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Sustained quality of life improvement after intracoronary injection of autologous bone marrow cells in the setting of acute myocardial infarction: results from the BONAMI trial

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## Abstract

**Purpose:** Cardiac cell therapy is a promising treatment for acute myocardial infarction (AMI), leading to cardiac function improvement. However, whether it translates into quality of life (QoL) improvement is unclear. We hypothesized that administration of bone marrow cells (BMC) to patients with AMI improves QoL.

**Methods:** In the multicenter BONAMI trial (NCT00200707), patients with reperfused AMI and decreased myocardial viability were randomized to intracoronary autologous BMC infusion (n=52) or state-of-the-art therapy (n=49). QoL data, derived from the Minnesota Living with Heart Failure questionnaire (MLHFQ), were obtained 1, 3, and 12 months after AMI and analyzed using a Rasch-family model.

**Results:** Using this model, QoL improved over time in the BMC group ( $p=0.025$ ) but not in the control group. Furthermore, the BMC-group patients displayed a better QoL than the control-group patients at 3 and 12 months post-AMI ( $p=0.034$  and  $p=0.003$ , respectively). These findings were not detected when analyzing MLHFQ data using a standard method. Cardiac function, myocardial viability, mortality, and number of major adverse cardiac events did not differ between treatment groups.

**Conclusion:** Our results suggest that BMC therapy can improve QoL, stressing the need for confirmation trials and for systematic QoL assessment in cardiac cell therapy trials.

## Background

Cardiac cell therapy is a promising treatment for patients with acute myocardial infarction (AMI) and left ventricular dysfunction. Overall, previous studies reported significant but modest improvements in cardiac function [1]. Nevertheless, whether these variations in surrogate markers translate into mortality, morbidity and quality of life (QoL) improvement is still unclear. To date, analysis of QoL after cardiac cell therapy is limited to few studies with dissimilar methodologies and reveals mixed results [1].

A preferred method to measure health-related QoL in clinical trials utilizes patient self-report questionnaires. However, in longitudinal studies, incomplete or missing questionnaires are frequent and can cause biased estimates and poor statistical power [2]. Utilization of Rasch-family models that can take into consideration all available data including incomplete questionnaires may address these issues [3].

We investigated the impact of cardiac cell therapy on QoL, using Rasch-family models. The present study tested if, in the setting of AMI with left ventricular dysfunction, bone marrow cell (BMC) infusion improved heart failure-related QoL (HFQoL) and cardiac function over a 1-year follow-up period in the BONAMI trial [4]. Also, we tested if the use of the Partial Credit Model, a Rasch-family model, could improve assessment of changes in QoL.

## Methods

In the randomized multicentre ‘BMC therapy for acute myocardial infarction’ (BONAMI) trial (NCT00200707), 101 patients with successfully reperfused acute myocardial infarction, residual left ventricular ejection fraction (LVEF)  $\leq 45\%$ , and decreased myocardial viability were randomized to intracoronary BMC infusion (n=52) or state-of-the-art therapy (control group, n=49) [4].

LVEF and myocardial viability were assessed 7 days (baseline), 1, 3, and 12 months after myocardial infarction, using echocardiography and single-photon emission computed tomography (SPECT), respectively.

We assessed HFQoL with the French version of the Minnesota Living with Heart Failure questionnaire (MLHFQ) at 1 (M1), 3 (M3), 6 (M6), and 12 (M12) months after AMI.[5,6] For each of the 21 items of the MLHFQ, six response categories are available, ranging from 0 (no) to 5 (a lot).

We first used the standard method to analyze MLHFQ data, which is based on computation of the MLHFQ score, defined as the sum of answers to the 21 items (range 0-105). Higher MLHFQ score denotes worse quality of life. Importantly, using this method, if an answer to one item is missing, MLHFQ score cannot be computed.

To compare MLHFQ score data between treatment groups, we performed a mixed model analysis, taking into account the correlations between repeated measures for the same patient.

Next, to take into account incomplete questionnaires, an alternative method using the partial credit model was applied to individual item responses. This model has the same properties than the Rasch model and therefore belongs to Rasch-family models. The Rasch-family models explain the probability of a response to an item as a function of the HFQoL and items' parameters (difficulties). The item difficulty is an item characteristic. The lower the item difficulty is, the higher the probability of positive answer is (favorable response of the patient to this item regarding the HFQoL).

