EVIDENCE-BASED PERSPECTIVES ON ANAPLASTIC LARGE CELL LYMPHOMA (ALCL) IN BREAST IMPLANT PATIENTS

March 2017 Update

What is ALCL?

ALCL (anaplastic large cell lymphoma) is a rare type of non-Hodgkin lymphoma most often characterized by abnormal growth of T-cells expressing the cell-surface marker CD30.[1-3] These cells can appear in the lymph nodes, skin, bones, soft tissues, lungs, or liver.[4] Primary systemic ALCL is an aggressive disease, while ALCL limited to the skin (cutaneous ALCL) typically has a favorable prognosis.[5] ALCL is further classified based on its expression of the protein anaplastic lymphoma kinase (ALK) into ALK^+ or ALK^- disease.[1, 6, 7] Breast Implant-Associated ALCL (BIA-ALCL) is found in either the fibrous capsule or seroma fluid (effusion) surrounding the implant and is similar to cutaneous ALCL with respect to the presence of $CD30^+$ and ALK^- cells.[7,8]

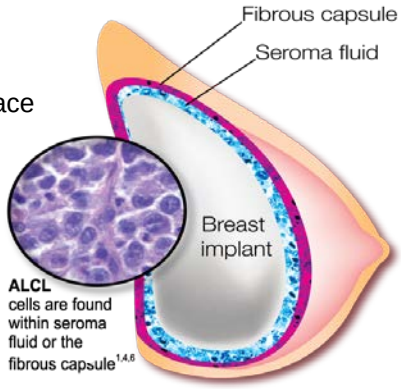

Figure 1. Schematic representation and histology of BIA-ALCL

How common is BIA-ALCL?

In 2011, it was estimated at least 5-10 million women currently have breast implants worldwide.[9] In March of 2017, the U.S. Food and Drug Administration (FDA) reported that they had received a total of 359 medical device reports (MDRs) of BIA-ALCL.[3] However, the FDA cautioned that the MDR system may contain incomplete, inaccurate, untimely, unverified, biased, under-reported or duplicate reporting of events.[3] The FDA has previously noted that "*because the risk of ALCL appears very small, FDA believes that the totality of evidence continues to support a reasonable assurance that FDA-approved breast implants are safe and effective when used as labeled*."[9] In their updated statement released in March 2017, FDA states that "*all of the information to date suggests that women with breast implants may have a very low but increased risk of developing ALCL*."[3]

Historically reported rates range from 1:1000 to 1:3,000,000.[10-16] A recent study, by Deva and others, of 46 BIA-ALCL cases diagnosed in Australia and New Zealand since 2007, indicates that within that population, the rate of BIA-ALCL may be 1:30,000 overall, and in women with a single implant history, reported rates include 1:4,344 (Biocell™), 1:60,631 (SILTEX® Texture), 1:2,492-4,984 (estimated polyurethane). [15] Dr. Deva also notes that the incidence of BIA-ALCL is not the same for different types of surface textures .[15]

Is the reported incidence of BIA-ALCL the same across all implant types?

In their March 2017 update on BIA-ALCL, the FDA reported that of the 359 (Medical Device Reports) MDRs received by FDA, only 231 of those reports contained information on the implant surface, with 203 implants having a textured surface, 28 a smooth surface.[3] Additionally, only 312 reports included implant type with 186 of the implants being silicone and 126 being saline filled.[3] Although the March 2017 FDA update indicated that there were 28 cases of BIA-ALCL associated with smooth implants reported via the MDR system, they did not provide further detail as to the surface texture of any previous implants. In fact, of the totality of the MDR reports received, the FDA stated "most of the reports contained no information about the surface textures of any previous implants."[3]

The FDA also states that "several recent journal articles explore the risk factors for BIA-ALCL, including the methods used to create surface texture of the implant".[3] It should be noted that different types of texturing processes (eg, imprinted, salt-loss) are used by different manufacturers.

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In July 2016, the French government regulatory authority ANSM issued an update on their on-going investigation of BIA-ALCL. ANSM has identified 29 cases of BIA-ALCL in France, as well as estimated sales of 400,000 breast implants between 2007 and 2014.[13] ANSM further reported observations on the uneven distribution of cases among manufacturers, stating that "In France, to date, there appears to be an over-representation in the number of textured implants manufactured by Allergan".[13] This is consistent with recent data from Dr. Deva [15] and with data for broader populations published in reports and presentations by Dr. Garry Brody and the RAND Corporation (Gidengil et al.) on the topic.[17, 18]

Both Dr. Brody and the RAND Corporation reported the distribution of BIA-ALCL cases among device manufacturers. Of the 173 cases of ALCL cited by Dr. Brody, only 3 (1.7%) were associated exclusively with Mentor implants and another 3 cases included device histories that included Mentor implants and those of another manufacturer.[17] Of the 54 cases of BIA-ALCL, noted by the researchers from the RAND Corporation, none were associated with Mentor implants.[18]

