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CONSENSUS

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Cell-based therapy injections for the management of knee osteoarthritis: The ESSKA–ICRS consensus. Recommendations using the RAND/UCLA appropriateness method for different clinical scenarios

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Abstract

Purpose: The aim of this consensus was to develop evidence/expert-based patient-focused recommendations on the appropriateness of intra-articular point-of-care (POC) cell-based therapy (CBT) injections in different clinical scenarios of patients with knee osteoarthritis (OA).

Methods: The RAND/UCLA Appropriateness Method was used by European experts of the *European Society of Sports Traumatology, Knee Surgery and Arthroscopy* (ESSKA) and the *International Cartilage Regeneration and Joint Preservation Society* (ICRS) to reach a consensus and produce recommendations for specific patient categories, combining best available scientific evidence with the collective judgement of a panel of experts.

Results: A total of 144 scenarios were developed based on five factors: cell source (bone marrow vs. adipose tissue), age (<50 vs. 50–65 vs. 66–80 vs. >80 years), joint involvement (prevalent tibio-femoral vs. patello-femoral), OA level (Kellgren–Lawrence [KL] Grade 0–I vs. II–III vs. IV) and body mass index (BMI) (<18.5 vs. 18.5–35 vs. >35 kg/m^2). Following two voting rounds,

For affiliations refer to page 3063.

Abbreviations: BMI, body mass index; ESSKA, European Society of Sports Traumatology, Knee Surgery, and Arthroscopy; ICRS, International Cartilage Regeneration and Joint Preservation Society; KL, Kellgren–Lawrence; MSCs, mesenchymal stromal cells; OA, osteoarthritis; ORBIT, Orthobiologic Initiative; POC, point-of-care solution; RAM, RAND/UCLA Appropriateness Method; SIFK, subchondral insufficiency fracture of the knee; SONK, spontaneous osteonecrosis of the knee; TKA, total knee arthroplasty.

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agreement was reached for all 144 (100%) scenarios: the indication was considered appropriate in 11.8%, inappropriate in 34.7% and uncertain in 53.5%. The parameters with the highest appropriateness were OA Grade II–III (35.4% appropriate scenarios), age <50 years (22.2% appropriate) and BMI 18.5–35 kg/m^2 (20.8% appropriate). The parameters with the highest inappropriateness were age >80 years (88.9% inappropriate), OA grade IV (62.5% inappropriate) and BMI > 35 kg/m^2 (50.0% inappropriate).

Conclusions: This ESSKA–ICRS expert consensus provides recommendations on the appropriateness of cell-based injectable therapies for knee OA. POC-CBT may be considered, after failure of other non-operative and injectable options, in patients aged ≤65 years with BMI ≤ 35 kg/m^2 and KL Grade II–III OA. Unlike bone marrow–derived CBT, adipose-derived CBT was also considered appropriate in patients 66–80 years old with BMI 18.5–35 kg/m^2 and KL Grade II–III OA. On the other hand, CBT was considered inappropriate in patients over 80 years old and in those with KL Grade IV OA. These findings may help improve patient selection, although they should not be interpreted as a rigid treatment algorithm but rather as expert-informed guidance for the use of POC-CBT in knee OA.

Level of Evidence: Level I.

KEYWORDS

cell-based therapy, consensus, injection, knee, mesenchymal stromal cells, osteoarthritis, RAND/UCLA

INTRODUCTION

Cell-based therapies (CBTs) have emerged over the past years as a novel therapeutic option for knee osteoarthritis (OA), and their injectable use, particularly for point-of-care (POC) solutions, is increasingly adopted in clinical practice [10, 25]. The interest in CBT is largely driven by the presence of mesenchymal stromal cells (MSCs), which are considered particularly relevant in OA due to their paracrine activity with anti-inflammatory and immunomodulatory functions [6, 24]. MSCs can act on the joint inflammatory environment, contributing to symptom relief and potentially to structural modification of the disease [8, 29]. In fact, preclinical evidence suggested that cell-based injectable products can induce disease-modifying effects in the treatment of OA, slowing down the progression of cartilage damage, reducing synovitis and positively modulating inflammatory and cartilage biomarkers [7, 27, 31]. While disease-modifying effects have not been confirmed in humans, clinical studies have reported encouraging outcomes in terms of pain and functional improvements, with stronger evidence for adipose-derived and bone marrow-derived CBTs [11, 32]. However, despite the promising findings for knee OA treatment, the current body of literature on CBT remains heterogeneous.

Treatment response to CBT appears to be influenced by patient-related factors and OA-specific characteristics, as observed with other orthobiologic interventions such as platelet-rich plasma [20], leading to variability in outcomes across studies [9]. For this reason, while randomized controlled trials and systematic reviews are essential to define the overall potential of CBT, clinical translation requires a broader perspective. Integrating available scientific evidence with expert consensus can be fundamental to optimizing the use of CBT in knee OA management and clarifying its role in the therapeutic algorithm [4]. The Orthobiologic Initiative (ORBIT) of the *European Society of Sports Traumatology, Knee Surgery, and Arthroscopy* (ESSKA) recently carried out a consensus project using the ESSKA formal Consensus Methodology, which suggested the potential of CBT in knee OA, treatments which may be considered when other non-operative and injectable options have failed [14]. Building upon the conclusions of this consensus, ESSKA and the *International Cartilage Regeneration and Joint Preservation Society* (ICRS) collaborated to establish clinical recommendations using the RAND/UCLA Appropriateness Method (RAM). This is a structured process that integrates current evidence with expert opinion, with the benefit of generating patient-tailored recommendations [17, 25]. This consensus is intended to define clinically relevant recommendations by identifying the clinical scenarios where POC-CBT use can be appropriate or not, providing guidance for its application in clinical practice.

The aim of this ESSKA–ICRS consensus was to create evidence- and expert-based patient-focused

recommendations on the appropriateness of POC-CBT in different clinical scenarios of patients with knee OA.

MATERIALS AND METHODS

Consensus design

This Consensus design was deliberately focused on POC products derived from adipose tissue and bone marrow, as these represent the most readily applicable cell-based options in current clinical practice. Other orthobiologic strategies, such as culture-expanded cells (ATMPs) or allogeneic cell products, were not considered because their routine clinical applicability remains limited and still far from widespread use. Moreover, only European experts were included, as this consensus was designed to reflect the European perspective on orthobiologics, which may differ from that of other continents due to differences in clinical practice, regulatory frameworks and treatment availability.

