EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Quality aspects for cell-based products for cardiac repair

CAT-DGTI Workshop

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Why quality matters?

- Basic understanding of quality parameters always needed for research and commercial production, e.g. activity, impurities etc.
- If the product is not characterised and its´ quality not defined, non-clinical and clinical results may not be comparable and will be difficult to repeat

  → efficacy signals are diluted → failure of multisite clinical trials ?
- Product target profile is required for clinical studies to ensure patient safety

cell based medicinal product DEFINITIONS AND QUALITY

PRODUCT DEFINITION – qualified cell population (s) in the appropriate vehicle for the intended action

PRODUCT CHARACTERISATION - Very relevant to ensure:

- Consistency of the active substance / finished product
- Validation of the manufacturing process
- Comparability when manufacturing changes are introduced
- Stability throughout shelve life
- Release specifications selected from characterisation studies

SPECIFIC REQUIREMENTS FOR CBMP : Directive 2009/120/EC + GL CBMP

Identity – phenotypic profile - cell markers
Purity and **Viability** – relevant population / populations in mixture / viable cell %
Impurities – unwanted cells, reagents, adventitious agents, sterility, endo, mycoplasma
Potency – quantitative measure of the biological activity – related to the intended action
karyology, **tumourigenicity**, **genetic stability –** specially relevant for dividing differentiating cell populations

[Intervention Review]

Stem cell treatment for acute myocardial infarction

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Editorial group: Cochrane Heart Group.

Review content assessed as up-to-date: 23 July 2011.

Main results

Thirty-three RCTs (1765 participants) were eligible for inclusion. Stem/progenitor cell treatment was not associated with statistically significant changes in the incidence of mortality (RR 0.70, 95% CI 0.40 to 1.21) or morbidity (the latter measured by re-infarction, hospital re-admission, restenosis and target vessel revascularisation) A considerably high degree of heterogeneity has been observed among the included trials. In short-term follow up, stem cell treatment was observed to improve left ventricular ejection fraction (LVEF)

Authors' conclusions

Despite the high degree of heterogeneity observed, the results of this systematic review suggest that moderate improvement in global heart function is significant and sustained long-term. However, because mortality rates after successful revascularization of the culprit arteries are very low, larger number of participants would be required to assess the full clinical effect of this treatment. Standardisation of methodology, cell dosing and cell product formulation, timing of cell transplantation and patient selection may also be required in order to reduce the substantial heterogeneity observed among the included studies.

CARDIAC REPAIR CELL STRATEGIES

heterogenious cell preparations FOR MI or CHF

1ST WAVE

bone marrow aspirate - autologous
Minimal manipulation
- Separation / centrifugation

Moderate results / no results

2ND WAVE

MSC immuneselected / MPC - EPC
Cell expansion
Other sources – PBMC / adipocytes / placenta
allogeneic
Commited cells - Cardiomyocytes

Inconclusive

3RD WAVE ?

Embryonic stem cells
iPSC

results ?

Cell product definition
Can conclusions be drawn from experience?

Cardiomyocytes progenitor ? Endothelial progenitor ? Both ?

Progenitor cells vs cardiomyocytes – differentiation stage ?

Autologous vs allogeneic- Immunoregulatory properties ?

Different Sources of progenitor cells – different clinical outcome?

- Bone marrow – " gold standard" ?
- Adipocytes – Peripheral blood – cord blood – placenta ?
- Characterisation beyond ISCT ?

Table 1. Summary of criteria to identify MSC

1	Adherence to plastic in standard culture conditions		
2	Phenotype	Positive (≥ 95% +)	Negative (≤ 2% +)
		CD105	CD45
		CD73	CD34
		CD90	CD14 or CD11b
			CD79α or CD19
			HLA-DR
3	*In vitro* differentiation: osteoblasts, adipocytes, chondroblasts (demonstrated by staining of *in vitro* cell culture)		

CAT Expert meeting – quality aspects

- ✓ Non-manipulated (non-selected and selected) CBMPs derived from BM, apheresis
- ✓ Expanded CBMPs (MSCs, cardiac stem cells etc.)
- ✓ Questions posed to the experts:

-identity: how different sources of the starting material impact on the intended action and, if from bone marrow non manipulated, should they be considered "homologous" use (the same function as in their origin)?

- purity: to what extent it is known what type of cells are relevant and what cells can be deleterious for the indication considering also the sourcing of the substance?

- potency - how to address potency in terms of functionality in relation to the clinical indication and dose

Discussion on quality and manufacturing issues

Cell origin, donation, separation:

-Issues related to cell origin and donation (donor medication, age etc.)

-Impact of the techniques used to retrieve cells (BMCs)

-Difficulties in defining required therapeutic cell composition

-number of stem cells in cell population is low → increase of stem cells (GM-CSF) → impact of mobilization on cell composition/quality??

-Cellular impurities and their impact on efficacy/safety?

Cell purity – possible to single out relevant and deleterious cell components ?

How relevant the mixed population -

How relevant engraftment vs paracrine

How relevant cells vs targeted growth factor

What cells can have deleterious effect - impurities

Embryonic or iPS – lineage consistency – future possible ?

Manufacturing

-Cell processing –manual vs. automatic

-Impact of cell separation techniques on quality of the final product, choice of cell markers and antibodies/selection methods

-Culture and differentiation of cells towards intended cell population (MSC-, cardiac-,…), how to demonstrate functionality and correct phenotype/genotype?

-Reagents for manufacturing – quality and impact on cells (growth factors, cytokines etc.)

-Product- and process-related impurities

-How to manage variability?

Potency testing

- Precise mechanism of MI? → difficulties in defining the exact mode of action for cell-based products for MI
- Potency testing should ideally follow MoA – sorted cells vs. BM/blood MNCs vs. cultured cells?
- First claim that mononuclear cells or MSCs would form new cardiac tissue, later paracrine effects proposed. Markers/ function to follow for potency testing? Paracrine – what indicators ?
- Cultured cardiomyocytes form new tissue – functionality? aligning to correct beating rythm or arythmia?
- Persistence of cells and their migratory capacity? Engraftment – how to measure ?
- Potency testing and link to efficacy

Administration and dose

- Administration devices and their impact on cells (cell number and quality)
- How to define the dose (cell number per volume or also other parameters/markers etc.) – conceivable to define dose / biological activity units instead of number of cells ?
- Choice of excipients
- Impact of storage on cell number and functionality?

General issues

- Product standardisation in multisite production and trials?
- Analytical techniques and their comparability across labs?
- The underlying disease and patient condition to be considered, different healing capacities → different treatment options for different indications (AMI, CHF,..)??

Thank you for your attention!