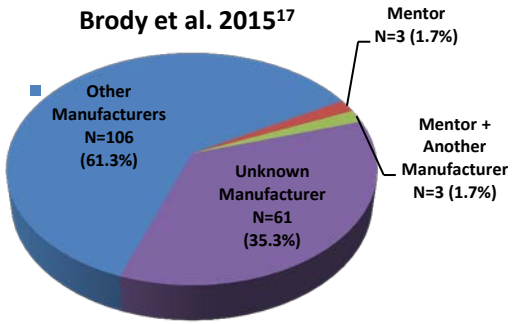
This uneven distribution is further observed in cases of BIA-ALCL reported in the scientific literature, with a consistently low representation of MENTOR® SILTEX® "microtextured" Breast Implants (Table 1). [13, 15-19]

Table 1

Author	Implants studied	Mentor Associated BIA-ALCL Cases
Brody et al.[17]	Allergan/Inamed/McGhan/CUI, Nagor, PIP, Silimed/Sientra/Polytech/Mentor	3 Mentor only cases (1.73%), 3 cases involving Mentor + another manufacturer (1.73%) out of a total of 173 cases
Giedingil et al.[18]	Allergan/Inamed/McGhan/CUI, Nagor, Silimed/Sientra/Polytech, Mentor	No Mentor cases observed out of a total of 54 cases
Knight et al.[15]	Allergan, Mentor, Polyurethane	1 Mentor-only case (1.8%), 3 cases involving Mentor* + another manufacturer (5.4%) out of 56 implants
Doren et al.[16]	Allergan, Mentor	5 Mentor only cases (5%), 3 cases involving Mentor + another manufacturer (3%) our of 100 patients
Srinivasa et al.[19]	Allergan, CUI, Inamed, Mcghan, Mentor, Silimed	20 cases (8.7%) out of 229 MAUDE MDRs
ANSM[13]	Implants previously and currently marketed in France	"over-representation" of cases associated with textured Allergan implants

*includes 2 cases with MENTOR ® smooth implants in patients who also had other textured implants of another manufacturer [as previously noted, there are currently no confirmed cases of BIA-ALCL in patients whose implant history included only smooth implants].

The disparity in the number of BIA-ALCL cases by manufacturer cannot be explained by differences in either total devices sold or total textured devices sold worldwide, as Mentor has approximately half the market share for total breast implants sold worldwide.



What about cases designated as "unknown"?

Prior to increased awareness and reporting of BIA-ALCL cases, many pathologists and surgeons did not note the manufacturer of explanted implants, which may have resulted in the inability to attribute a case of BIA-ALCL to an implant from a specific manufacturer. BIA-ALCL cases where the manufacturer was not noted or cannot be identified are termed "unknown cases". It has also been suggested that differences in implant marking may affect the numbers of known vs. unknown cases, thus leading to assumptions about the distribution cases in which the manufacturer is unknown. Marking of implants (with the Mentor logo/lot #) was initiated at the end of 2002 for those implants produced in Leiden (for sale outside the U.S.) and in 2003 for those implants made in Irving, Texas. Before that, MENTOR® Breast Implants were identifiable by the presence of a tab imprinted with the implant volume. There is no data to suggest that implants reported in the literature and reporting databases as "unknown" would distribute differently than distributions for known implants.

How is a BIA-ALCL diagnosis linked to a particular implant in women with a history of more than one device?

While associating a BIA-ALCL case with a particular implant may be straightforward in women who have had only one breast implant, interpreting the case history becomes more difficult when patients have had multiple implants, particularly when most cases of BIA-ALCL are diagnosed 8-9 years after implantation.[18, 20, 21] The patient history of most BIA-ALCL cases related to MENTOR® Breast Implants involved prior implants made by other or unidentified manufacturers.

The importance of considering total device history in patients with BIA-ALCL is further highlighted by 2 of the BIA-ALCL cases whose device history included MENTOR® Breast Implants. Based on clinical histories, both cases involved breast reconstruction patients who were originally implanted for 16 years with salt-loss textured implants made by another manufacturer, followed by approximately 1.5 years with smooth or textured MENTOR® Devices. In both cases, either part or all of the capsular tissue (the typical localization of BIA-ALCL) was not removed at the time of the implant exchange.[22]

What are the clinical features of BIA-ALCL?

