



ESSKA ORBIT Consensus

Use of injectable orthobiologics for the treatment of knee osteoarthritis

Part 2: Cell-based Therapies (CBTs)

Chairpersons: Laura de Girolamo, Lior Laver

Consensus Advisor: Philippe Beaufils

This brochure is a summary of the ESSKA Orthobiologics Consensus-Part 2 Cell-Based Therapy. It does not contain every statement, and some of the included content may be summarized.

To access the complete material of this project, please visit:
<https://www.esska.org/page/Consensus>

GRADING DESCRIPTION

- *Grade A: high scientific level*
- *Grade B: scientific presumption*
- *Grade C: low scientific level*
- *Grade D: expert opinion*

STEERING AND LITERATURE GROUP MEMBERS

Ferran Abat (Spain)
Kristoffer Barfod (Denmark)
Ricardo Bastos (Portugal)
Ramon Cugat (Spain)
Giuseppe Filardo (Italy)

Michael Iosifidis (Greece)
Baris Kocaoglu (Turkey)
Elizaveta Kon (Italy)
Jeremy Magalon (France)

Rodica Marinescu (Romania)
Marko Ostojic (Bosnia)
Mikel Sanchez (Spain)
Thomas Tischer (Germany)

SCIENTIFIC ADVISORS

Jasmin Bagge (Denmark)

Konrad Slynarski (Poland)

Lucienne Vonk (Sweden)

OTHER CONTRIBUTORS

(literature search and other relevant tasks)

Diego Delgado (Spain)
Montserrat Garcia (Spain)
Patricia Laiz (Spain)

Angelo Boffa (Italy)
Alessandra Colombini (Italy)
Enrico Ragni (Italy)

Yossi Sourugeon (Israel)
Caterina Visconte (Italy)

All the statements are based on the combination of the experts' opinions and the current existing literature findings. As such, the recommendations regarding POC-CBT products are referred only to those obtained by medical devices that have been clinically tested and appropriately studied in the literature.

PRESIDENTIAL FOREWORD

There is great variation across Europe when it comes to medical praxis. Agreeing a common approach to pathologies or procedures has always been a challenge. But some such agreement is important, if we are to ensure standards.

For years now, ESSKA has developed a strict and painstaking methodology which employs our considerable European expertise. We call it ESSKA European Consensus. Mixing scientific evidence and clinical expertise, this format aims to facilitate the dissemination of knowledge among the daily practitioners.

One must underline the scientific value of such a project which should not be regarded as a simple expert opinion but as the result of a complex process based on high level scientific criteria such as pluralism (large European

representativeness), iterative process, independence of the different involved groups.

Five ESSKA consensuses have already been delivered. More information is available on www.esska.org/page/Consensus.

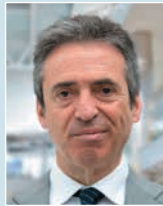
This year, at ESSKA 2024 Milan Congress, we are delighted to launch ESSKA European Consensus on The Use of Injectable Orthobiologics for Knee OsteoArthritis. Part 2: Cell-based Therapy (CBT).

We thank Laura de Girolamo and Lior Laver - the Project leaders - as well as the members of the Steering, Rating, and Peer Review Groups for their tremendous efforts and dedication.

A special acknowledgement also for our staff, and particularly Mrs Anna Hansen Rak, without whom this would not have been possible.



Roland Becker
ESSKA President
2022-2024



Joan Carles Monllau
ESSKA President
2024-2026



Philippe Beaufils
Consensus Projects
Advisor

CHAIRPERSONS FOREWORD

After the successful release of the Part 1 of the Consensus project on the use of injectable blood-derived products for the treatment of knee osteoarthritis, the same group of experts of the ESSKA ORthoBlologics InitiaTive (ORBIT) has prepared a second part on the use of injectable cell-based therapy products (CBT).