Specific objectivity is a property of the Rasch model. It allows obtaining consistent estimations of the parameters associated with the HFQoL independently from the items used for these estimations. Indeed, even if some patients do not respond to all items, estimates of the HFQoL parameters can be considered as unbiased.

MLHFQ has polytomous items whereas the Rasch model is valid only for dichotomous items. Therefore, for this study, we used the partial credit model, an extension of the Rasch model for polytomous items with or without different numbers of response modalities.

Validation of the model fit was assessed using RUMM® software (v2030, Rumm Laboratory Pty Ltd®, Australia) [7]. Three items (items 1, 10 and 20) displayed a bad fit and could not be included in the analysis. Overall, a correct fit of the model could not be rejected ( $p=0.33$ ). Then, the mean level of HFQoL was calculated for each treatment group and at each time-point [8]. The partial credit model was implemented using the NLMIXED procedure in SAS® software (v9.3, SAS Institute Inc®, USA).

## **Results**

### *Adverse events*

Over a 1-year follow-up period, 1 patient died in the BMC group and none in the control group. Major adverse cardiovascular events did not differ between treatment groups (table 1).

### *Cardiac function*

Myocardial viability was assessed by SPECT at baseline, M3, and M12 in 38 control and 46 BMC patients (table 2). Myocardial viability parameters did not differ between treatments groups at M12, whereas, as previously published [4], a trend for greater improvement in viability was observed at M3 in the BMC group.

Left ventricular function and remodeling were assessed by echocardiography up to M12 in 40 control and 46 BMC patients (table 2). LVEF remained stable over time ( $p=0.12$ ) and did not differ between treatments groups ( $p=0.28$ ). Left ventricular end-diastolic volume increased over time ( $p<0.0001$ ) but did not differ between treatments groups ( $p=0.58$ ).

### QoL data

For the 101 enrolled patients, 83 to 93 questionnaires could be obtained at each time point of the study.

The standard method could be applied to 72% of the questionnaires (questionnaires without missing data). Observed differences on MLHFQ score between treatment groups (figure 1) were 2.4, 8.2, 4.8 and 6.4 points at M1, M3, M6 and M12, respectively. Differences between treatment groups did not differ among time of measurement (not significant interaction,  $p=0.29$ ). Results remained similar after adjustment on age and gender.

The partial credit model could be applied to 86% of the questionnaires ( $p=0.0462$  vs. standard method, Fisher exact test; supplemental data figure 1). The rate of usable questionnaires did not differ between treatment groups or between time-points.

The level of HFQOL was estimated by the partial credit model at each time-point for BMC and control groups (Figure 2). At M1, the level of HFQOL did not differ between treatment groups ( $p=0.85$ ). Over time, the level of HFQOL decreased significantly in the BMC group ( $p=0.03$ , M12 vs. M1), whereas it remained stable in the control group ( $p=0.20$ , M12 vs. M1). At M3 and M12, the level of HFQOL was significantly lower in the BMC group as compared to the control group ( $p=0.03$  and  $p=0.003$ , respectively), denoting a better quality of life in the BMC group. A non-significant difference was observed at M6 ( $p=0.08$ ).

### **Conclusion**

Our study shows that, in the setting of AMI with left ventricular dysfunction, BMC therapy improved QoL from 3 months up to 1-year of follow-up, when QoL data was analyzed using a Rasch-family partial credit model, which took into account a greater number of questionnaires. Interestingly, we did not observe a concomitant improvement in cardiac function.

As health-related QoL can predict cardiovascular outcome after AMI [9,10], these findings are likely to be clinically relevant. In addition, the observed difference in MLHFQ score between treatment groups at M3 and M12 was greater than the Minimal Clinically Important Difference for MLHFQ which was previously defined as 5 points [11,12].

Interestingly, we did not observe a significant difference between control and BMC groups at M6. We could not identify any clinical justification related to this non-significant effect of cell therapy at M6. However, when analyzing the number of questionnaires with no missing data at each time-point, we observed that this number was lower at M6 as compared to any other time-point (data not shown). This suggests that if Rasch-family model performs better than conventional method in the presence of missing data, it logically remains sensitive to missing data.