- Clinical presentation:[18, 20]
    - BIA-ALCL in women most often presents as a "late seroma" (more appropriately termed an effusion) that develops at least 12 months after the most recent surgery, with an average 8 to 9 years from time of implantation to diagnosis;
    - BIA-ALCL may present as a palpable mass fixed to the capsule; and
    - Some cases have been discovered during surgery for severe (Baker IV) capsular contracture.
- Histopathology:
    - Lymphoma cells ($CD30^+$) are found in the effusion fluid (seroma) surrounding the implant or in the fibrous capsule rather than in the breast tissue (Figure 1).[5, 7, 8]
- Diagnosis:
    - Ultrasound has been reported to have the highest sensitivity (84%) in detecting effusion in cases of BIA-ALCL[23]
    - The newly released National Comprehensive Cancer Network (NCCN) guidelines for the diagnosis and treatment of BIA-ALCL recommend aspiration and screening of symptomatic peri-prosthetic effusions for CD30 by immunohistochemistry and flow cytometry.[24] The NCCN guidelines are free and can be found at: www.nccn.org/hematologic/nhl/BIA-ALCL.

- FDA currently recommends that Health Care Providers consider the possibility of BIA-ALCL in patients with late onset, persistent peri-implant seroma.[1, 3, 9] FDA recommended testing and diagnostic criteria can be found at: www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm
- Other diagnostic criteria have been proposed by the American Society of Plastic Surgeons (ASPS) and the American Society for Aesthetic Plastic Surgery (ASAPS) [25-27] and other leading researchers in the field.[28]

- Treatment:
  - Multidisciplinary treatment team: oncologic referral, plastic surgeon, other specialties.[3, 21, 24]
  - The American Society of Plastic Surgeons (ASPS), the American Society for Aesthetic Plastic Surgery (ASAPS), The Plastic Surgery Foundation (PSF), the International Society of Aesthetic Plastic Surgery (ISAPS) and FDA continue to surveil the scientific evidence in relation to BIA-ALCL and provide recommendations to their members and patients[25-27, 29, 30] More information can be found at:
    - ASPS: www.plasticsurgery.org/alcl
    - ASAPS: www.surgery.org/professionals
    - PSF: www.thepsf.org/research/clinical-impact/profile.htm
    - FDA: www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm
    - ISAPS: www.isaps.org
  - The NCCN states that BIA-ALCL localized to the capsule may be treated with surgery alone in the majority of cases, however, extended BIA-ALCL with lymph node involvement warrants adjuvant chemotherapy. Local residual or unresectable disease may require radiation therapy and the NCCN recommends following their established guideline regimens for systemic ALCL treatment for cases with distant organ metastasis.[24]
- Prognosis:[5, 8, 31, 32]
  - Like cutaneous ALCL, BIA-ALCL most often has a favorable clinical course if diagnosed and treated in a timely and appropriate manner.
  - In most cases, women presenting with effusion (late seroma) in the absence of a mass have had positive outcomes after surgical removal of the implant.
  - In contrast, some evidence suggests that patients with BIA-ALCL presenting with a mass may have an increased risk of relapse or refractory ALCL.

Are there any recommendations regarding precautions that can be taken to reduce the risk of developing BIA-ALCL?

- There are currently no confirmed cases of BIA-ALCL in patients whose implant history included only smooth implants.[16]
- Health authorities have indicated that BIA-ALCL appears to develop more frequently in women with textured implants.[3, 13, 14]
  - Although the March 2017 FDA update indicated that there were 28 cases of BIA-ALCL associated with smooth implants reported via the MDR system, they did not provide further detail as to the surface texture of any previous implants these patients may have been implanted with. In fact, of the totality of the MDR reports received, the FDA stated "most of the reports contained no information about the surface textures of any previous implants."[3]

- Because the risk of ALCL is rare, societies and health authorities do not recommend additional screenings or removal of implants.[1, 3, 9, 14, 26, 33]
- Up-to-date recommendations from The American Society of Plastic Surgeons (ASPS), the American Society for Aesthetic Plastic Surgery (ASAPS), The Plastic Surgery Foundation (PSF) and FDA [3, 25-27, 29] can be found at:
  - ASPS: www.plasticsurgery.org/alcl
  - ASAPS: www.surgery.org/professionals
  - PSF: www.thepsf.org/research/clinical-impact/profile.htm
  - FDA: www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm
- **14 Point Plan:** Leading researchers hypothesize that device-associated infection may play a role in the development of BIA-ALCL and have released have outlined operative strategies aimed at reducing the risk of bacterial contamination during the time of device placement. These recommendations are known as the '14-point Plan' can be found at: www.saferbreastimplants.org [34]

How are ALCL cases in women with breast implants reported and monitored?