The RAM approach was used to develop recommendations on the appropriateness of injectable POC-CBT in patients affected by knee OA. The RAM process involved three interdependent groups chosen within ESSKA and ICRS European members: A core panel, an expert voting panel, and a discussers' panel, selected based on their scientific and clinical expertise in knee OA and CBT while ensuring geographical representation and gender balance (Table 1). The core panel, composed of six members, defined the scenarios of the RAM and guided the expert panel through the RAM tasks with the help of a project management team. The expert panel, composed of 15 voting members, conducted its ratings using predefined scenarios and response grids prepared by the core panel. The six discussers (both clinicians and translational scientists) enriched the discussion to reach a consensus during the different steps of the project by providing a multispecialty perspective.

Clinical scenarios

The RAM process was preceded by an extensive literature review undertaken by the steering group of the 'Formal Consensus Project' by the ORBIT Initiative of ESSKA on CBT in knee OA [14]. This literature review was used by the core panel to develop the consensus scenarios and ensured that panellists had access to the body of evidence for the rating phase. These clinical scenarios were presented in the form of a matrix detailing demographic data, characteristics of the joint, and clinical features. Five factors that can potentially influence the appropriateness of the procedure were selected, based on literature evidence [14, 20] and the clinical experience of the core panel:

1. *Cell source: Bone marrow-derived vs adipose tissue-derived*

   This parameter was included to understand the appropriateness of the two more common sources of autologous POC-CBT, bone marrow and adipose tissue [11, 16, 32]. These groups included any type of procedure or device aimed at producing a cell-based product without cell-culture or enzymatic digestion (POC). Specific limitations related to the single product were not taken into account. For bone marrow and adipose tissue, no specific harvesting site was considered, although the possible difference in terms of cell concentration from different sites and the possible difficulties of harvesting related to specific patients' characteristics were discussed (e.g., higher MSC count in bone marrow from iliac crest compared to proximal tibia, lower adipose tissue quantity from underweight patients).
2. *Age (<50 years vs. 50–65 years vs. 66–80 years vs. >80 years old)*

   The age category <50 years old was chosen to identify the appropriateness of the indications in patients with higher cell regenerative potential but also high activity expectations, and where the literature shows the worst results of total knee arthroplasty (TKA) [28, 33]. The 50- to 65-year-old category is the subject population of the majority of the published evidence on CBT and orthobiologics in general [14]. This is also a category where there is an increasing number of TKAs performed, although TKA failures are double those in older patients [26]. In the 66- to 80-year-old category, CBT showed inferior results, while this represents the main age range for performing TKA. Finally, inferior results can be expected from CBT in older patients, but the >80 years old category has been identified, given TKA is often contraindicated [21], thus leaving fewer alternatives to manage these patients.
3. *Joint involvement (tibio-femoral vs. patello-femoral)*

   Although it is common not to have exclusively tibio-femoral or patello-femoral OA, this category refers to the prevalent joint involvement where OA manifestations mainly affect one site or the other, to account for the different aetiology, symptomatology and different levels of evidence, as most studies on CBT have focused on tibio-femoral OA [14].
4. *OA grade (Kellgren–Lawrence [KL] Grade 0–I vs Grade II–III vs. Grade IV)*

   The grade of OA is another key parameter potentially influencing the treatment results. The majority of the literature included patients with KL I–III OA, but evidence shows that CBT can also be used in severe knee OA (KL IV) with some clinical benefit (although lower) [14]. Thus, OA has been divided into three levels: Early, mild/moderate and advanced (0–I vs. II–III vs. IV KL grade), to account for the different severity of the disease and the

different results reported in the literature based on OA grades [14].

5. *BMI (<18.5 vs. 18.5–35 vs. >35 kg/m^2)*

   BMI was chosen as an indicator of the metabolic state of the patient due to its ease of use and comprehension. The group with BMI 18.5–35 kg/m^2 includes a population with BMI from normal to moderate obesity, representing the large majority of the population and the patients analyzed in clinical trials. The group with BMI < 18.5 kg/m^2 refers to the underweight population, which represents patients where harvesting of adipose tissue may be challenging. The group with BMI > 35 kg/m^2 includes a population with severe obesity, also defined as pathological obesity. In addition to the adverse mechanical environment, the quality of the cell sources in this group may be affected by the metabolic and inflammatory state of the patient [13]. Clearly, this classification and the chosen subgroups represent an oversimplification, which does not take into account individual variability (e.g., BMI 30 in a muscled athlete vs. in an elderly woman) and the inter-group variability (e.g., BMI 19 vs. BMI 34 included in the same group). Experts were invited to largely envisage the group division as an underweight population, a normal to non-pathologically obese population, and a pathologically obese population.

Further considerations

Further considerations have been taken into account to interpret the scenarios developed: No major osseous malalignment (indicatively varus/valgus within 5° or patello-femoral maltracking not requiring surgery at the physician discretion), no ligamentous injury requiring treatment, knee OA affecting patients' quality of life, patients wishing to go back to their previous activities (professional players were not considered), no osteochondritis dissecans/focal lesions, no SIFK/SONK and no major flexion contracture. Moreover, no preventive use of CBT aimed at slowing OA progression was considered, nor was the subchondral application. Finally, since no evidence clearly supports the advantage of specific CBT types or injective protocols [14], no distinction was made in this consensus when considering these aspects.

Based on the five clinical variables selected by the core expert panel, a set of 144 clinical scenarios was developed. The scenarios were grouped into four 'chapters' based on patient age (Figure 1). Panellists were asked to individually assess the appropriateness of the indication for CBT injection treatment for each of the scenarios. The scenarios were presented to the voting experts in the form of a question: 'A … old patient presents to your attention with symptoms related to knee OA, unresponsive to other conservative and injectable treatments and the following characteristics. How appropriate do you rate the indication for CBT POC injection treatment?'.

Consensus process

The appropriateness of the indication for injectable POC-CBT treatment in each of the different scenarios was rated in two rounds. The two-round RAM process is designed to identify whether discrepant ratings are due to real clinical disagreement over the use of the procedure ('real' disagreement) or to fatigue or misunderstanding ('artefactual' disagreement) [17]. In the first round, the expert panellists received the clinical scenarios by email and were asked to rate the appropriateness of the CBT indication. According to the methodology [17], each panellist ranked, independently of the other panellists, the appropriateness of each scenario. A 9-point Likert-scale was used with the range 1–3 considered 'inappropriate', 4–6 'uncertain' and 7–9 'appropriate'. The expert panellists were invited to consider the synthesized literature review evidence provided by the ORBIT ESSKA 'Formal Consensus Project' on CBT in knee OA. They were asked to base their ratings on an 'average patient' presenting to an 'average physician' practising in an 'average health care setting' for each scenario, and not to consider the cost and cost-effectiveness of the procedure in rating the appropriateness of the scenarios.