In the BONAMI trial, we did not observe any improvement in cardiac function in the BMC group as compared to the control group [4]. Cardiac function and QoL parameters have been previously reported as independent predictors of clinical outcome after AMI [9,10]. This suggests that cardiac function and QoL parameters are complementary approaches to assess efficacy of cardiac cell therapy, and that, together with cardiac function, QoL should be monitored in cardiac cell therapy trials.

These results, together with previous reports, show that utilization of Rasch-family models, which are robust in the presence of missing data,[3,13] may be preferentially used to monitor QoL in longitudinal clinical trials. In our study, mixed model and partial credit model analyses led to different conclusions, as we only observed a significant treatment-related improvement in QoL when using the partial credit model. Indeed, the respective performance of distinct statistical methods cannot be evidenced from a single dataset and simulation studies are usually needed for such comparisons. As a matter of fact, both statistical methods that were applied in this study (mixed models on observed QoL scores and Rasch model on item responses) have been previously compared in previous simulation studies.[3,13] These simulations studies have shown that Rasch models performed better than mixed models for the analysis of incomplete patient-reported outcomes data regarding power. Thus, the results that we have observed in this study seem to be perfectly in line with what we have observed in our simulation studies comparing the two statistical methods.

Our study has several limitations. It was open labeled therefore potentially biasing patient-reported QoL. However, we believe that this bias is unlikely as QoL data did not differ between treatment groups at M1. Indeed, our results should be considered as provocative and will have to be confirmed in a larger cohort of patients. However, we believe that this bias is unlikely as QoL data did not differ between treatment groups at M1. Also, we only recorded HFQoL in this study. Therefore we cannot conclude on the impact of cardiac cell therapy on QoL related to other symptoms such as angina.

In summary, using a Rasch-family model, we showed that cardiac cell therapy improved QoL after AMI. We suggest that further clinical trials on cardiac cell therapy efficacy should systematically monitor QoL in addition to cardiac function and that Rasch-family model may be considered as an appropriate method to analyze QoL data.

### **Compliance with Ethical Standards**

**Funding:** This work was supported in part by a PHRC (Programme Hospitalier de Recherche Clinique) from the French Department of Health, and grants from the Association Française contre les Myopathies and the Fondation de France. There was no relationship with industry.

**Conflict of Interest:** Authors declare that they have no conflict of interest.

**Ethical approval:** All procedures involving human participants performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The ethics review board of Nantes University Hospital approved the protocol. **Informed consent:** Informed consent was obtained from all individual participants included in the study.

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### Figure legends

**Figure 1:** Mean Minnesota Living with Heart Failure Questionnaire (MLHFQ) score at one (M1), three (M3), six (M6) and twelve (M12) months follow-up visits for control (CTL) and BMC groups.

**Figure 2:** HFQOL level assessed by Partial Credit Model at one (M1), three (M3), six (M6) and twelve (M12) months for control and BMC groups. \*: indicates a significant difference between treatment groups ( $p < 0.05$ ).

**Table 1:** Adverse Events at 1 year follow-up visit

Number of patients with event, n (%)	Control	BMC	
Death	0	1 (1.9)	p=0.49
Re-hospitalization for heart failure	3 (6.2)	4 (7.7)	p=0.71
Angina or Acute Coronary Syndrome	4 (8.3)	4 (7.7)	p=1
Revascularization	13 (27.1)	12 (23.1)	p=1
Thrombosis (excluding coronary artery thrombosis)	2 (4.2)	4 (7.7)	p=0.43
Documented cardiac arrhythmia	2 (4.2)	2 (3.8)	p=1
Cancer	0	0	
Stroke	0	0	

**Table 2:** Cardiac function assessed by SPECT and echocardiography

	<b>BMC</b>	<b>Control</b>	
<b>Improvement in myocardial viability vs. baseline: number of patients (%)</b>			
M3	16 (34)	7 (16)	p=0.06
M12	16 (34)	9 (23)	p=0.25
<b>Left Ventricular Ejection Fraction %, mean±SD (n)</b>			<b>p=0.89</b>
Baseline	38.2±7.9 (50)	39.8±7 (46)	
M3	39.14±10.2 (47)	41.5±8.8 (44)	
M12	38.5±10.5 (46)	41.3±9.2 (40)	
<b>Left Ventricular End-Diastolic Volume Index ml/m<sup>2</sup>, mean±SD (n)</b>			<b>p=0.32</b>
Baseline	57.9±15.6 (50)	56.9±13.1 (45)	
M3	69.4±23 (47)	66.1±18.4 (43)	
M12	73.2±25.2 (46)	69.4±25.9 (40)	