While the consensus group acknowledges the wide variability in terms of the use among European countries and the lack of solid evidence for some aspects of these therapies, at the same time the group recognizes that CBTs are widespread in most countries, and for this reason practical guidance was needed to avoid misuse. For this reason, the Consensus group felt the need to provide daily practitioners with a document reporting answers to the most common practical questions, based on the most up-to-date clinical literature and expert opinion. The Delphi methodology followed during the process ensures the document's objectivity, plurality (51 experts between steering, rating group and scientific advisors, representing 21 European countries), as well as specialty representativeness and iterative process among independent groups.

The aim of this consensus is to provide general recommendations based on evidence and expert opinion to improve indications and decision-making related aspects when using CBTs. Presenting information on the various

specific techniques or commercial systems available was not within the scope of this Consensus, although the recommendations regarding POC-CBT products are referred only to those obtained by medical devices that have been clinically tested and appropriately studied in the literature.

During the Consensus process, some aspects concerning the regulatory and ethical issues around CBT were not taken into consideration given the wide inter-countries variability. Therefore, and as per the Delphi methodology, peer reviewers representing the ESSKA national affiliated societies reviewed the document in term of geographical availability. With the exception of two countries that did not consider the document applicable to their national realities and two that by their own admission were unable to provide experts of the field, all others were in favor.

Note: Within the Consensus, the term CBTs refers to a wide variety of products that are prepared from autologous or allogeneous tissues, such as adipose tissue and bone marrow, and fetal annexes (umbilical cord, placenta, amniotic membrane), respectively. In particular POC-CBTs indicates products prepared at the point-of-care by minimal manipulation and expanded-CBTs indicates in vitro/laboratory expanded cells by extensive manipulation.



Laura de Girolamo
Chairperson



Lior Laver
Chairperson

CBT - RATIONALE/INDICATIONS

Does current evidence support the use of CBT for knee OA? (Point-of-care products)

Current scientific evidence has shown that the use of **Point-of-care (POC) CBT products** for knee OA can provide clinical benefit and is a safe treatment option, although certain limitations of current evidence exist due to heterogeneity of products and lack of studies on larger populations. Clinical improvement has been shown at both shorter (6 months) and longer (12 months) durations in most of the studies available in literature. **The consensus group therefore concludes that there is sufficient clinical evidence to support the use of POC-CBT as a treatment option for knee OA** (see following questions addressing CBT specifications and indications).

However, due to the lack of sufficient high-quality studies in larger populations, as well as lack of superiority in some studies compared to CSI or PRP, the full clinical benefit and role of POC-CBT products in the treatment algorithm for knee OA, is not fully understood and as such, **the consensus group currently does not recommend the use of POC-CBT as a first line injectable treatment for knee OA**. The consensus group therefore does agree that CBTs could be considered when other non-operative and other injectable measures have failed and in circumstances where surgery is not yet indicated or medically appropriate. *Grade B*

Does current evidence support the use of CBT for knee OA? (In-vitro expanded cells)

Current scientific evidence supports the clinical benefit/efficacy and safety of **Expanded-CBT** for knee OA, confirming the findings of preclinical research. Clinical improvement has been shown at both shorter (6 months) and longer (up to 24 months) durations in most of the published studies. **The consensus group therefore concludes that there is sufficient pre-clinical and clinical evidence to support**

the use of **Expanded-CBT** as a treatment option for knee OA (see following questions addressing Expanded-CBT specifications and indications) when regulatory approval exists. *Grade A*

Due to the complexity of the preparation procedure of autologous Expanded-CBT products, **the consensus group currently does not recommend the use of Expanded-CBTs as a first line injectable treatment for knee OA**. The consensus group does agree that Expanded-CBTs could be considered when other non-operative and other injectable measures have failed and in circumstances where surgery is not yet indicated or not medically appropriate. *Grade B*

For which degrees of knee OA is CBT indicated/recommended?

Current evidence has shown the clinical benefit of CBTs in knee OA Kellgren-Lawrence (KL) grades 1-4, however most studies involved populations with KL grades 2-3. **The consensus group recommends CBTs can be used for knee OA mainly in grades 1-3, although clinical benefit have also been shown in KL grade 4.** (This statement is valid for both POC products and in vitro-expanded Cells). *Grade B*

Are there advantages of CBT use in comparison to Corticosteroids for treating knee OA?