In the second round, the experts' and core panels met under the leadership of a moderator. Each panellist received an individualized document showing their Round 1 rating and the anonymized distribution of the entire expert group's first rating round. During the meeting, panellists discussed the ratings, focusing on areas of disagreement. Panellists were given the opportunity to revise their initial ratings after the discussion with a new rating. In addition, modifications to the original list of indications and/or definitions were allowed if deemed necessary. The panel was not forced to reach a consensus and, after discussing each chapter, experts individually and anonymously re-rated the appropriateness of the indication of POC-CBT for each scenario [17].

Data analysis and statistical method

The final scores of the 9-point Likert scale of each expert were then pooled to generate a median appropriateness score for each scenario. The presence of voting dispersion was calculated by statistical analysis according to the BIOMED Concerted Action on Appropriateness [17] to define the presence of 'disagreement' among votes in each scenario.

TABLE 1 Members involved in the consensus process.

Core panel	Laura de Girolamo (IT) Elizaveta Kon (IT) Lior Laver (IL) Thomas Tischer (DE) Kristof Sas (BE) Giuseppe Filardo (CH) – *Moderator*	
Discusser group	Jasmin Bagge (DK) Ramon Cugat (ES) Francesca De Caro (IT) Jérémy Magalon (FR) Mikel Sanchez (ES) Lucienne Vonk (NL)	
Project management team	Luca Andriolo (IT) Angelo Boffa (IT)	
Voting panel	Kristoffer W. Barfod (DK) Ricardo Bastos (PT) Alessandro Di Martino (IT) Matej Drobnič (SL) João Espregueira-Mendes (PT) Micheal Iosifidis (GR) Baris Kocaoglu (TUR)	Laura Mangiavini (IT) Rodica Marinescu (RO) Stefan Nehrer (AUT) Marko Ostojić (CRO) George Skarpas (GR) Konrad Słynarski (PL) Martyn Snow (UK) Tobias Winkler (DE)

'Disagreement' is a formal measure used to identify when a panel of experts holds widely divergent views through a mathematical formula [17]. Finally, the use of CBT for each scenario was classified:

- 'Appropriate': median score of ≥7 without disagreement
- 'Inappropriate': median vote of ≤3 without disagreement

A scenario receiving a score between 4 and 6, or a scenario with disagreement, was classified as 'uncertain'. An 'uncertain' recommendation can reflect either the ambiguous state of current evidence or equivocal appropriateness due to a moderately unfavourable risk profile or to limited efficacy. The 'uncertain' classification is not intended to be a negative recommendation or to preclude the use of the treatment for the specific scenario a priori, relying instead on the physician–patient interaction in determining the most appropriate treatment decision in the context of the risk–benefit ratio due to individual characteristics, comorbidities and preferences. The consensus rate is the sum of appropriate and inappropriate rates; thus, uncertain scenarios were not accounted for in the documented consensus rate.

RESULTS

Details of experts' ratings with median, agreement value, and recommendation for each clinical scenario are reported in Figures 2–5. Following the voting rounds, disagreement was found in 0% of the scenarios: in 17 scenarios (11.8%), the indication for CBT was considered appropriate without disagreement, in 50 (34.7%), inappropriate without disagreement, and in 77 (53.5%), the indication was uncertain.

Appropriateness, inappropriateness and uncertain areas

Experts considered bone marrow-derived CBT injections appropriate in all scenarios, including patients aged ≤65 years with BMI ≤ 35 kg/m^2 and with knee OA Grade II–III, regardless of tibio-femoral or patello-femoral joint involvement (scenarios nos. 7, 9, 25, 27, 43, 45, 61 and 63). Similarly, adipose tissue-derived CBT injections were considered appropriate in scenarios including patients aged ≤65 years with BMI ≤ 35 kg/m^2 and with knee OA Grade II–III, regardless of tibio-femoral or patello-femoral joint involvement (scenarios nos. 8, 10, 26, 28, 44, 46 and 64), with the only exception of patients aged 50–65 with BMI < 18.5 OA Grade II–III and patello-femoral involvement, where the appropriateness was uncertain (scenario no. 62). Moreover, adipose tissue-derived CBT injections were considered appropriate also in patients aged 66–80 with BMI 18.5–35, OA Grade II–III and both tibio- and patello-femoral involvement (scenarios nos. 82 and 100).

Conversely, CBT injections were considered inappropriate in patients aged >80 [scenarios grouped under *a*], except for adipose tissue-derived CBT for patients with BMI 18.5–35 with OA Grade 0–III, which were considered uncertain (scenarios no. 112, 118, 130 and 136). For both bone marrow-and adipose tissue-

