALCL cases within the PROFILE Registry so far from which the clinical history is available have had textured implants at some point in their history[4]. An important message from Dr. Clemens was that awareness among physicians is critical; when diagnosed in time and treated adequately, this disease has a very good prognosis. There is no reason to screen asymptomatic patients. Lastly, Dr. Clemens shared his knowledge on possible mechanisms involved in the development of BIA-ALCL and on different treatment options.

Dr. Hinne Rakhorst (the Netherlands) presented the work being done within the Dutch Breast Implant Registry (DBIR). According to Dr. Rakhorst, the DBIR provides unique opportunities for research due to two reasons: first, it is a very complete registry since all procedures performed in the Netherlands are registered unless a patient explicitly denies consent (which is known as opt-out), and second, the registry is paid through clients and health insurances, being completely independent from industry. In addition, the data from the DBIR can be combined with data from the nationwide network and registry of histo- and cytopathology diagnosis present in the Netherlands (PALGA Foundation).

[1]SCHEER = Scientific Committee on Health, Environmental and Emerging Risks; link to the advice: https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_007.pdf
[2] https://jamanetwork.com/journals/jamaoncology/article-abstract/2667737
[3]https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm
[4]https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm481899.htm

Prof. Anand Deva (Australia) shared some of his research from Australia and New Zealand via videoconference. He showed how breast implants with high surface area and roughness may be associated with a higher risk of BIA-ALCL. An interesting theory is that bacterial contamination on the implant biofilm can cause antigenic stimulation in susceptible hosts (e.g. women with a certain genetic background, such as STAT3 and TP53 mutations). Increased friction, silicone particles or allergies could be other sources of a local inflammation ultimately leading to BIA-ALCL.

The last two speakers of the day were Prof. Roberto Miranda (United States) and Prof. Daphne de Jong (the Netherlands). Prof. Miranda presented an overview of the pathological diagnosis, disease progression and pathogenic mechanisms of BIA-ALCL. He explained the differences between ALCL occurring in the breast (BIA-ALCL) and ALCL occurring elsewhere in the body. While all types of ALCL consistently express the marker CD30 and are characterized by large anaplastic cells, BIA-ALCL can be considered a distinct disease clinically, pathologically and pathogenetically. Unlike other ALCL types, BIA-ALCL is always negative for the anaplastic lymphoma kinase (ALK) marker, and chemotherapy is often not required for treatment. A chronic T-cell induced immune response to either implant materials or to bacteria were mentioned as possible etiologic factors. Lastly, Prof. Miranda postulated that the disease is currently underdiagnosed. Prof. de Jong, in turn, focused on the molecular aspects of BIA-ALCL. She agreed that BIA-ALCL is a very distinct disease; it shows a remarkably complex genetic landscape (with copy number gains and losses, as well as mutations) that may distinguish it from other types of ALCL.

Afternoon session

The afternoon discussions took place in three separate groups, each of them being multidisciplinary and with representatives from different countries, in order to foster debate due to a diversity of perspectives. The discussions focused on the following: identification of research questions on BIA-ALCL, requirements for performing such research, types of studies suitable to answer the research questions, and how to organize future research in terms of parties involved, roles of each party, funding, and time frame. The main outcomes of these discussions are summarized below.

Research topics

Future research should focus on four main areas: patient, implant, and tumor characteristics, as well as biofilm formation around the implant.

1. Can <u>patient characteristics</u> be identified that make one patient more susceptible to getting BIA-ALCL than another?
    - Possible factors to study are: autoimmune conditions, genetics, atopic constitution, age at first implantation, indication (cosmetic vs reconstruction).
    - With lower priority, the following could be studied: impact of other sources of infection such as previous dental procedures, race/ethnicity (there is so far only a low number of BIA-ALCL reports in Asian women, which could have to do with differences in immunology), being immuno-compromised (e.g. having had a bad flu, EBV or HPV infection, chemotherapy).