Although the literature is sparse with regards to direct comparisons between CBT and corticosteroid injections, current available evidence does not show the clinical superiority of CBT compared to CSI. However, CSI have been shown to have detrimental effects on chondrocytes and can lead to accelerated cartilage degeneration, especially with multiple/repeated injections, although corticosteroids are strong anti-inflammatory agents and can provide short term relief in knee OA (mainly less than 3 months), CBT injections

have been shown to have the potential for a longer effect in comparison to the shorter-term effect of corticosteroids injections. They also seem to provide a safer use profile with less potential related complications compared to CSI, especially when considering the potential need for repeated injections in knee OA patients, more so in younger patients. Therefore, the consensus group considers CBT injections to be a non-chondro-toxic and effective treatment option, with potentially expected longer term clinical improvements compared to corticosteroids injections. (This statement is valid for both POC products and in vitro-expanded Cells). *Grade D*

Are there advantages of CBT use in comparison to Hyaluronic acid injections (HA) for treating knee OA?

Several high-level studies as well as meta-analyses exist comparing the effectiveness of CBTs to hyaluronic acid (HA) for knee OA, with the majority favoring CBTs in terms of overall clinical improvement and a longer-lasting effect documented to last up to 12 months.

Based on current available evidence, the consensus group acknowledges that CBTs seem to have superiority over HA for knee OA due to overall clinical improvement and expected longer-lasting effects, whilst also acknowledging that there are different formulations of the products that may introduce some bias in the conclusions of meta-analyses (This statement is valid for both POC products and in vitro-expanded Cells). *Grade B*

However, due to the more invasive and complex preparation process of CBTs, the consensus group recommends that its use should be reserved as a 2nd line injectable treatment option (This statement is valid for both POC products and in vitro-expanded Cells). *Grade D*

Are there advantages of CBT use in comparison to PRP for treating knee OA?

Current literature with regards to the advantage or superiority of CBTs compared to PRP is limited and inconclusive, with few studies performed with direct comparisons between CBTs and PRP. Therefore, based on current evidence the consensus group does not acknowledge a superiority or clear advantages of CBT over PRP for knee OA (This statement is valid for both POC products and in vitro-expanded Cells). *Grade C*

Moreover, considering the relatively invasive and more complex nature of the preparation procedure of CBT compared to PRP, the consensus group recommends that PRP should be used as a 1st line orthobiologic injectable treatment option in knee OA, while CBT could be considered as a 2nd line orthobiologic treatment option (This statement is valid for both POC products and in vitro-expanded Cells). *Grade D*

CBT - PREPARATION/CHARACTERIZATION

Is there a difference between Bone Marrow Aspirate (BMA) or Bone Marrow Concentrate (BMAC) for the management of knee OA?

Current evidence is lacking controlled clinical studies directly comparing BMAC and BMA for the management of knee OA. Nevertheless, data indicates that BMA obtained with the most appropriate instruments and technique provide a similar number of cells (BM-MSc) as in single-spin BMAC from a sample harvested without specific techniques aimed at minimizing peripheral blood contamination. When using the same equipment and technique for bone marrow harvesting, BMAC (obtained by centrifugation) will result in a product with a higher cell number, although with a lower volume. The consensus therefore agrees it is essential to adopt the most suitable technique and instrument for bone marrow collection in order not to compromise the resulting product or concentration procedure when relevant. A Double spin BMAC protocol is reported to increase the cell concentration while significantly reducing the volume. Double-spin BMAC products produce a higher BM-MSCs number which seem to positively influence clinical benefit and therefore, when considering BMAC use for knee OA. *Grade D*

Is there a difference between mechanical SVF and Microfragmented Fat products for the management of knee OA?