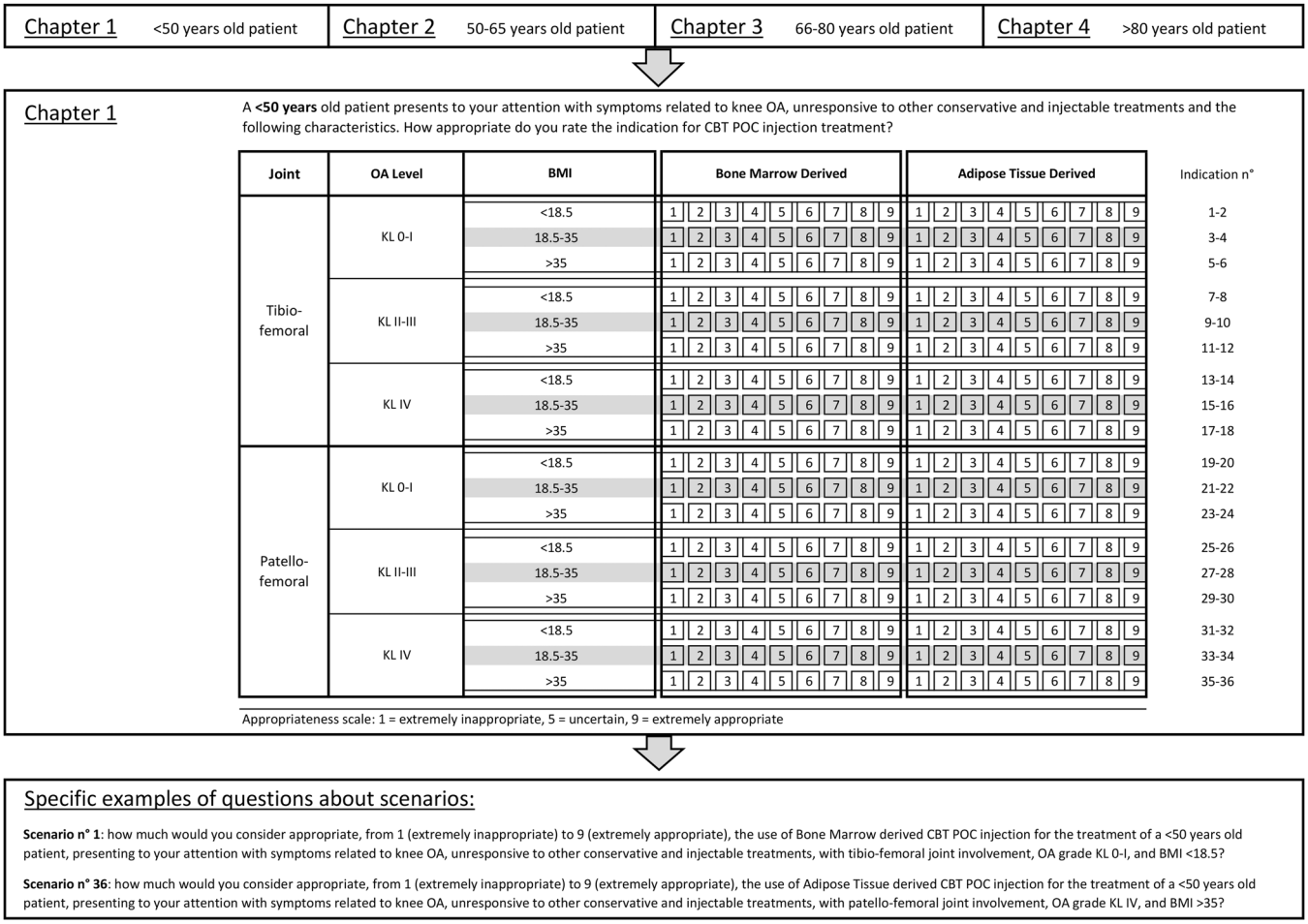


FIGURE 1 Examples of clinical scenarios presented to the voting panel. Chapter 1 (<50 years old patients). Two specific scenarios are shown in detail.

derived CBTs, patients with OA Grade IV and BMI > 35 were considered inappropriate scenarios [β]. Moreover, the use of CBT was considered inappropriate for the other scenarios with patients aged 66–80 and OA Grade IV (scenarios no. 85, 86, 103, 104, 105 and 106), except for patients with BMI 18.5–35 and tibio-femoral involvement, where the appropriateness was uncertain (scenarios nos. 87 and 88).

Areas of uncertainty were represented for both bone marrow- and adipose tissue-derived CBT patients with OA Grade 0–I and aged ≤80 [γ], patients with OA Grade IV aged ≤65 and BMI ≤ 35 kg/m^2 [δ], and patients with OA Grade II–III and BMI > 35 or aged >65 [ε], with the two exceptions previously described (scenarios nos. 82 and 100).

Changes of appropriateness within parameters

The analysis demonstrated that certain factors were more influential in determining the appropriateness of CBT injections:

1. OA grade influenced 73 out of 144 possible treatment indication changes (50.7%).
2. BMI influenced 48 out of 144 possible treatment indication changes (33.3%).
3. Age influenced 48 out of 144 possible treatment indication changes (33.3%).
4. Cell source influenced 7 out of 72 possible treatment indication changes (9.7%).
5. Tibio-femoral or patello-femoral prevalent joint involvement influenced 3 out of 72 possible treatment indication changes (4.2%).

Appropriateness for each parameter

The parameters evaluated in the clinical scenarios had different appropriateness results for the indication of CBT use (Figure 6).

The parameters with the highest appropriateness were OA Grade II–III (35.4% of appropriate scenarios), age under 50 years (22.2% of appropriate scenarios) and BMI 18.5–35 kg/m^2 (20.8% of appropriate scenarios). Conversely, the parameters with the highest

Chapter 1

A **<50 years old** patient presents to your attention with symptoms related to knee OA, unresponsive to other conservative and injectable treatments and the following characteristics. How appropriate do you rate the indication for CBT POC injection treatment?

Joint	OA Level	BMI	Bone Marrow Derived	M	DIS	Adipose Tissue Derived	M	DIS	Indication n°
Tibio-femoral	KL 0-I	<18.5	2 0 0 0 8 0 3 0 2	5	U+	2 1 0 1 7 1 1 0 2	5	U+	1-2
		18.5-35	2 0 0 0 8 0 2 1 2	5	U+	1 1 0 1 6 0 3 1 2	5	U+	3-4
		>35	2 1 0 3 6 0 1 1 1	5	U+	1 3 0 1 6 1 1 1 1	5	U+	5-6
	KL II-III	<18.5	0 0 1 1 0 1 5 6 1	7	A+	0 1 2 0 1 0 2 7 2	8	A+	7-8
		18.5-35	0 0 1 1 0 1 3 7 2	8	A+	0 0 1 0 0 1 1 9 3	8	A+	9-10
		>35	0 2 2 1 5 1 2 1 1	5	U+	0 3 0 0 4 4 2 1 1	6	U+	11-12
	KL IV	<18.5	1 1 2 0 7 2 2 0 0	5	U+	2 2 1 1 5 2 2 0 0	5	U+	13-14
		18.5-35	1 1 2 0 7 3 1 0 0	5	U+	1 1 0 1 6 2 3 1 0	5	U+	15-16
		>35	1 4 5 1 3 1 0 0 0	3	I+	2 3 4 0 3 3 0 0 0	3	I+	17-18
Patello-femoral	KL 0-I	<18.5	2 0 0 1 6 3 1 1 1	5	U+	2 1 1 1 4 2 2 1 1	5	U+	19-20
		18.5-35	2 0 0 1 5 2 3 1 1	5	U+	1 0 1 1 4 2 4 1 1	6	U+	21-22
		>35	2 1 1 2 5 1 2 0 1	5	U+	1 2 2 1 4 2 2 0 1	5	U+	23-24
	KL II-III	<18.5	0 0 2 0 0 3 8 2 0	7	A+	0 2 1 1 1 1 7 1 1	7	A+	25-26
		18.5-35	0 0 1 1 0 3 7 2 1	7	A+	0 0 1 0 0 1 9 2 2	7	A+	27-28
		>35	0 2 1 1 3 5 2 1 0	6	U+	0 3 0 0 2 6 3 0 1	6	U+	29-30
	KL IV	<18.5	1 1 2 5 5 1 0 0 0	4	U+	2 2 3 4 2 1 1 0 0	4	U+	31-32
		18.5-35	1 2 2 4 5 1 0 0 0	4	U+	1 2 3 3 3 2 0 1 0	4	U+	33-34
		>35	2 4 6 1 2 0 0 0 0	3	I+	2 2 6 3 1 1 0 0 0	3	I+	35-36

Appropriateness scale: 1 = extremely inappropriate, 5 = uncertain, 9 = extremely appropriate

FIGURE 2 Clinical scenarios for <50 years old patients (chapter 1). A, appropriate; BMI, body mass index; DIS, disagreement; Green, appropriate scenarios; I, inappropriate; KL, Kellgren–Lawrence; M, median value; red, inappropriate scenarios; U, uncertain; yellow, uncertain scenarios; +, without disagreement; −, with disagreement.

inappropriateness were age over 80 years old (88.9% of inappropriate scenarios), OA Grade IV (62.5% of inappropriate scenarios) and BMI > 35 kg/m^2 (50.0% of inappropriate scenarios). No scenario characterized by one of these three parameters was considered appropriate, as well as for OA Grade 0–I (0% of appropriate scenarios for all of them).

