Medical Device Advisory

MD11/052019

Health Products Regulation Group
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10 May 2019

Dear Healthcare Professional

POTENTIAL RISK OF BREAST IMPLANT ASSOCIATED-ANAPLASTIC LARGE CELL LYMPHOMA (BIA-ALCL)

The Health Sciences Authority (HSA) would like to update healthcare professionals on the potential risk of Breast Implant Associated-Anaplastic Large Cell Lymphoma (BIA-ALCL), a rare type of lymphoma that usually develops around breast implants. HSA has reviewed the available scientific data and global reports of BIA-ALCL and in consultation with our Expert Panel[1] on Breast Implants, we are disseminating this communication to all healthcare professionals.

About BIA-ALCL

2 BIA-ALCL is a rare type of non-Hodgkin's T-cell lymphoma that usually develops around breast implants. It usually involves a swelling around the implant and has been reported to occur as early as 1 year and as late as 37 years after the breast implant surgery. There have been approximately 800 reports (both confirmed and unconfirmed reports) of BIA-ALCL worldwide. This should be viewed in the context of an estimated 10 to 35 million breast implants that have been implanted (as approximated in the scientific literature).

3 Breast implants have a silicone outer surface that is either smooth or textured. The estimated incidence rates of BIA-ALCL reported in literature[2] ranges from 1 in 3,817 to 1 in 30,000 patients with textured breast implants. Further review of the global reports on BIA-ALCL indicates a relatively higher incidence rate in patients implanted with macro-textured breast implants.

[1] Expert Panel comprises a group of healthcare professionals from both public and private hospitals.
[2] Loch-Wilkinson et al, 2017 and Doren et al, 2017 (Plastic Reconstruction Surgery)

4 While the majority of patients who have developed BIA-ALCL globally have had textured implants, there have been a few unconfirmed reports of BIA-ALCL in patients who have received smooth-surfaced implants[3]. The possible association is currently being investigated by regulators globally.

5 If diagnosed early, BIA-ALCL can be successfully treated with surgery. However, in cases where the cancer has spread to other parts of the body, further treatment such as radiation or chemotherapy and targeted immunotherapy have been used.

Local situation and HSA's advisory

6 There are currently eight registered brands of breast implants in Singapore. Allergan Natrelle breast implant is the only macro-textured breast implant registered in Singapore. As a precautionary measure, HSA has disallowed the sale of the Allergan Natrelle breast implant in Singapore since April 2019.

7 Since 2017, following emerging scientific reports on BIA-ALCL, HSA has required manufacturers of breast implants to include cautionary statements regarding the risk of BIA-ALCL in the package inserts of breast implants that are registered in Singapore. HSA had also informed relevant healthcare professionals in October 2017 to highlight the risk of BIA-ALCL and the possible association with textured surface breast implants to patients, and advised them to report any BIA-ALCL cases they encounter to HSA.

8 Given the growing global concerns on BIA-ALCL, HSA convened an Expert Panel in February 2019 to discuss the risks of BIA-ALCL and the relevant mitigation measures. Based on current scientific data, the Expert Panel assessed that although textured surface implants appeared to be associated with a higher risk than smooth ones, the risk factors associated with the disease are still unclear. The panel noted that BIA-ALCL occurrences are rare and the associated mortality rates remain low. While regulatory agencies are actively investigating the risk of BIA-ALCL, it is advised that timely detection and appropriate clinical management remain the key factors in managing BIA-ALCL effectively.

9 To date, HSA has received one report of BIA-ALCL locally. The patient had pain in the breast and was diagnosed early. According to her doctor, her prognosis is good, and she is recovering.

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[3] "Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)", 2019, FDA, US Food and Drug Administration https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm

10 HSA advises healthcare providers managing breast implant patients on the following precautionary measures:

- Always inform patients of the risks and benefits of the different types of implants and to take informed consent prior to breast implant surgery (regardless of whether the implant is for reconstruction or augmentation purposes). Patients should also be informed and advised to be vigilant on the common presenting symptoms of BIA-ALCL, such as delayed effusion/seroma or less commonly, a mass or lymphadenopathy.
- Consider the possibility of BIA-ALCL when treating a patient with late onset peri-implant seroma. This may present in patients as a mass adjacent to the breast implant.
- Our Expert Panel advises that if you have a patient with suspected BIA-ALCL, an ultrasound evaluation to determine the presence and extent of an effusion and presence of a mass may be considered, depending on the individual patient's condition. For confirmation of diagnosis on BIA-ALCL, fine needle aspiration (or core biopsy) of an effusion (mass) may be considered for further analysis. Patients should be referred to a specialist for follow-up.