Reporting:

- Healthcare providers in the U.S. should report confirmed cases of BIA-ALCL in breast implant patients to the manufacturer of the implant, as well as to FDA via the Medwatch program: http://www.fda.gov/Safety/MedWatch/default.htm.
- In addition, the American Society of Plastic Surgeons (ASPS), The Plastic Surgery Foundation (PSF) and other clinical experts are collaborating with FDA in a registry of women with breast implants and BIA-ALCL known as the PROFILE registry. Case reports of BIA-ALCL should be submitted to the PROFILE registry at: http://www.thepsf.org/research/clinical-impact/profile-investigating-breast-implant-associated-alcl.htm
- BIA-ALCL cases occurring outside the U.S. should be reported to the appropriate international regulatory authority (eg, MHRA, ANSM, TGA).[33, 35, 36]

Monitoring:

- In the U.S., one method the FDA uses to track reports of ALCL in breast implant patients through the Manufacturer and User Facility Device Experience (MAUDE) database: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/TextSearch.cfm
- This publicly-available system includes voluntary reports of adverse events from healthcare professionals and consumers (since 1993) and mandatory reports from manufacturers (since 1996), importers (since 1993) and user facilities (since 1991).

Conclusions:

As detailed above, the available evidence demonstrates that:

1. BIA-ALCL Health Authorities globally state that Breast Implant – Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) overall remains a rare condition. [1, 3, 13, 14]
2. Reported cases of BIA-ALCL are not equally distributed among manufacturers and recent scientific and health authority data regarding diagnosed cases of BIA-ALCL has consistently shown a low representation of MENTOR® SILTEX® "microtextured" Breast Implants.[13, 15-19]
3. Texturing processes differ across manufacturers. The totality of evidence demonstrates the safety and effectiveness of MENTOR® Breast Implants in primary and revision augmentation and reconstruction patients.[37-42]

Important Safety Information:
MENTOR® MemoryGel® Breast Implants, MENTOR® MemoryShape® Breast Implants, and MENTOR® Saline-filled Breast Implants are indicated for breast augmentation in women (at least 22 years old for MemoryGel® Implants and MemoryShape® Implants, and 18 years old for Saline Implants) or for breast reconstruction. Breast implant surgery should not be performed in women with active infection anywhere in their body, with existing cancer or precancer of their breast who have not received adequate treatment for those conditions, or who are currently pregnant or nursing.
Breast implants are not lifetime devices and breast implantation may not be a one-time surgery. The most common complications for breast augmentation and reconstruction with MemoryGel® Implants include any reoperation, capsular contracture, and implant removal with or without replacement. The most common complications with MemoryShape® Implants for breast augmentation include reoperation for any reason, implant removal with or without replacement, and ptosis. The most common complications with MemoryShape® Implants for breast reconstruction include reoperation for any reason, implant removal with or without replacement, and capsular contracture. A lower risk of complication is rupture. The health consequences of a ruptured silicone gel breast implant have not been fully established. MRI screenings are recommended three years after initial implant surgery and then every two years after to detect silent rupture. The most common complications with MENTOR® Saline-filled Implants include reoperation, implant removal, capsular contracture, breast pain, and implant deflation.

For MemoryGel® Implants, patients should receive a copy of Important Information for Augmentation Patients about MENTOR® MemoryGel® Breast Implants or Important Information for Reconstruction Patients about MENTOR® MemoryGel® Breast Implants. For MemoryShape® Implants, patients should receive a copy of Patient Educational Brochure – Breast Augmentation with MENTOR® MemoryShape® Breast Implants or Patient Educational Brochure – Breast Reconstruction with MENTOR® MemoryShape® Breast Implants, and a copy of Quick Facts about Breast Augmentation & Reconstruction with MENTOR® MemoryShape® Breast Implants. For MENTOR® Saline-filled Implants, patients should receive a copy of Saline-Filled Breast Implants: Making an Informed Decision. Your patient needs to read and understand the information regarding the risks and benefits of breast implants, with an opportunity to consult with you prior to deciding on surgery.

The ARTOURA™ Breast Tissue Expander or CONTOUR PROFILE® Breast Tissue Expander can be utilized for breast reconstruction after mastectomy, correction of an underdeveloped breast, scar revision, and tissue defect procedures. The expander is intended for temporary subcutaneous or submuscular implantation and is not intended for use beyond six months. Do not use the ARTOURA™ Tissue Expander nor CONTOUR PROFILE® Tissue Expander in patients where an MRI may be needed. The device could be moved by the MRI causing pain or displacement, potentially resulting in a revision surgery. The incidence of extrusion of the expander has been shown to increase when the expander has been placed in injured areas. For detailed indications, contraindications, warnings, and precautions associated with the use of all MENTOR® Implantable Devices, which include MENTOR® Saline-filled Implants, MemoryGel® Implants, MemoryShape® Implants, ARTOURA™ Expanders, and CONTOUR PROFILE® Expanders, please refer to the Product Insert Data Sheet provided with each product or visit www.mentorwwllc.com.

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