The parameters associated with the highest consensus (on appropriateness or inappropriateness) were age over 80 years (88.9%), OA Grade IV (62.5%) and patello-femoral joint involvement (57.2%). The parameters associated with the highest uncertainty were OA Grade 0–I (79.2% of uncertain scenarios), age 50–65, <50 and 66–80 years old (69.4%, 66.7% and 66.7% of uncertain scenarios, respectively).

A graphic representation of the overall consensus results is found in Figure 7.

DISCUSSION

The main finding of this ESSKA–ICRS consensus is that POC-CBT is considered an appropriate therapeutic option in patients aged ≤65 years with BMI ≤ 35 kg/m^2 and with knee OA Grade II–III, regardless of whether the tibio-femoral or patello-femoral joint is predominantly involved or which cell source is used. Unlike bone marrow–derived CBT, adipose-derived CBT was also considered appropriate in patients 66–80 years old with BMI 18.5–35 kg/m^2 and knee OA Grade II–III. On the other hand, the use of CBT was considered inappropriate in patients over 80 years old and/or in those with KL Grade IV OA.

The use of cell-based injectable therapies for the intra-articular treatment of knee OA is explored by growing clinical evidence, with numerous clinical trials investigating the effects of POC-CBT derived from adipose tissue or bone marrow [11, 16, 32]. In light of the available clinical evidence and real-world experience, a recent ORBIT formal consensus [14] stated that these treatments may be considered when other non-operative and injectable options have failed. The experts involved in that consensus also emphasized that CBT should not be taken into consideration as a first-line injectable treatment for knee OA, nor as a first-line orthobiologic injectable option. Given these premises, it is no surprise that in this consensus, most scenarios were deemed uncertain. In this context, the

Chapter 2

A **50-65 years old** patient presents to your attention with symptoms related to knee OA, unresponsive to other conservative and injectable treatments and the following characteristics. How appropriate do you rate the indication for CBT POC injection treatment?

Joint	OA Level	BMI	Bone Marrow Derived	M	DIS	Adipose Tissue Derived	M	DIS	Indication n°
Tibio-femoral	KL 0-I	<18.5	2 0 0 0 4 5 2 1 1	6	U+	2 1 1 0 3 3 3 1 1	6	U+	37-38
		18.5-35	1 0 1 0 4 5 1 2 1	6	U+	1 0 0 0 3 4 4 2 1	6	U+	39-40
		>35	1 1 2 2 4 2 2 0 1	5	U+	1 1 1 1 3 5 2 0 1	6	U+	41-42
	KL II-III	<18.5	0 0 2 0 0 0 9 3 1	7	A+	1 1 2 0 1 0 6 1 3	7	A+	43-44
		18.5-35	0 0 2 0 0 0 9 2 2	7	A+	0 0 1 0 0 0 6 4 4	8	A+	45-46
		>35	0 2 2 0 5 2 2 2 0	5	U+	0 2 1 0 4 3 2 2 1	6	U+	47-48
	KL IV	<18.5	1 1 2 0 6 3 2 0 0	5	U+	2 1 1 2 5 2 1 1 0	5	U+	49-50
		18.5-35	1 1 2 0 7 3 1 0 0	5	U+	1 1 0 1 5 3 3 1 0	5	U+	51-52
		>35	1 2 7 0 4 1 0 0 0	3	I+	2 2 5 1 3 1 1 0 0	3	I+	53-54
Patello-femoral	KL 0-I	<18.5	2 0 0 2 3 4 4 0 0	6	U+	2 1 1 1 3 2 5 0 0	5	U+	55-56
		18.5-35	2 0 0 2 3 4 4 0 0	6	U+	1 0 0 1 4 2 7 0 0	6	U+	57-58
		>35	2 1 1 2 4 3 2 0 0	5	U+	1 1 1 1 5 4 2 0 0	5	U+	59-60
	KL II-III	<18.5	0 0 2 0 0 3 7 2 1	7	A+	1 2 1 0 2 3 2 1 3	6	U+	61-62
		18.5-35	0 0 1 1 0 2 8 2 1	7	A+	0 0 1 0 1 1 7 2 3	7	A+	63-64
		>35	0 2 1 2 6 1 1 2 0	5	U+	0 3 1 1 4 2 1 2 1	5	U+	65-66
	KL IV	<18.5	1 2 0 6 5 1 0 0 0	4	U+	2 2 3 2 5 0 0 0 1	4	U+	67-68
		18.5-35	1 2 1 5 5 1 0 0 0	4	U+	1 2 0 4 6 0 1 0 1	5	U+	69-70
		>35	1 6 4 3 1 0 0 0 0	3	I+	2 4 6 1 1 1 0 0 0	3	I+	71-72

Appropriateness scale: 1 = extremely inappropriate, 5 = uncertain, 9 = extremely appropriate

FIGURE 3 Clinical scenarios for the age range 50–65 (chapter 2). A, appropriate; BMI, body mass index; DIS, disagreement; Green, appropriate scenarios; I, inappropriate; KL, Kellgren–Lawrence; M, median value; red, inappropriate scenarios; U, uncertain; yellow, uncertain scenarios; +, without disagreement; −, with disagreement.

purpose of the present consensus was to identify specific clinical scenarios where the use of adipose- or bone marrow–derived CBT can be considered appropriate or inappropriate, considering parameters such as OA grade, age, BMI and predominant tibio-femoral or patello-femoral involvement.

Among all parameters, OA grade exerted the greatest influence on the experts' judgement regarding CBT appropriateness, accounting for more than 50% of all possible treatment indication changes. In detail, CBT use was considered appropriate only in cases of mild to moderate OA (KL II–III), a stage where joint degeneration is established but may not be severe enough to require prosthetic replacement. Conversely, the use of CBT in patients with early OA (KL 0–I) was largely rated as uncertain, probably because pain in these patients may originate from factors other than OA itself, and because current evidence does not support the ability of CBT to delay disease progression in these clinical scenarios [5, 14]. Nonetheless, the experts did not consider CBT use inappropriate in this subgroup, except for patients older than 80 years, thus leaving the final decision on the appropriateness to the clinician, particularly in cases where clinical and imaging evaluations exclude other potential sources of knee pain. Regarding KL Grade IV scenarios, the use of these products never reached an appropriateness rating and was even considered inappropriate when patients also presented advanced age or abnormal BMI values. This assessment reflects the limited clinical evidence available for this subgroup of patients, for whom TKA remains the recommended treatment option [23]. However, in younger patients with normal BMI, the use of CBT cannot be completely excluded from the treatment algorithm in cases with KL IV OA, as it may represent a non-surgical alternative when joint replacement is either contraindicated due to co-morbidities or not desirable for the patients.