11 HSA has prepared an infographic for doctors to facilitate their communication and discussion with patients on the risk and presenting symptoms of BIA-ALCL. Doctors may forward this infographic to their patients who have already been implanted with breast implants to promote greater awareness. HSA has also prepared a list of frequently asked questions on this topic. Please refer to Annexes A and B. These materials can also be found on our website at www.hsa.gov.sg/bia-alcl.

12 The National Cancer Centre Singapore (NCCS) and the National University Cancer Institute Singapore (NCIS) have produced an advisory to provide doctors with supplementary information. Please refer to Annex C. The Chapter of Plastic, Reconstructive and Aesthetic Surgeons, Academy of Medicine, Singapore has also prepared an advisory on BIA-ALCL. The information can be found at www.ams.edu.sg/view-pdf.aspx?file=media%5C4831_fi_549.pdf&ofile=PRAS+Advisory+BIA-ALCL+20190315.pdf

Reporting of adverse events

13 Healthcare professionals are reminded to report all suspected and confirmed cases of BIA-ALCL in individuals with breast implants to the Medical Devices Branch, Medical Devices Cluster, Health Products Regulation Group, HSA at Tel: 6866 1048, Fax: 6478 9028, Email: HSA_Medical_Device@hsa.gov.sg, or report online at www.hsa.gov.sg/ae_online.

14 HSA will continue to closely monitor the global developments and review the evolving scientific information regarding this safety issue. HSA will update with more information should there be any significant new findings.

Thank you.

Yours faithfully,

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DR SETHURAMAN RAMA
DIRECTOR (MEDICAL DEVICES BRANCH)
MEDICAL DEVICES CLUSTER
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cc Director of Medical Services, Ministry of Health

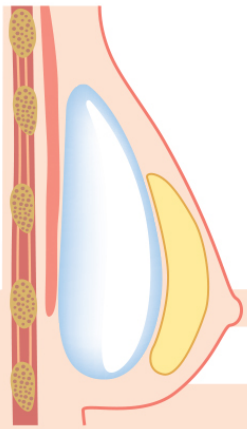
Please scan this QR code for abstracts of Dear Healthcare Professional Letters issued by HSA, Pharmaceutical or Medical Device companies.

ANNEX A

RISK OF BREAST IMPLANT ASSOCIATED-ANAPLASTIC LARGE CELL LYMPHOMA

MAY 2019

WHAT IS BREAST IMPLANT ASSOCIATED-ANAPLASTIC LARGE CELL LYMPHOMA (BIA-ALCL)?



- A rare type of non-Hodgkin's lymphoma (cancer of the immune system) that usually develops around breast implants. It is not a cancer of the breast tissue.
- Usually involves swelling of the breast, which can occur as early as 1 year after the surgery, and as late as 37 years after the surgery.
- In some cases, it can spread to other parts of the body.

WHO IS AT RISK OF BIA-ALCL?

- Majority of patients who have developed BIA-ALCL globally have had **textured implants**. Further review of the global reports indicates a relatively higher incidence rate in patients implanted with macro-textured implants.
- There were also a few unconfirmed reports of BIA-ALCL in patients who have received **smooth-surfaced implants**[1]. The possible association is currently being investigated.

WHAT IS THE RISK OF BIA-ALCL?

Estimated incidence rates reported in literature[2]

1 in 3,817 ◄——► **1 in 30,000**

Persons with textured breast implants

- The Expert Panel on Breast Implants[3], convened by the Health Sciences Authority in February 2019, noted that BIA-ALCL occurrences are rare and the associated mortality rates **remain low**.

IF YOU ARE CONSIDERING BREAST IMPLANT

It is important to discuss with your doctor on the risks and benefits of the different types of implants, whether for reconstruction or augmentation purposes.

IF YOU HAVE A BREAST IMPLANT

- Monitor and check for swelling, lumps or pain around your implant after the surgical incision has healed. Consult your doctor immediately if you have any of the symptoms.
- Continue with regular follow-up with your doctor post implantation.