Although different in composition and structure, mechanical stromal vascular fraction (SVF) and microfragmented adipose tissue (MFAT) show a similar safety and efficacy profile for the treatment of knee OA, with satisfactory subjective results up to 24 months. Until further studies are conducted to determine whether one product is clinically superior to the other, the consensus group currently does not support one type of adipose-derived CBT over the other and considers both mechanical SVF and MFAT valid options for the management of knee OA when this approach is considered. *Grade D*

When using expanded mesenchymal stem cells (MSCs), what is the optimal/most appropriate number of cells to inject?

The majority of available dose-response studies reported the use of $<100 \times 10^6$ MSCs, however, due to lack of stringency and high heterogeneity in the design of the available studies and due to the absence of a clear correlation between cell numbers and clinical outcomes, as well as various cell numbers in different studies, currently no consensus exists about the most appropriate number of expanded MSCs to inject in the treatment of knee osteoarthritis. The consensus group concludes that defining the optimal MSC number for the management of knee OA is complex and includes many variables, and therefore currently optimal cell ranges for the treatment of knee OA cannot be defined. *Grade C*

Is there a clinical difference between expanded-CBTs and POC-CBTs for the management of knee OA?

The literature involving direct comparisons between expanded-CBTs and Point of care (POC)-CBTs is sparse and limited. Treatments involving both expanded cells and POC products have been shown to be safe treatment options and to have the ability to provide clinical benefit for up to 12-24 months. Expanded cell products have been shown to provide more consistent cell numbers, although they entail a higher production cost and a more complex two-stage procedure (in autologous products). Discrepancies in the clinical settings, in production protocols and the lack of stratification of OA patients based on the radiologic classification currently limit any recommendation on the use of either product group in clinical practice and therefore the consensus group does not recommend the use of one group over the other and currently considers both expanded-CBTs and cell concentrate products/POC-CBTs as acceptable products for the management of knee OA. *Grade C*

CBT - PROTOCOL

For CBT Injections in knee OA – is 1 injection sufficient per treatment cycle?

Current literature is scarce with regards to the optimal number of CBT injections per treatment cycle for the management of knee OA. To date no study involving autologous POC-CBT includes more than one injection protocol, whereas a few studies using expanded MSCs reported the outcomes of multiple injections in a short interval. Although studies using expanded cells with more than one-injection protocols have shown to provide clinical benefit, there is lack of sufficient data to support multiple injection protocols over single-injection protocols and therefore the consensus group cannot recommend one protocol over the other for either POC-CBTs or expanded-CBTs for the management of knee OA (This statement is valid for both POC products and in vitro-expanded Cells). *Grade C*

Is Antibiotics administration recommended around CBT use?

Evidence on antibiotics administration around CBT use is lacking. **Therefore, the consensus group does not recommend the routine use of antibiotics around CBT use.** However, unlike other injectable products for the knee joint, autologous CBT preparation process involves tissue harvesting (mainly but not only fat or bone-marrow) and therefore some

degree of infectious risk should be taken into consideration. To reduce the infectious risk the consensus group recommends to perform CBT procedures in an appropriate and dedicated environment (i.e. sterile office area, operating theater or similar environments). Nevertheless, the consensus group suggests taking a cautious approach in specific cases and consider the administration of antibiotics in populations with higher risk factors for infections such as diabetics, heavy smokers, previous joint infections or wound complications (This statement is valid for both POC products and in vitro-expanded Cells). *Grade D*

Is there any clinical benefit combining PRP to cell-based products?

Current pre-clinical and clinical literature suggest some potential benefits combining PRP with cell-based products, with the majority of studies focusing on culture-expanded cells, evidence is still lacking regarding the clear benefits of using these products in combination over using CBT alone. **Therefore, based on current evidence the consensus group does not see clear advantages from combining PRP to CBT products for knee OA and does not recommend a combined treatment** (This statement is valid for both POC products and in vitro-expanded Cells). *Grade C*

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Contact Information

ESSKA Office

Anna Hansen Rak

Project Manager

Phone: +352 4411 7026

Fax: +352 4411 7678

e-mail: info@esska.org

www.esska.org