Telomerase Activator TA-65 Combats Immune Aging and Inflammation in Subjects Post-Myocardial Infarction:

A Randomized, Double-Blind, Placebo-Controlled Trial

By:
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Myocardial infarction (MI), commonly referred to as a "heart attack," is a catastrophic event resulting in irreversible damage to the heart due to prolonged oxygen deprivation. As one of the leading causes of human morbidity and mortality, MI affects around 3 million people worldwide annually, with approximately 805,000 cases in the United States.[1,2] An estimated 200,000 of those in the United States are recurrent attacks.[2] Despite advances that have led to significant improvements in short- and long-term prognosis for MI, patients who experience an MI remain a high-risk population, even in those whose disease is stable 1 year post-MI.[3]

A growing body of evidence underscores a close relationship between immune status and both cardiovascular and noncardiovascular diseases. Some patients exhibit lymphopenia after an MI, triggered by the activation of the hypothalamic-pituitary-adrenal axis through an inflammation-related mechanism, which enhances secretion of glucocorticoids. In turn, elevated circulating glucocorticoids induce trafficking of blood lymphocytes to the bone marrow, resulting in a reduced level of circulating lymphocytes and other changes to cellular immunity.[4] Lymphopenia is therefore a strong risk factor for immunosenescence, a state of immune function dysregulation and organ reorganization that leads to an impaired capacity to mediate appropriate immune responses.[5]

Immunosenescence has been implicated as a major contributing factor in age-related functional decline and chronic inflammation, including the development of cardiovascular disease.[6] Numerous studies have demonstrated that MI precipitates accelerated immunosenescence and telomere shortening in leukocytes.[7-10] Since lymphocyte proliferation is mediated by telomerase activation,

this suggests that reversing lymphopenia through telomerase activation might enhance the clinical outcomes for patients post-acute MI.

A recent study by Bawamia et al. delved into the potential of TA-65 to counteract immunosenescence in patients post-MI.[11]

Telomere Length - A Potential Therapeutic Target?

Telomeres are protective end caps of chromosomes that preserve the integrity of our genome during DNA replication. In humans, telomeres' critical role in cellular senescence — the irreversible cell cycle arrest — has been well documented.[12] An inverse relationship also exists between telomere length and human chronological age; thus, telomere length has long been regarded as an important hallmark of organismal aging.[13]

Telomerase is a DNA polymerase that consists of two subunits: telomerase reverse transcriptase (TERT), the catalytic subunit of telomerase; and an RNA component called telomerase RNA component (TERC). Other proteins such as Reptin, Nhp2, Pontin, Gar1, and Tcab1 are also required for proper telomerase assembly and recruitment to chromosomes.[14] The mRNA expression of human TERT is strictly controlled at the transcription level and is closely linked to telomerase activity and homeostasis. Experimental evidence suggests that TERT expression may be the limiting factor in human telomerase activity.[14,15]

TERT was once thought to be only expressed in highly proliferating cells or stem cells. It was also believed that TERT was localized in the nucleus, where it protects telomeres from shortening. However, it is now evident that TERT is also expressed in non- or low-proliferating tissues, including the heart.[16] Moreover, TERT demonstrates non-telomeric functions in mitochondria where it helps protects mitochondrial DNA by decreasing levels of reactive oxygen species, a key factor in senescence.

TA-65 is an encapsulated form of cycloastragenol, a triterpenoid saponin compound isolated from Astragalus membranaceus (Fisch.) Bunge. In vitro evidence suggests that TA-65 influences lymphocyte proliferation in a TERT-dependent way.[17] It also acts as a mitochondrial telomerase activator, where it has been shown to increase TERT within the mitochondria, thereby improving the outcomes of ischemia/reperfusion injury.[18]

The TACTIC Trial

The Telomerase ACTivator to reverse Immunosenescence in Acute Coronary Syndrome (TACTIC) trial was a single-center, randomized, double-blind, parallel-group, placebo-controlled phase 2A pilot study involving 90 subjects with coronary heart disease who had experienced an acute MI within 6 months prior to enrollment.