HSA Health Sciences Authority

1 "Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)", 2017, FDA, US Food and Drug Administration. https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm
2 Loch-Wilkinson et al, 2017 and Doren et al, 2017
3 Expert Panel comprises a group of healthcare professionals from both public and private hospitals.

Annex B

FREQUENTLY-ASKED QUESTIONS ON THE RISK OF BREAST IMPLANT ASSOCIATED-ANAPLASTIC LARGE CELL LYMPHOMA

Breast Implant Associated-Anaplastic Large Cell Lymphoma (BIA-ALCL)

1. What is BIA-ALCL?

Breast Implant Associated-Anaplastic Large Cell Lymphoma or BIA-ALCL is a rare type of lymphoma that usually develops around breast implants. It is a cancer of the immune system and is not a type of breast cancer. It usually involves a swelling around the implant and has been reported to occur as early as 1 year and as late as 37 years after the breast implant surgery.

2. Why is there a higher incidence of BIA-ALCL in textured implants as compared to smooth-surface implants?

Currently, the causes and the associated risk factors for BIA-ALCL are still unclear and are being actively investigated globally. The extent to which the surface of the breast implants being a risk factor in developing BIA-ALCL is also under investigation. While the majority of patients who have developed BIA-ALCL globally have had textured implants, there have been a few unconfirmed reports of BIA-ALCL in patients who have received smooth-surfaced implants. The possible association is currently being investigated.

HSA will continue to monitor and update the public should there be any significant new findings.

3. Have there been any deaths associated with BIA-ALCL in Singapore?

There have been no deaths associated with BIA-ALCL locally.

4. Aside from BIA-ALCL, what are the other common side effects associated with breast implants?

Some of the known adverse effects or complications associated with breast implants include implant rupture (a tear or hole in the implant's outer shell), reoperation/ implant removal and capsular contracture (tightening of the tissue capsule around an implant, resulting in hardening of the breast).

Advisory to consumers

5. I have breast implants. How do I know if I have BIA-ALCL?

You are advised to conduct regular breast self-examinations. If you notice enlargement, swelling or a lump, or experience pain around your implant, you should consult your doctor as soon as possible.

You should also continue with the periodic follow-up post-implantation, as scheduled by your doctor. Post-operative follow-up plays an important role for early detection of BIA-ALCL.

6. I have textured breast implants. Should I have them removed?

The Expert Panel convened by HSA, as well as the Chapter of Plastic, Reconstructive and Aesthetic Surgeons, do not recommend removal of implants for patients who do not experience any symptoms such as swelling or pain around the implant. If you are concerned about the risks of the implants, you should discuss your options with your doctor.

Generally, breast implants typically may require removal after 10 to 15 years, regardless of the risk of BIA-ALCL.

7. I am considering breast implantation. What factors should I consider when choosing between textured or smooth surfaced breast implants? Are smooth surfaced implants safer?

You should discuss the risks and benefits of breast implants and the different types of implants with your doctor, regardless of whether the implant is for reconstruction or augmentation purposes.

Your doctor would be best positioned to advise on the suitability of the different implants for you, by taking into consideration factors such as the nature of the surgery, as well as your physical and medical condition.

Regulation and usage of breast implants locally

8. How are breast implants regulated in Singapore?

Breast implants are classified as high risk medical devices in Singapore. These products are subject to registration by the Health Sciences Authority (HSA) to evaluate their safety, quality and efficacy prior to supply and usage in Singapore.

HSA also conducts post marketing surveillance to monitor the safety profile of marketed products and will take the necessary actions to remove the products from the market should any safety concerns be detected. Companies are also required to report serious adverse events related to their medical devices to HSA.

9. How many brands of breast implants are available in Singapore?

HSA has registered 8 brands of breast implants as of April 2019.

10. Are the other brands of breast implants registered for use in Singapore safe?

All breast implants are subject to registration by HSA to evaluate their safety, quality and efficacy prior to supply and usage in Singapore. This is complemented with a post market surveillance programme to monitor the safety profile of marketed products.

Global reports have indicated increased incidence of BIA-ALCL with the use of macro-textured breast implants. Currently, Allergan Natrelle breast implant is the only macro-textured breast implant registered in Singapore. As a precautionary measure, HSA has disallowed the sale of the Allergan Natrelle breast implant in Singapore since April 2019.