Age was another major parameter influencing the experts' assessment of CBT appropriateness, with the use of CBT considered appropriate only in patients younger than 80 years. In detail, for individuals aged below 65 years with KL Grade II–III OA, when prosthetic replacement is a less favourable option given the higher risk of complications, revision surgery, and postoperative patient dissatisfaction [15, 26, 28, 33], the use of CBT was considered appropriate, with no significant difference between those aged <50 and

Chapter 3

A **66-80 years old** patient presents to your attention with symptoms related to knee OA, unresponsive to other conservative and injectable treatments and the following characteristics. How appropriate do you rate the indication for CBT POC injection treatment?

Joint	OA Level	BMI	Bone Marrow Derived	M	DIS	Adipose Tissue Derived	M	DIS	Indication n°
Tibio-femoral	KL 0-I	<18.5	1 1 2 0 6 3 1 1 0	5	U+	2 1 1 1 3 6 1 0 0	5	U+	73-74
		18.5-35	1 1 2 0 6 3 1 1 0	5	U+	1 0 0 1 3 6 3 1 0	6	U+	75-76
		>35	2 2 1 2 5 2 1 0 0	5	U+	1 1 2 1 5 4 1 0 0	5	U+	77-78
	KL II-III	<18.5	0 1 3 0 4 3 2 2 0	5	U+	1 2 1 2 3 2 2 1 1	5	U+	79-80
		18.5-35	0 1 2 1 4 2 3 2 0	5	U+	0 1 0 0 2 0 7 4 1	7	A+	81-82
		>35	2 0 2 3 4 2 1 1 0	5	U+	1 2 0 3 4 2 2 1 0	5	U+	83-84
	KL IV	<18.5	1 3 5 2 1 3 0 0 0	3	I+	2 3 4 1 2 2 0 1 0	3	I+	85-86
		18.5-35	1 3 3 2 3 3 0 0 0	4	U+	1 2 3 1 3 3 1 1 0	5	U+	87-88
		>35	2 4 7 1 0 1 0 0 0	3	I+	1 5 6 1 2 0 0 0 0	3	I+	89-90
Patello-femoral	KL 0-I	<18.5	1 1 1 2 5 2 3 0 0	5	U+	2 1 1 2 4 3 2 0 0	5	U+	91-92
		18.5-35	1 1 1 2 5 2 3 0 0	5	U+	1 0 0 1 6 2 5 0 0	5	U+	93-94
		>35	2 1 1 4 4 2 1 0 0	4	U+	1 1 2 3 5 2 1 0 0	5	U+	95-96
	KL II-III	<18.5	0 1 2 1 3 3 4 1 0	6	U+	1 3 0 0 4 3 2 2 0	5	U+	97-98
		18.5-35	0 1 2 1 2 3 4 2 0	6	U+	0 1 0 0 4 0 7 2 1	7	A+	99-100
		>35	2 0 4 1 4 2 1 1 0	5	U+	1 1 3 2 4 3 0 1 0	5	U+	101-102
	KL IV	<18.5	1 6 5 1 2 0 0 0 0	3	I+	1 9 2 2 1 0 0 0 0	2	I+	103-104
		18.5-35	1 6 5 1 2 0 0 0 0	3	I+	1 6 3 3 1 1 0 0 0	3	I+	105-106
		>35	3 7 4 1 0 0 0 0 0	2	I+	3 6 3 2 0 1 0 0 0	2	I+	107-108

Appropriateness scale: 1 = extremely inappropriate, 5 = uncertain, 9 = extremely appropriate

FIGURE 4 Clinical scenarios for the age range 66–80 (chapter 3). A, appropriate; BMI, body mass index; DIS, disagreement; Green, appropriate scenarios; I, inappropriate; KL, Kellgren–Lawrence; M, median value; red, inappropriate scenarios; U, uncertain; yellow, uncertain scenarios; +, without disagreement; −, with disagreement.

50–65 years old. When analyzing the older age ranges, the group between 66 and 80 years showed the greatest uncertainty regarding CBT use, likely due to the negative age effects on CBTs and the fact that knee replacement surgery is generally considered more successful and appropriate in this population [22, 34]. Within this age range, experts rated as appropriate only adipose-derived CBT in patients with KL II–III OA and normal BMI, as a potential alternative to arthroplasty in cases where the patient either does not wish to or cannot undergo surgery. Therefore, in these patients who are not candidates for joint replacement, adipose-derived CBT may represent a possible treatment option if BMI is within normal limits.

On the other hand, CBT was considered overall inappropriate for patients over 80 years of age, and this likely reflects both the expected decline in the biological potential of cellular products and a reduced healing capacity for articular response to biologic injections [11, 18]. This consideration applies mainly to bone marrow–derived CBT, as ageing is associated with a decline in bone marrow cellularity and regenerative capacity, whereas adipose-derived products tend to maintain a more stable cell yield and viability over time [3, 12]. The experts reflected this biological difference between the two cell sources in their clinical indications, consistently rating the use of bone marrow–derived CBT as inappropriate in patients over 80 years of age, whereas the use of adipose-derived CBT was not considered inappropriate but rather uncertain in patients over 80 years old with KL Grade 0–III OA and normal BMI, leaving the decision regarding the use of the treatment to the clinician. Finally, both adipose- and bone marrow–derived CBT were considered inappropriate in patients over 80 years with either very low or very high BMI, given the increased risk of adverse effects associated with frailty and the reduced likelihood of clinical benefit due to mechanical overload or systemic disease and vulnerability.

BMI was another parameter that significantly influenced the experts' judgement on the appropriateness of CBT use in patients with knee OA. In particular, the use of these biological treatments never reached an appropriateness rating in patients with more than Grade 1 obesity (BMI > 35 kg/m^2). Obesity is recognized as a chronic inflammatory condition, and therefore, the quality of the harvested and processed tissues for injectable use may be compromised by the systemic

Chapter 4

A **>80 years old** patient presents to your attention with symptoms related to knee OA, unresponsive to other conservative and injectable treatments and the following characteristics. How appropriate do you rate the indication for CBT POC injection treatment?