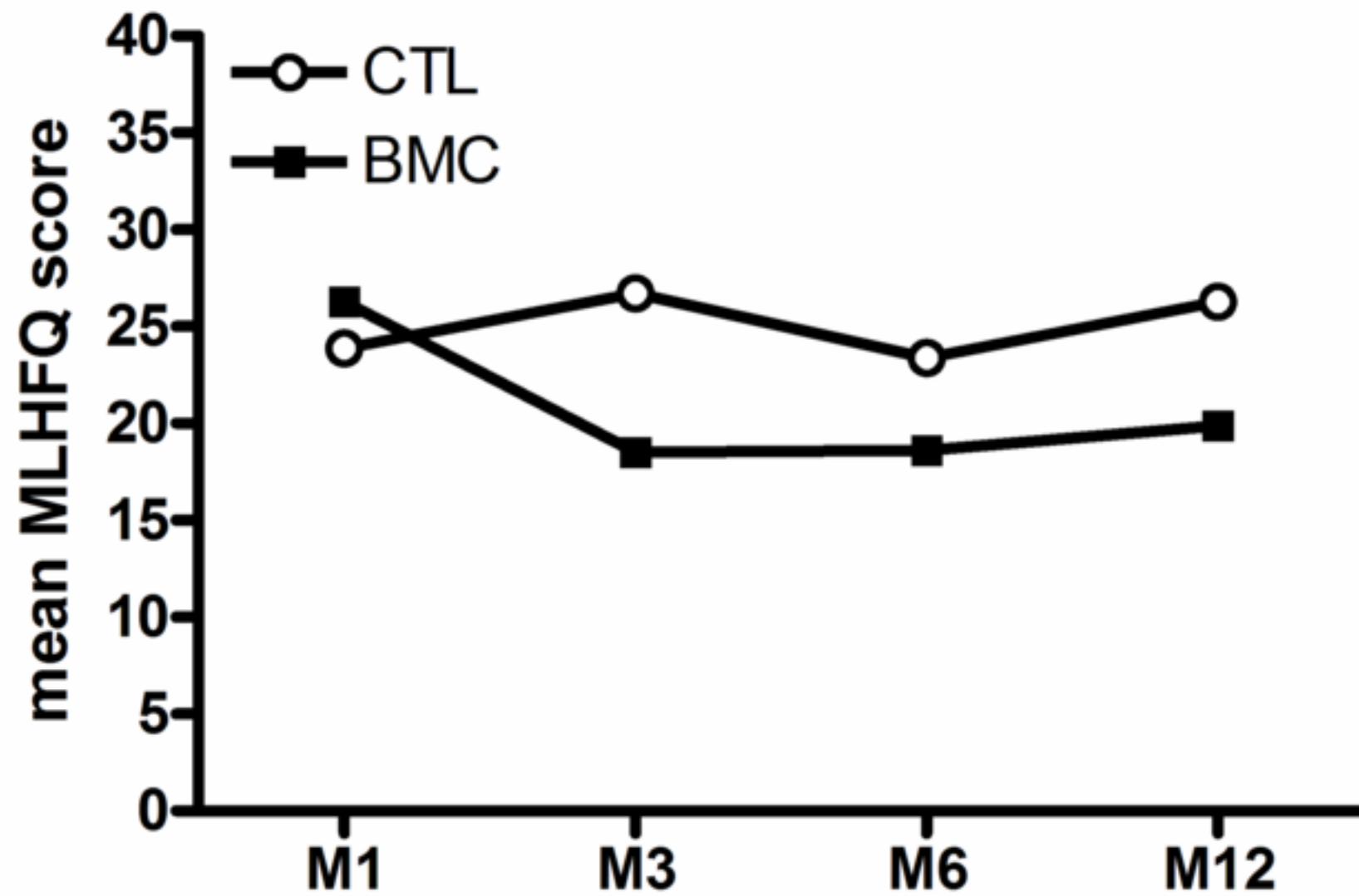
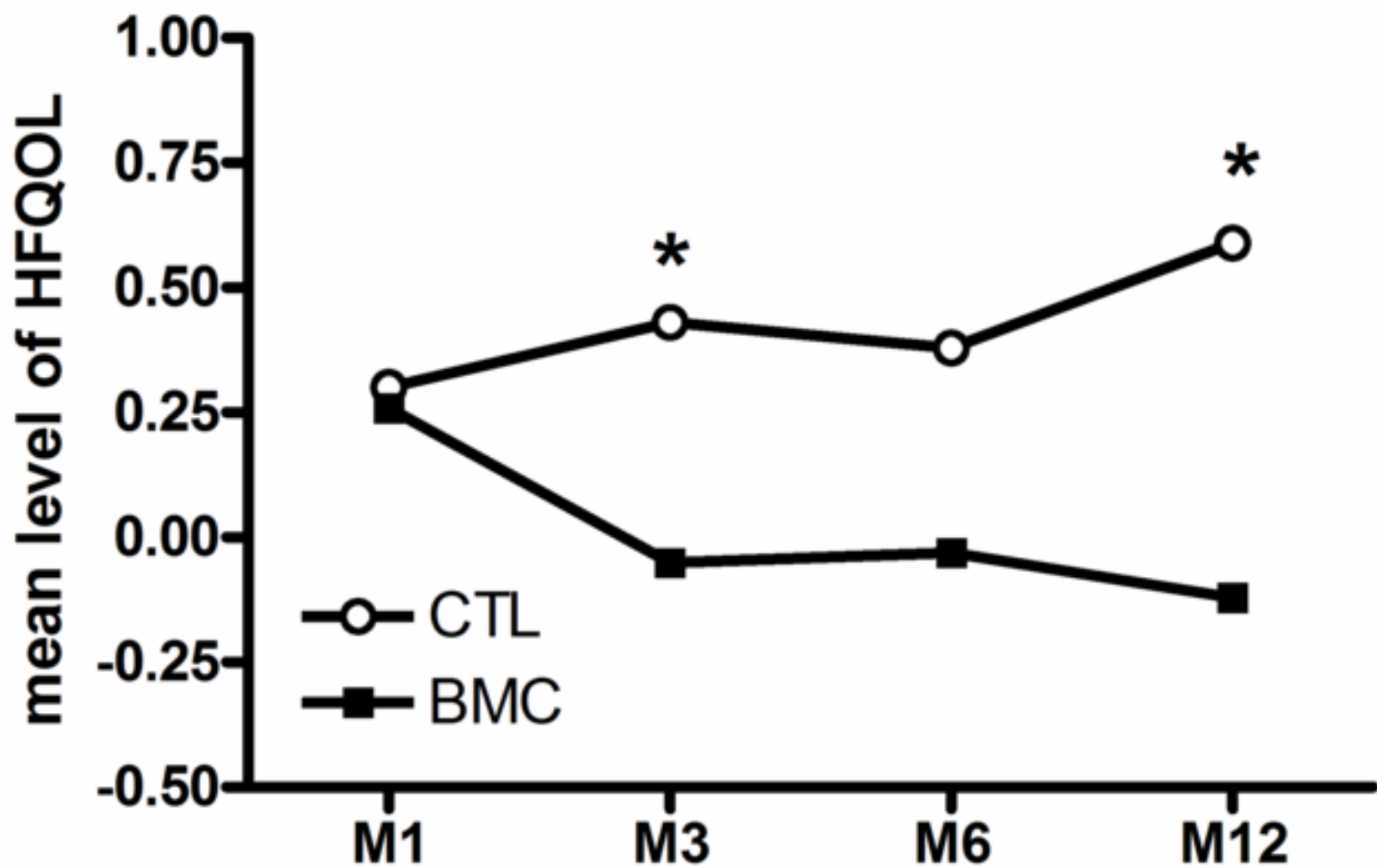


Figure 2



## Legends

**Supplemental data figure 1:** Rates of usable questionnaires for conventional and partial credit model (PCM) methods. Data are shown at one (M1), three (M3), six (M6) and twelve (M12) months follow-up visits for control (CTL) and bone marrow cell (BMC) groups.