Participants had to meet the following additional criteria to be eligible for the study:

- Sixty-five years of age or older
- Successful completion of revascularization or under medical management following MI
- Evidence of obstructive coronary artery disease on invasive coronary angiography (≥1 major epicardial vessel stenosis ≥70%)
- Enrollment occurred more than 24 hours post-MI

Exclusion criteria included:

- Conditions associated with immunological dysfunction (e.g., HIV)
- Clinical instability (e.g., arrhythmias, cardiogenic shock)
- Severe, uncontrolled hypertension
- Severe comorbidity likely to affect outcome within 2 years
- Use of immunosuppressants and/or nutritional

supplements derived from Astragalus root

- Known malignancy
- Current or previous substance addiction
- Diagnosis of insulin-dependent diabetes mellitus

Subjects received 8-mg doses of either TA-65 or the placebo twice daily for 12 months. At the end of the study, flow cytometric assays were used to measure the proportion of terminally differentiated effector memory CD8+ T cells (CD8+ TEMRA; CD3+CD4−CD8+CCR7−CD45RA+) in peripheral blood. Recent studies suggest CD8+ TEMRA cells have a strong potential as a biomarker for immunosenescence.[19]

Secondary outcome measures were as follows:

- Proportions and absolute counts of other leukocyte subsets
- Serum levels of high-sensitivity C-reactive protein (hsCRP)
- Nuclear telomerase activity in peripheral blood mononuclear cells, measured using the Telomerase Repeated Activation Protocol (TRAP) - quantitative polymerase chain reaction (qPCR) assay
- Oxidative stress, measured using the TBARS colorimetric assay
- Microvascular endothelial function, evaluated using the EndoPAT device
- Cardiac function, evaluated using transthoracic echocardiography and serum levels of NT-proBNP (N-terminal pro-B-type natriuretic peptide), a marker of myocardial stretch that correlates with left ventricular function
- Adverse events and adverse reactions