Joint	OA Level	BMI	Bone Marrow Derived	M	DIS	Adipose Tissue Derived	M	DIS	Indication n°
Tibio-femoral	KL 0-I	<18.5	4 3 4 3 1 0 0 0 0	3	I+	3 2 7 1 2 0 0 0 0	3	I+	109-110
		18.5-35	4 3 3 3 2 0 0 0 0	3	I+	1 1 4 1 6 1 1 0 0	5	U+	111-112
		>35	5 3 4 3 0 0 0 0 0	2	I+	2 5 4 2 1 1 0 0 0	3	I+	113-114
	KL II-III	<18.5	3 3 4 2 2 1 0 0 0	3	I+	2 3 6 1 2 1 0 0 0	3	I+	115-116
		18.5-35	3 3 3 2 2 2 0 0 0	3	I+	0 2 3 1 4 3 2 0 0	5	U+	117-118
		>35	5 4 3 1 1 1 0 0 0	2	I+	2 4 5 2 1 1 0 0 0	3	I+	119-120
	KL IV	<18.5	6 6 1 0 2 0 0 0 0	2	I+	5 5 3 0 1 1 0 0 0	2	I+	121-122
		18.5-35	6 6 1 0 2 0 0 0 0	2	I+	4 4 0 1 4 1 1 0 0	2	I+	123-124
		>35	8 5 1 1 0 0 0 0 0	1	I+	5 4 3 2 0 1 0 0 0	2	I+	125-126
Patello-femoral	KL 0-I	<18.5	4 3 4 3 1 0 0 0 0	3	I+	3 6 3 2 1 0 0 0 0	2	I+	127-128
		18.5-35	4 3 3 4 1 0 0 0 0	3	I+	2 3 2 2 4 1 1 0 0	4	U+	129-130
		>35	5 4 2 4 0 0 0 0 0	2	I+	3 6 2 4 0 0 0 0 0	2	I+	131-132
	KL II-III	<18.5	3 5 3 0 4 0 0 0 0	2	I+	2 6 4 0 3 0 0 0 0	2	I+	133-134
		18.5-35	3 4 4 1 2 1 0 0 0	3	I+	1 4 2 0 5 0 3 0 0	5	U+	135-136
		>35	6 5 2 1 1 0 0 0 0	2	I+	3 4 4 3 1 0 0 0 0	3	I+	137-138
	KL IV	<18.5	6 6 2 0 1 0 0 0 0	2	I+	6 6 2 1 0 0 0 0 0	2	I+	139-140
		18.5-35	6 6 2 1 0 0 0 0 0	2	I+	5 4 3 2 1 0 0 0 0	2	I+	141-142
		>35	8 5 1 1 0 0 0 0 0	1	I+	6 5 1 3 0 0 0 0 0	2	I+	143-144

Appropriateness scale: 1 = extremely inappropriate, 5 = uncertain, 9 = extremely appropriate

FIGURE 5 Clinical scenarios for >80-year-old patients (chapter 4). A, appropriate; BMI, body mass index; DIS, disagreement; Green, appropriate scenarios; I, inappropriate; KL, Kellgren–Lawrence; M, median value; red, inappropriate scenarios; U, uncertain; yellow, uncertain scenarios; +, without disagreement; −, with disagreement.

		A	U	I	CONSENSUS
SOURCE	Bone marrow	11.1%	51.4%	37.5%	48.6%
	Adipose tissue	12.5%	55.6%	31.9%	44.4%
JOINT	Tibio-femoral	12.5%	54.2%	33.3%	45.8%
	Patello-femoral	11.1%	52.8%	36.1%	57.2%
OA GRADE	KL 0-I	0%	79.2%	20.8%	20.8%
	KL II-III	35.4%	43.8%	20.8%	56.2%
	KL IV	0%	37.5%	62.5%	62.5%
BMI	<18.5	14.6%	52.1%	33.3%	47.9%
	18.5-35	20.8%	58.4%	20.8%	41.6%
	>35	0%	50.0%	50.0%	50.0%
AGE	<50	22.2%	66.7%	11.1%	33.3%
	50-65	19.5%	69.4%	11.1%	30.6%
	66-80	5.6%	66.7%	27.7%	33.3%
	>80	0%	11.1%	88.9%	88.9%

FIGURE 6 Rating of scenarios evaluated as Appropriate, Uncertain, or Inappropriate, for each parameter considered. Green indicates the highest rates of appropriateness, yellow the most uncertain parameters and red the highest rate of inappropriateness when considering the indication for cell-based therapy based on the different parameters evaluated. The last column refers to the overall consensus reached, representing the sum of appropriateness and inappropriateness rates; thus, the lack of uncertainty. A, appropriate; BMI, body mass index; KL Kellgren–Lawrence; I, inappropriate; OA, osteoarthritis; U, uncertain.

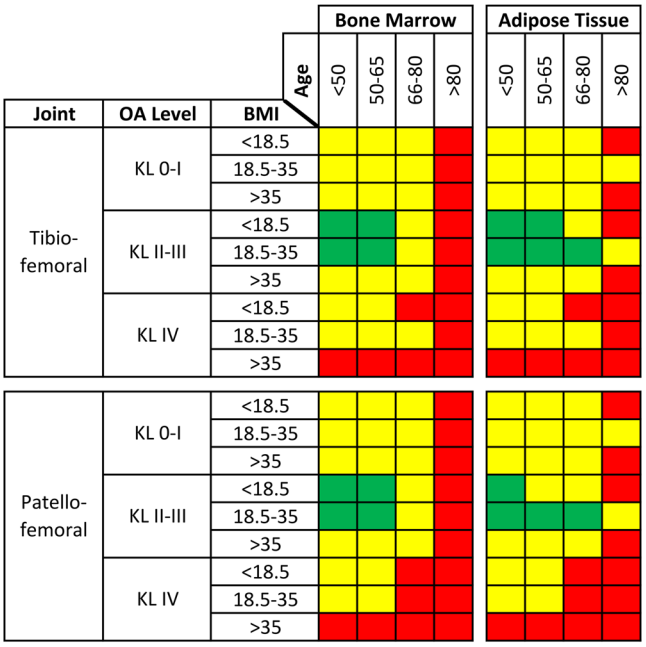


FIGURE 7 Graphic representation of the overall RAM consensus results on the appropriateness of point-of-care cell-based therapy for the management of knee osteoarthritis (green: appropriate; yellow: uncertain; red: inappropriate). BMI, body mass index; KL, Kellgren–Lawrence; OA, osteoarthritis.

inflammatory status [19]. This effect has been demonstrated especially for adipose tissue, with an in vitro study documenting a higher pro-inflammatory cytokine profile and stronger pro-inflammatory activity in adipose-derived products obtained from OA patients with high BMI [13]. In addition, obese patients may also have a poorer response to cellular treatments due to the systemic inflammation associated with obesity and to the increased mechanical load on the joint [1, 30]. Conversely, there were no differences in appropriateness between patients with BMI < 18.5 and those with BMI between 18.5 and 35 kg/m^2 in bone marrow-derived CBT. For adipose-derived CBT, it was considered appropriate when BMI was below 18.5 only in younger patients. Patients with BMI < 18.5 are typically considered underweight or frail, and therefore, the use of cell-based products, which involve a minimally invasive harvesting procedure, should be reserved for cases in which other injectable treatments have failed, leaving the decision regarding the appropriateness of the treatment to the clinician.