2. Can implant characteristics be identified that make one implant more prone to cause BIA-ALCL than another?
   - Possible factors to study are: composition of the raw material, chemicals used during the manufacturing process, technology used for texturing, degree of texture (i.e. do textured implants present a higher risk than smooth ones?), electrostatic charge of the implant, implant chemical composition after explantation (i.e. has this changed with respect to the original composition, e.g. changes in cross-linked density?).
   - Take into account that the United States had a moratorium on breast implants, followed by market approval of some implants with an obligation of manufacturers for prolonged clinical follow up studies. Preferred practice in the US has been to use smooth implants. These aspects will affect the data coming from the US.

3. Do tumors from different BIA-ALCL patients have similar characteristics?
   - Characterize tumors genetically

4. Does biofilm formation predispose to developing BIA-ALCL?
   - Studies on the effect of preventing biofilm formation on the incidence of BIA-ALCL (manufacturers may work on surfaces that repel bacteria, e.g. by charging the surface).
   - Studies on the influence of the free volume around the implant on biofilm formation (the larger the free volume, the larger volume of fluid around the implant and the easier biofilm is formed).

5. Other ideas discussed were:
   - Studies on the relationship between surgical procedure or protocol followed and BIA-ALCL. However, this was considered difficult due to the scarcity of BIA-ALCL cases per surgeon.
   - Studies on specific batches of implants. This was considered too specific due to the low prevalence of the disease.
   - Studies on registered old cases of systemic ALCL; the possibility exists that (some of) these cases have actually been originating from breast ALCL, and not been identified as such at that time due to lack of knowledge about the disease.

Requirements for research

1. Good registration of all implantations in as many countries as possible is key: which implant has been placed, why (indication), in which breast, and by whom. A minimum necessary dataset should be defined, data should be collected in different countries in the same way to be able to pool or compare data, and all registries should use the same definitions (i.e. standardization of data collection and definitions). The establishment of the UDI (Unique Device Identifier) will improve the accuracy of registration. It was noted that registries can only be made mandatory on a national level.
2. Definitions on a distinction between textured and smooth implants (including all variations) should be harmonized; currently definitions may differ per manufacturer and per country. The descriptions included in the informative Annex H of the ISO 14607 standard on mammary implants[5] may not be sufficient to encompass the large variability of existing implant types.

[5] https://www.iso.org/obp/ui/#iso:std:iso:14607:ed-3:v2:en

3. Information on implant manufacturing processes and implant characteristics needs to be available, including e.g. changes in (surface) technology, chemical composition of implants, electrostatic charge. Also, sales data are needed. However, the fact that manufacturers usually consider these data to be proprietary often prevents sharing of information.
4. Patient material for genetic studies (e.g. from ALCL, blood or a swab samples) and infrastructure to store and share this material (i.e. biobank).
5. A specific strategy for pooling and sharing information on ALCL and patient data internationally. Privacy regulations hamper exchange of data. Two possible solutions are: 1) sharing anonymized data between countries, 2) performing individual studies per country and share only the results or aggregated data. It is very important to have a proper and uniform informed consent and preferably include patients in a registry on an opt-out basis.
6. Limited number of expert centers on BIA-ALCL per country, where suspicious cases can be referred to.
7. Research independent from industry.
8. Long-term (sustainable) funding.

Type of studies/study design

1. Retrospective studies using data already available from existing (older) registries. Cases are patients with BIA-ALCL; controls are matched women with breast implants who did not develop ALCL. Ideally, cases and controls would be also matched on implant batch or type. A challenge here is how to collect more information about patients retrospectively (e.g. could be via surveys).
2. Prospective studies with data from the newer registries. With this design, more time is needed to get results. This option seems difficult in view of the low number of cases and the time to ALCL occurrence (estimated to occur approximately at 8-10 years after implantation)
3. Two other ideas came up in the discussion but were not further developed: studies in animal models (there is no animal model for ALCL available yet) and *in vitro* studies.