Results

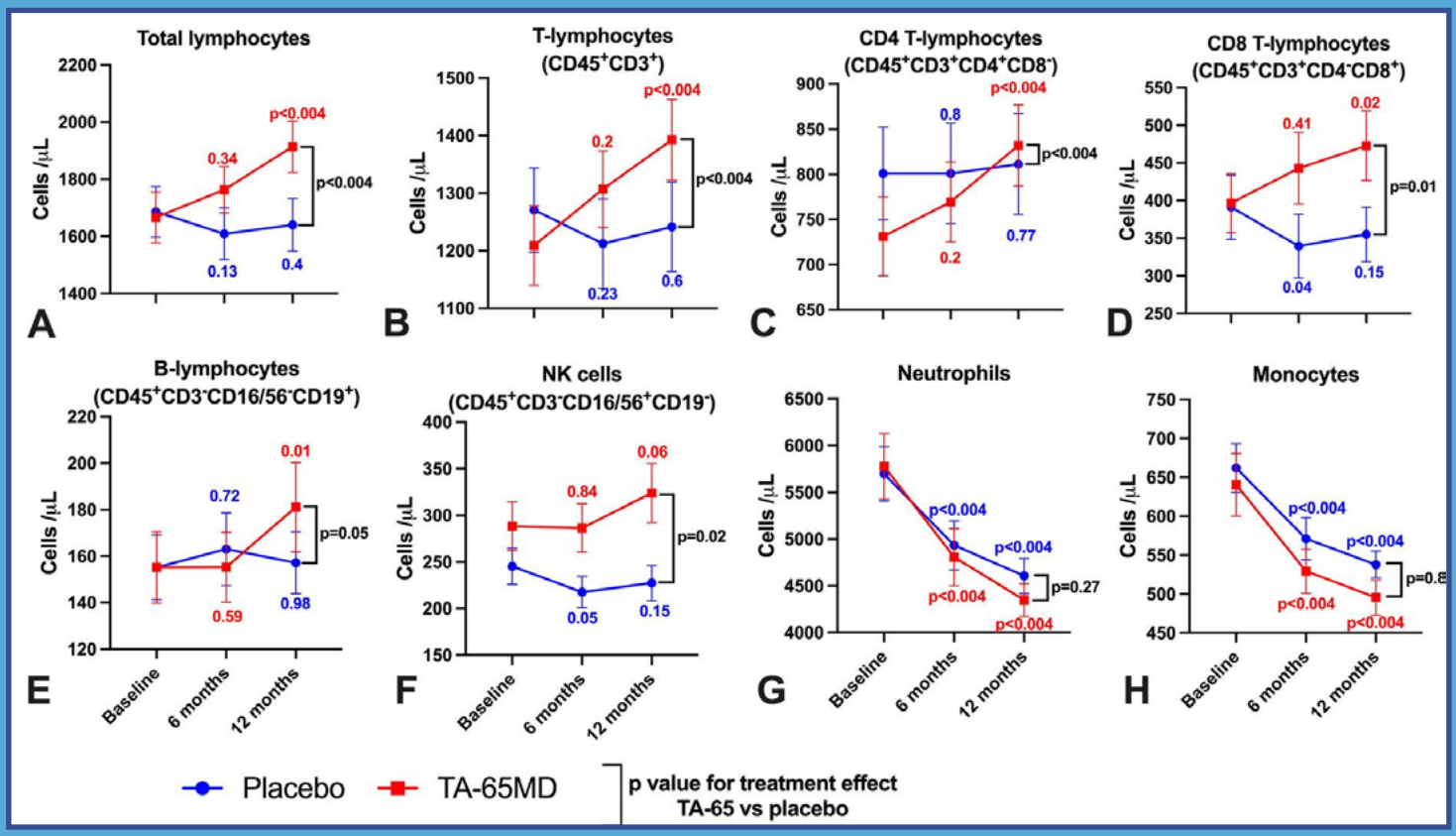

Figure 1
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10122201/

TA-65 Reverses Lymphopenia

The investigators observed considerable increases in CD4+ and CD8+ T-lymphocytes, B-lymphocytes, and natural killer cells in the TA-65 group, all of which contributed to a higher total lymphocyte count for the group. Figure 1 presents a comparison of absolute leukocyte counts (cells/µL from Trucount assay) between the TA-65 and the placebo groups at baseline, 6 months, and 12 months.

The mechanism by which TA-65 induced reversal of lymphopenia remains unclear. While the increase from baseline in total lymphocyte count was significant, the changes in specific lymphocyte subsets, such as T-cells and B-cells were not significant. Had the reversal been due to enhanced lymphocyte proliferation – indicating nuclear telomerase activation – certain subpopulations such as naïve CD8+CD57- cells should have differed in their response to TA-65 from CD8+CD57- cells. This, then, suggests a different mechanism of action.

TA-65 May Reduce Inflammation

Inflammation following acute MI plays a critical role in healing and scar formation.[20] The inflammatory response occurs in two phases: an initial pro-inflammatory response followed by an anti-inflammatory, reparative phase.[21] There is evidence that an excessive and persistent pro-inflammatory response to acute MI can worsen post-MI adverse left ventricular (LV) remodeling, a process associated with worse clinical outcomes. Therefore, therapeutic targeting of inflammation may improve outcomes in acute MI patients.[21]

High-sensitivity C-reactive protein (hsCRP) level, a surrogate marker for systemic inflammation, has been evaluated as a prognosticator of various adverse cardiovascular events and other human malignancies.[22-26] Specifically for MI, several studies have found that hsCRP level may correspond to late microvascular obstruction size, size of myocardial necrosis, new-onset atrial fibrillation, recurrence of ventricular tachycardia and fibrillation, risk of heart failure, and death.[27-32]

At baseline, the TA-65 and the placebo groups had similar hsCRP levels at 11.9 and 10.9 mg/L, respectively. However, at the end of the 12-month trial, hsCRP levels in subjects in the TA-65 group were 62.1% lower than those in placebo group subjects. Figure 2 depicts changes in mean hsCRP (mg/L) levels between the TA-65 and the placebo groups stratified by type of MI at baseline.

These findings indicate that TA-65 may mitigate inflammation in patients following acute MI. In turn, reduced inflammation may help delay the progression of coronary atherosclerosis and prevent adverse LV remodeling. Notably, unlike many drugs that improve acute MI clinical outcomes at the expense of a robust immune system, the results of the TACTIC trial did not show significant changes in myeloid cells in subjects treated with TA-65 compared to those treated with placebo. Subjects in the TA-65 group instead showed enhanced adaptive immunity, demonstrated by the increase in mean total lymphocyte count.

TA-65 May Activate Mitochondrial Telomerase
Mitochondrial dysfunction declines with age, contributing directly to senescence.[33] Desdín-Micó and colleagues demonstrated in mice that T-cells with dysfunctional mitochondria instigate senescence, triggered by the accumulation of pro-inflammatory cytokines. The results were characteristic of "inflammaging," including alterations to metabolic, cognitive, physical, and cardiovascular fitness. Together, the changes resulted in premature death of the mice.

Over the last several decades, studies have demonstrated that senescence accumulates in multiple cardiovascular cell populations, including those associated with myocardial dysfunction.[34,35] This evidence highlights the role of senescence in cardiovascular disease and the potential for senolytics to prevent or reverse disease progression. Furthermore, because mitochondria are required for the expression of the senescence-associated