The remaining registered breast implants are smooth or textured (not macro-textured as defined by the international standard for breast implants). We are closely monitoring the evolving scientific information and global reports regarding the continued safety of the breast implants. Consumers will be updated on any new significant information.

Annex C

ADVISORY

National Cancer Centre Singapore
SingHealth

National University Cancer Institute, Singapore
A member of the NUHS

10 May 2019

Dear Doctor

ADVISORY TO DOCTORS ON BREAST IMPLANT ASSOCIATED-ANAPLASTIC LARGE CELL LYMPHOMA

This advisory is produced by the National Cancer Centre Singapore (NCCS) and the National University Cancer Institute Singapore (NCIS). It provides additional information to support the doctor in providing counselling to patients concerning the risks associated with the use of breast implants, as well as in helping guide the management of a patient who has breast implants and where there is a suspicion that this malignancy is present. The advisory should be read in conjunction with the 10th May 2019 HSA update, regarding the risk of Breast Implant Associated – Anaplastic Large Cell Lymphoma (BIA-ALCL). There has been increasing evidence that patients with breast implants have a risk of developing this disease.

Background

2 Breast implants are commonly used for cosmetic breast augmentation, as well as for breast reconstruction following mastectomy to treat breast cancer. Breast implants are composed of a silicone shell, filled with silicone gel or saline. Historically, smooth-shelled implants were used in the 1970s and 1980s. In the late 1980s, textured-shell breast implants were introduced to reduce the incidence of capsular contracture, and their use significantly increased in the 1990s [1,2].

3 The Health Sciences Authority Singapore (HSA) has issued an advisory dated 10th May 2019, which seeks to increase awareness about an association between breast implants, used in cosmetic breast surgery as well as in post-mastectomy breast reconstruction, and Breast Implant Associated – Anaplastic Large Cell Lymphoma. BIA-ALCL is a rare peripheral T-cell lymphoma and not a cancer of the breast tissue. When a breast implant is placed in the body, it is either inserted behind the breast tissue or under the chest muscle. Over time, fibrous scar tissue (called a capsule) may

develop around the implant. In patients with breast implants, reported cases of BIA-ALCL were generally found adjacent to the implant and contained within the fibrous capsule around the implant.

4 BIA-ALCL was first reported in the medical literature in 1997 [3]. As of February 2019, more than 450 cases of BIA-ALCL have been reported to the United States Food and Drug Administration (FDA) [4,5] and there have been approximately 800 reports of BIA-ALCL world-wide. While the number of identified cases of BIA-ALCL is small compared to the estimated 10 to 35 million breast implants that have been implanted, the published medical literature suggests that patients with breast implants have an increased risk of developing BIA-ALCL. The estimated incidence of BIA-ALCL ranges from 1 in 30,000 cases [6,7], to 1 in 4,000 cases [8]. While this condition may occur in any patient with a breast implant, it appears to be higher in patients who received breast implants with textured surfaces. A higher incidence of BIA-ALCL has been reported in particular, in patients implanted with macro-textured breast implants. As a precautionary measure, HSA has disallowed the sales of Allergan Natrelle breast implants, which is the only registered macro-textured implants in Singapore. To date, HSA has received one report of BIA-ALCL locally.

5 Based on published medical information to date, the risk for developing BIA-ALCL is the same regardless whether the implant was inserted for cosmetic reasons or for post-mastectomy breast reconstruction. Prior breast cancer is not a risk factor. It is thought that the development of BIA-ALCL is a complex process involving many factors, including bacterial biofilm growth, textured implant surface, immune response, and patient genetics [4]. Because this is an uncommon disease, knowledge regarding this condition is being accumulated.

What are the symptoms of BIA-ALCL?

6 The most common clinical presentation is a late peri-implant effusion, manifesting as breast enlargement more than one year following the breast implant surgery. Other signs and symptoms include a mass adjacent to the implant, or axillary lymphadenopathy. The patient may also experience pain in the vicinity of the implant

and/or B type symptoms associated with lymphoma (fever, night sweats, lymphadenopathy and fatigue).

7 BIA-ALCL may affect patients with either silicone or saline filled implants. The average onset of BIA-ALCL is 10.7 years after the original breast implant surgery [6,7] but this condition has been reported in patients as early as one year and as late as 37 years after surgery.

