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EDITORIAL

Idiopathic Recurrent Pericarditis: Not Really So Idiopathic?

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In this issue of the *Journal of the American Heart Association* (*JAHA*), Peet[1] challenges the current concept of idiopathic recurrent pericarditis (IRP). Indeed, "idiopathic" means "arising spontaneously or from an obscure or unknown cause," which implies that the pathophysiology is not established, and the treatment should remain empirical. In 2 words, behind this learned word, we hide our ignorance.

See Article by Peet et al.

By contrast, the authors propose herein that IRP may be largely driven by the well-known interleukin-1 pathway. Given that interleukin-1 is well established as a key actor in many cardiovascular disorders, this new approach seems promising, especially because targeting interleukin-1β has already been demonstrated to be a potential means to struggle coronary disease,[2] in large-scale trials. The concept has been shown to be applicable for the first time in the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study).[3] Similarly, the 2 international large studies of colchicine in patients with coronary artery disease, LoDoCo2 (Low-Dose Colchicine 2)[4] in stable coronary artery disease and COLCOT (Colchicine Cardiovascular Outcome Trial)[5] in recent myocardial infarction, have shown a benefit of low-dose colchicine (0.5 mg per day). More important, colchicine has been shown to be safe too in these 2 studies recruiting >10 000 patients, followed up for >2 years. From a pathophysiological and pharmacological point of view, because colchicine targets at least in part interleukin-1β,[6,7] all of these considerations pave the way for the use of long-term strategies targeting interleukin-1β in various cardiovascular diseases.

Furthermore, more specifically in the field of pericarditis, colchicine is also the cornerstone for the prevention of recurrent episodes, as was demonstrated almost 2 decades ago.[8,9] More recently, drugs targeting interleukin-1β more directly have been shown of interest: rilonacept and anakinra (Figure).

In the AIRTRIP (Anakinra-Treatment of Recurrent Idiopathic Pericarditis) trial,[10] anakinra, an interleukin-1β recombinant receptor antagonist, reduced the risk of recurrence over a median of 14 months in a small population of patients with recurrent pericarditis (with ≥3 previous recurrences), elevation of CRP (C-reactive protein), colchicine resistance, and corticosteroid dependence (n=11 receiving anakinra, and n=10 receiving placebo).

Rilonacept is a soluble decoy receptor "trap," binding both interleukin-1α and interleukin-1β. In the RHAPSODY (Rilonacept Inhibition of Interleukin-1 Alpha and Beta for Recurrent Pericarditis: A Pivotal Symptomatology and Outcomes StudY) trial,[11] patients with recurrent pericarditis have been randomized to receive either rilonacept or placebo. On rilonacept, they presented nearly no recurrence at 12 months (n=31 receiving rilonacept versus n=30 receiving placebo).

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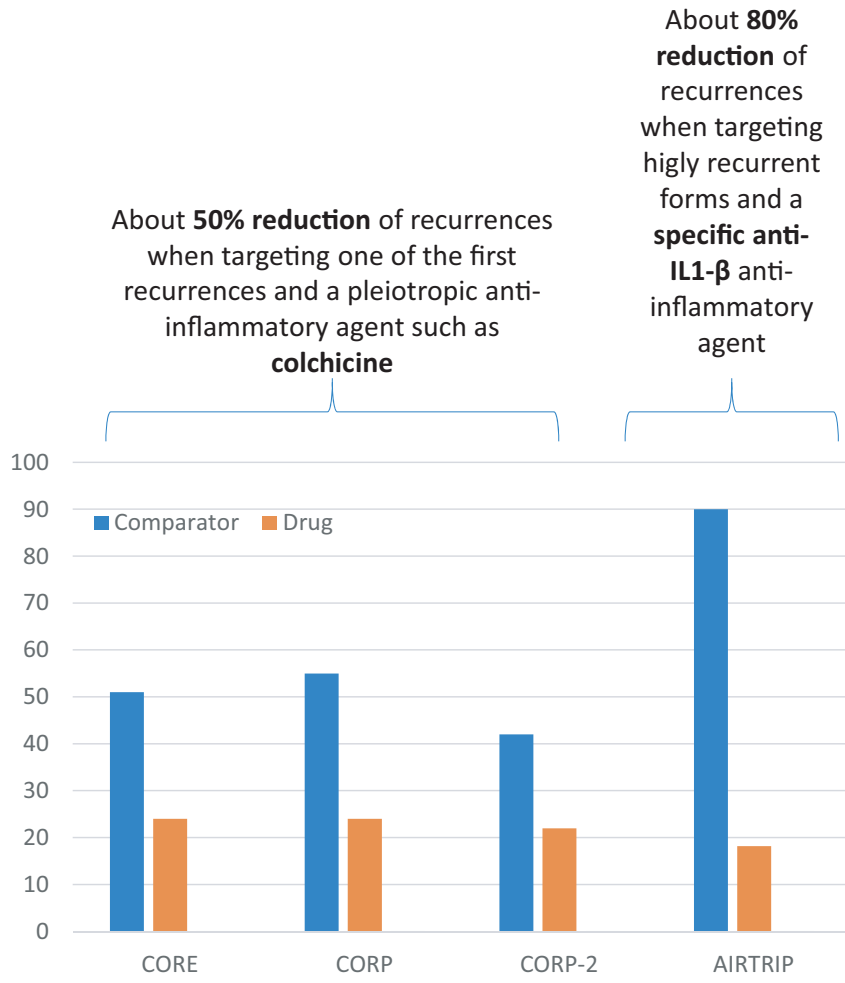