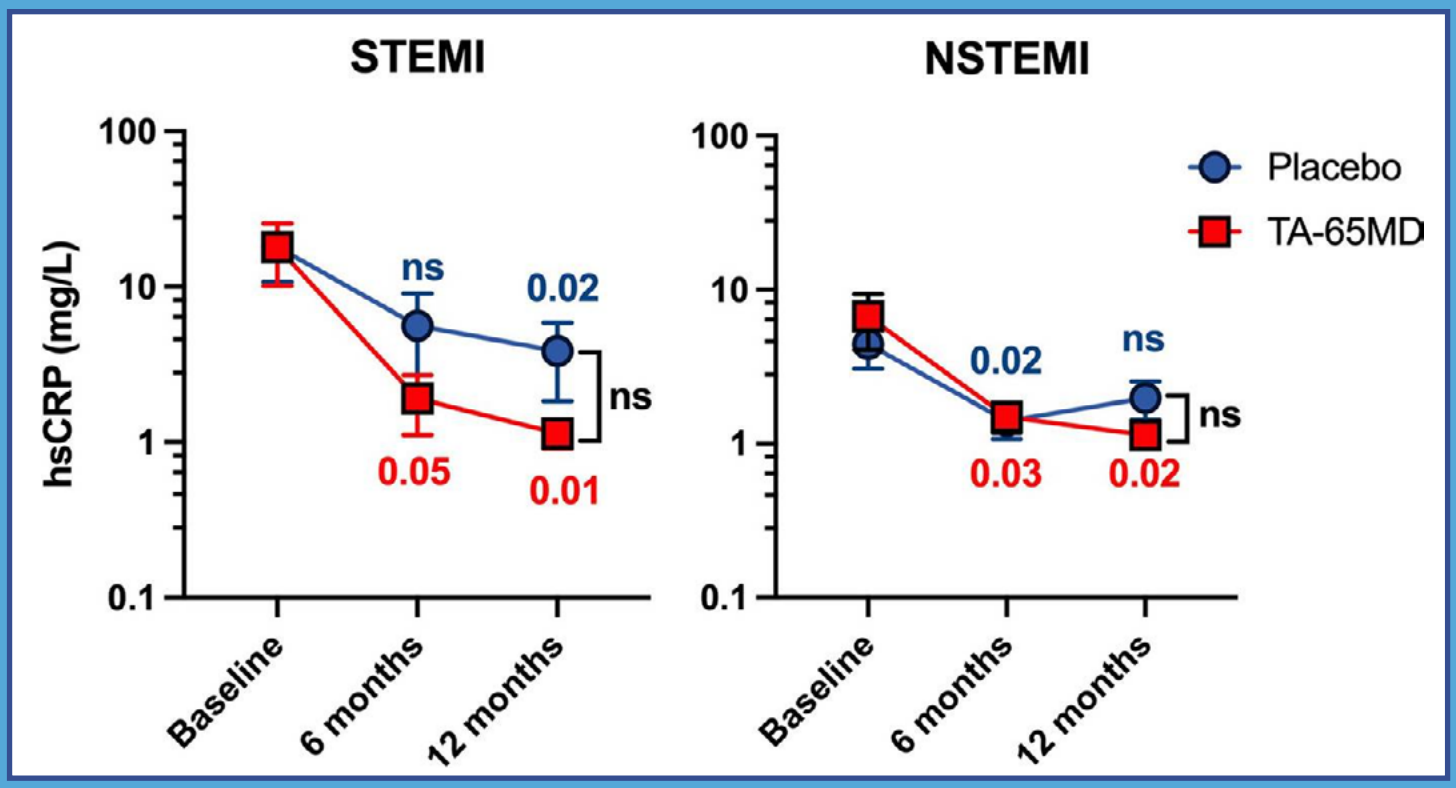

Figure 2
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10122201/

secretory phenotype, the authors hypothesize that the activation of mitochondrial TERT by TA-65 is the mechanism behind the reduced inflammation observed.

Conclusion

The TACTIC trial was the first study to investigate the effects of the telomerase activator TA-65 in patients following an MI. Given the favorable safety profile in addition to the significant increase in lymphocytes and reduction in hsCRP levels, TA-65 serves as a promising novel therapeutic approach to post-MI senescence.

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Initially trained and board certified in internal medicine, Dr Raffaele has been exclusively practicing in longevity medicine in New York City for 25 years with a focus on personalized hormone optimization and physiological age assessment. In 2007, he co-founded PhysioAge LLC, a web-based health analytics data collection and reporting system used by health care practices around the world to monitor and assess the effectiveness of their treatments. Since 2009, he has been involved in clinical telomere biology research and published 4 studies of the effect of oral telomerase activation on the immune system, metabolism, and telomere length in aging adults. He has lectured nationally and internationally on the clinical application of telomere biology. He routinely posts about telomere biology, geroscience research, hormone optimization, and biomarkers of aging. He received his B.A. in philosophy from Princeton University and his MD from Drexel University Medical School in 1989.

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