Inflammatory cytokines, life-threatening arrhythmias and premature mortality in chronic inflammatory arthritis: Time to focus on

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Pietro Enea LAZZERINI*, MD; Franco LAGHI-PASINI, MD; Maurizio ACAMPA, MD; Pier Leopoldo CAPECCHI.

Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Italy.

*Corresponding author:

Pietro Enea LAZZERINI,MD

Department of Medical Sciences, Surgery and Neurosciences,

University of Siena, Italy

Tel. +39-0577-5585743; Fax +39-0577-233318;

e-mail: lazzerini7@unisi.it

We read with much interest the paper by Ntari et al. [1], and would like to highlight how the high prevalence of fatal arrhythmic events that they found in Tg197 mice might have relevant implications in the clinical setting.

A solid body of data supports the evidence that in patients with chronic inflammatory arthritis (CIA), particularly rheumatoid arthritis (RA), the risk of death is significantly higher than in the general population, and that such a premature mortality is largely related to fatal cardiovascular events [2]. In this regard, two population-based studies provided evidence that the prevalence of cardiac arrest (CA), and sudden cardiac death (SCD) is ~2-times higher in RA than non-RA patients [3,4]. In addition, in RA patients the onset of an acute coronary syndrome is characterized by an increased short-term case fatality, as well as a higher risk to present with SCD when compared to non-RA subjects [5]. Altogether, these data strongly suggest that excess of mortality in CIA patients is due, at least in part, to an increased incidence of life-threatening ventricular arrhythmias [6].

In accordance with this view, accumulating evidence indicates that systemic inflammation may promote a pro-arrhythmic substrate in CIA, via multiple effects directly or indirectly increasing myocardial electric instability [6]. Indirect effects, including acceleration of coronary atherosclerosis and myocardial remodelling, are the most recognized. They may lead to an increased risk of ischemic heart disease and chronic heart failure, which are conditions inherently burdened by a high arrhythmogenic potential [6]. In addition, increasing data demonstrate that inflammatory cytokines, particularly TNFα, IL-6 and IL-1, directly affect cardiac electrophysiology by modulating the expression and function of specific ion channels in the cardiomyocyte resulting in a prolongation of ventricular action potential duration (APD) [6]. Accordingly, QTc interval, reflecting APD on surface electrocardiogram and representing a well-recognized risk factor for life-threatening ventricular arrhythmias and SCD in the general population, is frequently prolonged in RA patients [6], where strictly correlates with cytokine levels [7,8], also independently predicting

mortality [9]. In addition, a recent study on a large cohort of RA women demonstrated that IL-6 levels strongly predicted cardiovascular events, particularly fatal cardiovascular events [10].

Despite such evidence, prevalence and characteristics of ventricular arrhythmias in RA, and more in general in CIA patients, are substantially unknown, as to date population studies investigating this subject are surprisingly lacking. Thus, no direct evidence is currently available that the higher risk of SCD/CA in these patients is due to an increased incidence of lethal arrhythmias. Similarly, although increasing data indicate that treatment with anti-rheumatic drugs decreases the incidence of all cardiovascular events in CIA, such specific outcomes are so far largely unexplored [11].

In this view, the paper by Ntari et al. [1] provides important clues in order to fill this gap of knowledge. In fact, the authors provided for the first time direct demonstration that in a murine model of cytokine(TNFα)-mediated chronic polyarthritis premature mortality of unknown etiology is markedly increased (~50%) along with a high incidence of fatal arrhythmic events. In addition, the evidence that both premature death and arrhythmias occur relatively early (10-13 weeks of age) after mice had established arthritis (i.e. 8 weeks), supports the view that rapidly-occurring electrophysiological changes in the heart may represent an important contributing mechanism by which cytokine overexpression increases arrhythmic risk in these animals.

These findings of the study should be emphasized. In fact, in our opinion they warrant large population-based studies aimed at defining the actual prevalence of life-threatening arrhythmias and SCD in CIA, as well as clinical trials to evaluate the impact of anti-rheumatic therapies, particularly anti-cytokine biological agents, on arrhythmic events and premature mortality in these patients. This information, besides helping clarify the pathogenesis of the phenomenon, may open new treatment opportunities in CIA, possibly also including specific anti-arrhythmic interventions to date largely overlooked in these patients.

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