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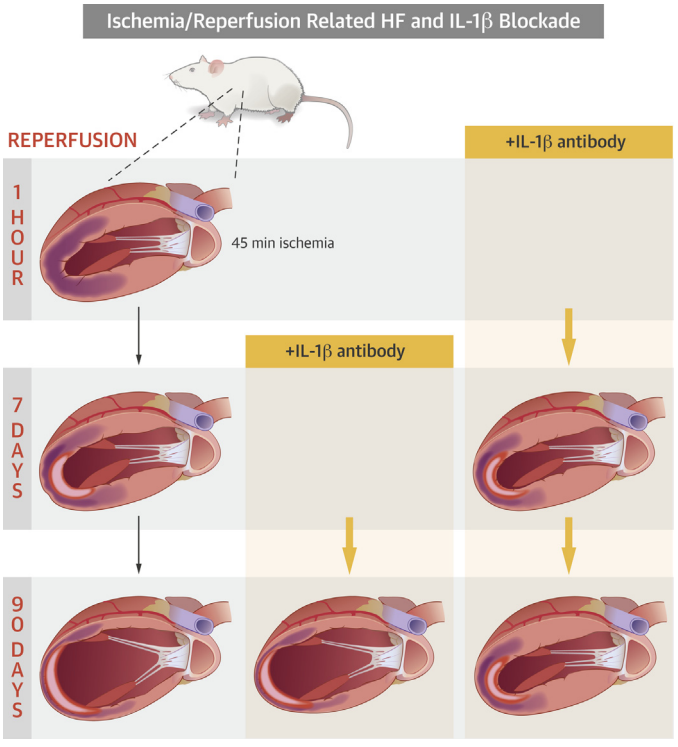
MINI-FOCUS: INFLAMMATION IN CARDIAC INJURY

The IL-1β Antibody Gevokizumab Limits Cardiac Remodeling and Coronary Dysfunction in Rats With Heart Failure

Najah Harouki, BS,[a,b,c] Lionel Nicol, PhD,[a,b,c,d] Isabelle Remy-Jouet, PhD,[a,b,c] Jean-Paul Henry, BS,[a,b,c] Anais Dumesnil, BS,[a,b,c] Annie Lejeune, BS,[a,b,c] Sylvanie Renet, BS,[a,b,c] Francesca Golding, BS,[a,b,c] Zoubir Djerada, PhD,[a,b,c,g] Didier Wecker, PhD,[e] Virginie Bolduc, PhD,[f] Muriel Bouly, PhD,[f] Jerome Roussel, PhD,[f] Vincent Richard, PhD,[a,b,c] Paul Mulder, PhD[a,b,c,d]

VISUAL ABSTRACT



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HIGHLIGHTS

- **Immediate IL-1β antibody gevokizumab administration reduces ischemia/reperfusion related infarct size.**
- **Immediate and late IL-1β antibody gevokizumab administration improves heart failure related left ventricular remodeling.**
- **IL-1β antibody gevokizumab improves heart failure related coronary dysfunction.**

From [a]INSERM U1096, Rouen, France; [b]Normandy University, IRIB, Rouen, France; [c]Unité de formation et de recherche de Médecine et Pharmacie, Rouen University, Rouen, France; [d]Plateau d'Imagerie CardioThoracique de l'Université de Rouen, Rouen, France; [e]Bruker Biospin MRI GMBH, Ettlingen, Germany; [f]Institut de Recherches Internationales Servier, Suresnes, France; and the [g]Pharmacology Department, Centre Hospitalier Universitaire de Reims, Reims, France. This work funded in part by Servier France and by European Union and Région Normandie. The European Union is associated with Normandy through the European Regional Development Fund (ERDF). Drs. Bolduc, Bouly, and Roussel are employees of Servier. Ms. Golding was a recipient of an Erasmus grant. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Antonio Abbate, MD, PhD, served as Guest Editor for this paper.