How should patients suspected of having BIA-ALCL be evaluated?

8 Patients suspected of having BIA-ALCL should be referred to a specialist who is able to evaluate and confirm the diagnosis of BIA-ALCL. A referral for consultation with a surgical oncologist is recommended if the surgeon looking after patients with breast implants, and in whom a concern about BIA-ALCL is raised, does not routinely perform complete surgical resection of cancer.

9 Ultrasound scanning is the first study of choice to evaluate a woman who presents with breast enlargement following previous breast implantation [4]. The ultrasound scan should include assessment of the entire capsule around the breast implant, the underlying chest wall, the related axillary field as well as the contra-lateral breast. This is because there have been documented cases of axillary lymph node involvement together with BIA-ALCL in the capsule around a breast implant, as well as cases of BIA-ALCL being associated with the implants in both breasts for the same patient. MRI may be used as an alternative imaging modality in the evaluation of a patient suspected to have BIA-ALCL. The sensitivity of detecting an peri-implant effusion is 84% and 82% with Ultrasound scanning and MRI scanning respectively [15]. In most cases, BIA-ALCL is confined to the effusion or seroma around the breast implant, without invasion of the capsule. Rarely, invasion through the capsule to form a mass adjacent to the capsule of the implant, lymph node and systemic spread may occur. If a peri-implant effusion or seroma is present, image-guided fine-needle aspiration of the fluid collection should be performed. Immunohistochemistry tests are performed on freshly aspirated fluid samples to confirm the diagnosis. BIA-ALCL is CD30 positive, epithelial membrane antigen positive, and ALK negative [9]. If BIA-ALCL is confirmed on cell-block cytology or histology, positron emission tomography

combined with computed tomography (PET/CT) is the preferred staging investigation to assess for systemic disease [10].

10 When a diagnosis of BIA-ALCL is made, doctors are reminded of the need to report this adverse event arising from a surgical implant to HSA. This is in addition to reporting to the cancer registry.

What is the treatment for patients with BIA-ALCL?

11 Most cases of BIA-ALCL present early with symptoms and with localized disease, which is confined within the capsule of the breast implant. They also often have an indolent clinical course. The recommended treatment in such patients is the complete removal of the capsule of the implant (total capsulectomy), together with the breast implant within the capsule. If the lymphoma has not extended beyond the capsule of the affected breast implant, there is no need for further intervention [10,11,12]. After complete excision, regular surveillance examinations and imaging investigations may be required.

12 Patients with more advanced disease, including patients with a tumour mass, lymph node involvement, and/or distant spread, should be referred to a medical oncologist early for an individualised treatment plan to be developed. More extensive surgery may be necessary and this includes implant removal, complete capsulectomy, resection of any associated mass and axillary lymph node dissection. Removal of the contralateral implant and total capsulectomy in all patients diagnosed with BIA ALCL should be considered, due to the possibility of occult / incidental contralateral disease (5%). In patients *suspected* of contralateral disease, the removal of the contralateral implant and capsule would be *recommended* [16]. In patients with lymph node involvement and/or systemic spread, systemic chemotherapy may be needed as an adjunct to surgery. Radiotherapy may be indicated in selected instances, particularly where there is concern about local residual disease despite surgery to remove the implant and surrounding capsule [4,10].

Further recommendations

13 Current recommendations from the US FDA state that there is no need to change routine medical care and follow-up for patients with breast implants solely on the basis of the risk of developing BIA-ALCL [13]. Additional screening or recommendations to remove breast implants in asymptomatic women is also not needed[13,14]. It is important for doctors to reassure their patients that BIA-ALCL remains a rare condition. Women with breast implants with further concerns should be encouraged to consult and discuss their concerns with the attending surgeon who had performed the breast implant surgery for them, or who continues to provide follow-up care for them.

14 Surgeons who perform breast implant surgery, whether for cosmetic or reconstructive purposes, must perform pre-operative counselling to advise prospective patients of the potential risks and complications associated with breast implantation, including the risk of BIA-ALCL. It should be emphasized to patients that BIA-ALCL may arise long after the initial surgery. Routine surveillance following implantation and long-term follow-up is recommended even though BIA-ALCL is an uncommon disease [4].

Thank you.

Yours faithfully,

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PROFESSOR CHNG WEE JOO
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