The prevalent involvement of the tibio-femoral or patello-femoral joint in the knee OA processes was the parameter that had the least impact on the experts' judgement on CBT appropriateness. Although the patello-femoral joint is recognized as biomechanically more complex than the tibio-femoral joint [2], and despite the more limited evidence regarding the use of CBT for patello-femoral OA, no substantial differences were observed in the appropriateness ratings between the two locations. This finding may be explained by the fact that few therapeutic options are available for patello-femoral OA when the disease is not yet advanced enough to warrant patello-femoral arthroplasty. Accordingly, in patients with predominantly patello-femoral OA of KL Grade II or III, cell-based injectable therapies may represent a viable treatment option, particularly when other conservative or injectable treatments have failed.

This study has several limitations. First, scenarios are a simplified representation of the different and specific characteristics of patients, who are all unique. For example, the BMI parameter was divided into three categories, underweight and severe/pathological obesity at the two extremes, leaving patients from normal to overweight and moderately obese in the middle, which is a wide range of BMI. Analogously, all categories present artificial and broad cut-offs to represent main patient groups, thus being a simplistic representation of clinical practice. The consensus limited its focus exclusively to POC-CBT from bone marrow and adipose tissue, which are more commonly used in the current clinical practice, without considering treatments involving other cell sources or culture-expanded cells. Moreover, it did not distinguish the heterogeneity of processing systems available for bone marrow and adipose tissue, and costs as well as cost-effectiveness of the different approaches were not considered. Different techniques and devices may inevitably produce different preparations with varying biological properties and therapeutic potential. Until high-quality comparative studies are available, it will remain difficult to draw definitive conclusions about which specific processing method or cell source is more appropriate for the treatment of knee OA. Another limitation lies in the intrinsic design of a consensus-based study. The RAM process provides structured expert opinion based on current evidence but does not provide strict indications, nor strict treatment algorithms as guidelines would do, rather offering recommendations to different types of scenarios, to be applied to the different patients in the clinical practice. Nonetheless, it allows the integration of clinical expertise, scientific evidence, and patient characteristics to guide decisions in real-world scenarios, especially in fields such as orthobiologics, where the evidence base is still evolving.

Overall, this consensus provides an overview for an evidence/expert-informed use of CBT in knee OA with a more rational patient selection. Given the heterogeneity of available products and the still-evolving evidence base, the results are not intended to serve as a rigid treatment algorithm, but rather as broad recommendations that help identify patient profiles in which CBT may provide clinical benefit or where its use should instead be avoided. These recommendations can help standardize clinical decision-making, optimize

patient selection and reduce the inappropriate use of cell-based injectable therapies in patients with knee OA.

CONCLUSIONS

This ESSKA–ICRS expert consensus provides recommendations on the appropriateness of cell-based injectable therapies for knee OA. POC-CBT may be considered, after failure of other non-operative and injectable options, in patients aged ≤65 years with BMI ≤ 35 kg/m^2 and KL Grade II–III OA. Unlike bone marrow–derived CBT, adipose-derived CBT was also considered appropriate in patients 66–80 years old with BMI 18.5–35 kg/m^2 and KL Grade II–III OA. On the other hand, CBT was considered inappropriate in patients over 80 years old and in those with KL Grade IV OA. These findings may help improve patient selection, although they should not be interpreted as a rigid treatment algorithm but rather as expert-informed guidance for the use of POC-CBT in knee OA.

SCENARIOS GROUPS

[α]: Scenarios nos. 109, 110, 111, 113, 114, 115, 116, 117, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 131, 132, 133, 134, 135, 137, 138, 139, 140, 141 and 142.

[β]: Scenarios nos. 17, 18, 35, 36, 53, 54, 71, 72, 89, 90, 107 and 108.

[γ]: Scenarios nos. 1, 2, 3, 4, 5, 6, 19, 20, 21, 22, 23, 24, 37, 38, 39, 40, 41, 42, 55, 56, 57, 58, 59, 60, 73, 74, 75, 76, 77, 78, 91, 92, 93, 94, 95 and 96.

[δ]: Scenarios nos. 13, 14, 15, 16, 31, 32, 33, 34, 49, 50, 51, 52, 67, 68, 69 and 70.

[ε]: Scenarios nos. 11, 12, 29, 30, 47, 48, 65, 66, 79, 80, 81, 83, 84, 97, 98, 99, 101 and 102.

AUTHOR CONTRIBUTIONS

All authors contributed to the consensus process. Study conceptualization was performed by Laura de Girolamo, Lior Laver and Giuseppe Filardo. The core panel comprised Laura de Girolamo, Elizaveta Kon, Lior Laver, Thomas Tischer and Kristof Sas, with Giuseppe Filardo acting as the moderator. The expert voting panel included Kristoffer Weisskirchner Barfod, Ricardo Bastos, Alessandro Di Martino, Matej Drobnič, João Espregueira-Mendes, Michael Iosifidis, Baris Kocaoglu, Laura Mangiavini, Rodica Marinescu, Stefan Nehrer, Marko Ostojić, George Skarpas, Kristof Sas, Martyn Snow and Tobias Winkler. The discussion group consisted of Jasmin Bagge, Ramon Cugat, Francesca de Caro, Jérémy Magalon, Mikel Sánchez and Lucienne Vonk. Project management was conducted by Angelo Boffa and Luca Andriolo, who were also responsible for drafting the manuscript. All authors critically reviewed the manuscript and approved the final version.

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DATA AVAILABILITY STATEMENT

All consensus data are included in the manuscript.

CONFLICT OF INTEREST STATEMENT

Francesca de Caro is consultant for ConMed, Clover Orthopedics and Smith & Nephew. Elizaveta Kon reports consulting for Cartiheal ldt, Green Bone, Geistlich and Bioveex and speaking for Zimmer Biomet and Fidia Farmaceutici SPA. Lucienne Vonk is employed by and has stock options in Xintela AB. Board of Directors or committee member: International Cartilage Regeneration & Joint Preservation Society. Editorial or governing board: Journal of Cartilage & Joint Preservation. Tobias Winkler is consulting for ReLive, Pluri, Enlivex, Liposphere, Heraeus Medical, Causeway Therapeutics and is holding shares of Myotec, Sunac and TCS, and he is on the board of the Advanced Therapies in Orthopaedics Foundation ATiO. The other authors declare no conflicts of interest.

ETHICS STATEMENT

The authors have nothing to report.

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