Involved parties and roles

1. Industry: key role in providing implant data. It is necessary to populate an international device library.
2. Implant registries worldwide. Next to the countries that have or will soon have a registry and that are willing to collaborate (Sweden, Netherlands, UK, Denmark, Italy, Australia, New Zealand, US), it is necessary to get other countries involved, especially those where breast implants are used often (e.g. China, Brazil, South-Korea, Mexico). Colombia is also interesting since they have a cancer registry in place. The International Collaboration of Breast Registry Activities (ICOBRA™) was proposed as intermediary to align the breast implant registries worldwide.
3. Researchers (including clinicians, pathologists, epidemiologists and chemists), ideally from academia given their independent position and possibilities for funding via e.g. PhD studies.
4. Government
5. Lay representatives

Funding

1. According to some participants, obtaining funding for research on BIA-ALCL seems to be easier in some countries than in other. In some countries, BIA-ALCL is not a main priority given the low incidence of the disease.
2. Various funding sources were mentioned: the European Commission (e.g. through a dedicated call for research on BIA-ALCL), research funds for rare diseases; Horizon 2020 (although only for Europe and limited duration), philanthropic organisations (e.g. Bill and Melinda Gates Foundation).
3. A general opinion was that the manufacturers should be involved in providing funding, since research results are of interest to them as well. However, the majority of participants also strongly believed that industry should not have influence on the specific research being done. Some options mentioned were that industry would help keeping registries funded in the long term or would put money in a general fund for research. An unresolved question was how to define what each industry needs to pay (e.g. based on market share?).

Time frame

The group agreed that no immediate answers are possible, but that this meeting was a landmark day on BIA-ALCL and a starting point for future research. Concrete short-term actions were formulated:

- Set up an international consortium with various work packages (including project management, epidemiology, laboratory research/pathology, clinical performance of implantation, data mining, data aggregation, privacy) to prepare research proposals. The RIVM can act as intermediate to bring all relevant parties together in this global consortium.
- Engage as many countries as possible, if necessary reach out to them via the RIVM and regulators.
- Meet in the second half of 2019, if necessary via webinar to discuss progress and if possible start the research.
- A face-to-face meeting in 2 years.
- Identify privacy issues in each country/region which may hamper progress and find ways to overcome them (e.g. find out what information can be shared).
- Build up an international funding strategy with multiple funding partners.

Several participants were of the opinion that awareness among clinicians and women with breast implants about the disease and its symptoms should increase. When clinicians are aware of the problem, they will more closely follow-up their patients and report suspected cases; they will also more accurately report cases to the manufacturers, who, in turn, will timely report to the regulators. In addition, when BIA-ALCL is diagnosed in an early stage, it represents an indolent and curable disease. On the other side, women with breast implants need to be aware as well of the importance of attending her follow-up appointments. Providing clinicians and patients with proper information will help increase awareness.

Annex I

Speakers' affiliations

Speaker	CV
Dr. Wim de Jong	Senior researcher at RIVM, the Netherlands; Member of the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER), DG for Health and Food Safety, European Commission; Chair SCHEER Working Group on PIP silicone breast implants
Prof. Flora van Leeuwen	Netherlands Cancer Institute, Amsterdam, the Netherlands
Dr. Mark Clemens	Plastic surgeon at MD Anderson Cancer Center, Houston, USA
Dr. Hinne Rakhorst	Chair Dutch Breast Implant Registry, Board member International Confederation of Plastic Surgery Societies ICOPLAST, plastic surgeon
Prof. Anand Deva	Head of Plastic and Reconstructive Surgery and Co-Director of the Surgical Infection Research Group, Macquarie University, Sydney, Australia
Prof. Roberto Miranda	Professor in Hematopathology, MD Anderson Cancer Center, Houston, USA
Prof. Daphne de Jong	Professor in Hematopathology, Amsterdam UMC, VU University Medical Center, the Netherlands

Annex II

Speakers' presentations:

1. Dr. Wim de Jong
2. Prof. Flora van Leeuwen
3. Dr. Mark Clemens
4. Dr. Hinne Rakhorst
5. Prof. Roberto Miranda

The presentations are included in a separate document, see: https://www.rivm.nl/documenten/summary-international-expert-meeting-on-bia-alcl-november-19th-2018.