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SUMMARY

This study reports preclinical data showing that the interleukin (IL)-1β modulation is a new promising target in the pathophysiological context of heart failure. Indeed, in nondiabetic Wistar and diabetic Goto-Kakizaki rats with chronic heart failure induced by myocardial infarction, administration of the IL-1β antibody gevokizumab improves 'surrogate' markers of survival (i.e., left ventricular remodeling, hemodynamics, and function as well as coronary function). However, whether IL-1β modulation per se or in combination with standard treatments of heart failure improves long-term outcome in human heart failure remains to be determined. (J Am Coll Cardiol Basic Trans Science 2017;2:418–30)

ABBREVIATIONS AND ACRONYMS

GK = Goto-Kakisaki

I/R = ischemia/reperfusion

IL = interleukin

LV = left ventricle/ventricular

LVEDP = left ventricular end-diastolic pressure

LVEDPV = left ventricular end-diastolic pressure–volume relationship

LVESP = left ventricular end-systolic pressure

LVESPVR = left ventricular end-systolic pressure–volume relationship

ROS = reactive oxygen species

SOD = superoxide dismutase

Enhanced interleukin-1β (IL-1β) levels are involved in the immediate and long-term consequences of myocardial ischemia/reperfusion (I/R), as suggested by acute as well as chronic increases in IL-1β plasma levels observed in patients and rodents following myocardial infarction (1,2). Indeed, after the abrupt but transient increase of cardiac the IL-1β gene expression within the first hour to 1 day after ischemia (3,4), a second and sustained IL-1β upregulation is observed (5,6). This specific time course of IL-1β expression may be important in terms of left ventricular (LV) remodeling and/or LV dysfunction as IL-1β signaling is essential both during (5,7) and beyond the infarct healing period (8). Indeed, IL-1β plays an orchestrating role in the inflammatory response to myocardial injury, including enhanced synthesis of other proinflammatory mediators, activation of profibrotic pathways (5), and promotion of cytokine-induced cardiomyocyte apoptosis (9) but also exerts direct negative inotropic effects on myocyte contractility (9–11).

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Although the deleterious role of IL-1β in the acute consequences of cardiac I/R injury has been well established (7,12), the neutralization and modulation of IL-1β after myocardial infarction in mice has been suggested as a therapeutic target in the prevention of long-term consequences of I/R (i.e., development of heart failure [HF]) (7,13,14). Thus, the aim of this study was to determine the short- and long-term effects of treatment with the IL-1β modulating antibody gevokizumab (15,16), initiated either 1 h following reperfusion after myocardial ischemia and continued for 7 (early short-term) or 90 (early long-term) days or initiated 7 days following reperfusion after myocardial ischemia and continued for 83 (delayed long-term) days on I/R-induced LV remodeling or dysfunction and coronary dysfunction. Moreover, as several pathologies, notably diabetes, are known to aggravate myocardial I/R injury, we also evaluated Gevokizumab in the setting of type 2 diabetes, using Goto-Kakisaki (GK) rats.

Our results showed that the IL-1β antibody gevokizumab induces an immediate but sustained improvement of I/R-induced cardiac and coronary dysfunctions in "healthy" as well as diabetic rat models. However, whether IL-1β modulation may be a therapeutic option for the acute and long-term consequences (i.e., survival of cardiac I/R in humans remains to be determined).

MATERIALS AND METHODS

The investigation conforms to the Guide for the Care and Use of Laboratory Animals (U.S. National Institutes of Health publication 85-23, revised 1996) and was approved by the local ethical committee (CENOMEXA number 54; ref. 0871.01).

ANIMALS AND EXPERIMENTAL DESIGN. This study was performed in either 12-week-old male Wistar (Janvier Labs, Saint Berthevin, France) or GK (Metabrain, Chilly-Mazarin, France) rats, anesthetized with intraperitoneal administration of ketamine/xylazine (150 and 5 mg · kg^{-1}, respectively), subjected to either sham surgery or transient ischemia followed by reperfusion, the latter being verified visually before closing the chest, as previously described (17), provoked by temporary left coronary artery occlusion (Wistar rats: 45 min; GK rats: 20 min), followed by reperfusion for 2, 7, or 90 days.

Independent protocols were performed to study the short- and long-term effects of gevokizumab. A first protocol assessed long-term gevokizumab treatment initiated (10 mg·kg^{-1}, intraperitoneally) either 1 h (early long-term) or 7 days (delayed long-term) following reperfusion and continued for 90 or 83 days, respectively, at a dose of 10 mg·kg^{-1} subcutaneously once per week. This dosage regimen resulted