Number of patients included, n	84	120	240	21
Inclusion	1st recurrence	1st recurrence	>1st recurrence	>3rd reccurence
Comparator arm	Standard therapy	Placebo	Placebo	Placebo
Drug	colchicine	colchicine	colchicine	anakinra
Follow-up (months)	18 m	18 m	6 m	8 m

Figure. Main studies discussed in the article, presented shortly.
We could obtain about 50% reduction of recurrences when targeting one of the first recurrences with a pleiotropic anti-inflammatory agent, such as colchicine. By contrast, a deeper reduction (about 80%) is observed when targeting highly recurrent forms with a specific anti—interleukin-1β anti-inflammatory agent. AIRTRIP indicates Anakinra-Treatment of Recurrent Idiopathic Pericarditis; CORE, COlchicine for REcurrent Pericarditis; and CORP, Colchicine for Recurrent Pericarditis.

In these 2 studies, safety was particularly good. One major limitation is the small size of the included populations, but this is often the case for this rare clinical setting. Because the uptake of evidence-based therapies remains limited, corroborating the involvement of interleukin-1β in pathophysiology of IRP remains mandatory. Herein, the authors studied in depth their cohort of 136 patients with IRP and 1910 patients with rare monogenic

interleukin-1–mediated systemic autoinflammatory diseases. This is a fairly large population, representing a larger population than the 2 studies cited above combined, and the largest published IRP cohort with detailed clinical features. That is the reason why, although this is an observational cohort with its well-known biases, the authors consider herein a longer follow-up and a real-life population, so that this approach appears complementary to the randomized trials.

Consistent with the available literature, patients with IRP show excellent responses to colchicine and anti–interleukin-1 drugs, suggesting common mechanisms and providing a paradigm for the approach to IRP treatment. Interestingly, the authors underline the potential adverse effects of corticosteroids, which would increase chronic symptoms after the acute phase. This consideration, which is not so new, prompts a better understanding of the underlying pathophysiology.

Herein, the authors propose a comprehensive genetic analysis in IRP of the coding regions of the 4 genes known to cause interleukin-1–mediated inflammation. They confirm that IRP is a feature of each of the 4 monogenic interleukin-1–mediated autoinflammatory diseases. They even show that certain mutations may play a role in IRP, suggesting autoinflammation as a disease mechanism. All these results taken into consideration, pericarditis could now be considered at least partly related to an autoinflammatory process, and IRP appears to be a new manifestation of autoinflammation. This is important not only from a pathophysiological point of view, but also from a therapeutic approach.

Indeed, the autoinflammatory process implies an early and adequate therapy to fight against the vicious circle, but also paves the way for targeted therapies, as in other clinical settings, such as the canakinumab, another anti–interleukin-1β biotherapy, dedicated to rare autoinflammatory diseases. Specific and targeted management, or step-by-step management, could then be tailored, particularly on the basis of pharmacological and pharmacogenomic approaches, depending on genetic analysis.

As highlighted in the Figure, targeting inflammation through a pleiotropic anti-inflammatory drug, such as colchicine, offers a reduction of about 50% of recurrences. By comparison, in the highly recurrent forms, where autoinflammatory process linked to the interleukin-1β pathway is suggested, the size of effect on frequent recurrences is even larger.

Finally, this article is hypothesis generating, suggesting a new way of considering pericarditis. New actors could also be taken into considerations, including the COVID-19 or other viruses, that could interfere with autoimmunity.

Prospective studies of both acute and recurrent pericarditis are much needed.

ARTICLE INFORMATION

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Disclosures

None.

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