

Recurrent Pericarditis: Is Immunotherapy the Answer?

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KEY WORDS: recurrent pericarditis, immunotherapy, interleukin 1 (IL1), intravenous immunoglobulin (IVIG)
IMAJ 2018; 20: 190–191

Pericarditis is considered recurrent when reappearance of symptoms occurs after resolution of the initial acute attack, usually after 4 to 6 weeks. This complication is seen in up to 32% of acute pericarditis cases, and may increase up to 50% in untreated cases [1].

The pathogenesis and specific etiologies of recurrent pericarditis are still largely unknown, and therefore it is also referred to as idiopathic recurrent pericarditis. Autoimmunity, however, seems to play a crucial role. The autoimmune and autoinflammatory nature of the disease can be shown by the prevalence of autoantibodies in recurrent pericarditis patients [2] and in the effectiveness of immunosuppressant therapies in the disease [1].

The management of recurrent pericarditis is challenging. The efficacy of colchicine [3,4] and non-steroidal anti-inflammatory drugs (NSAID) [1] in prevention of recurrence is well-established, as are certain corticosteroid regimens in refractory cases [5]. In the case of corticosteroids, however, aside from their well-known adverse effects on other organ systems, they have also been associated with an increased recurrence of pericarditis, making them a double-edged sword [6]. Certain immunosuppressive therapies, such as azathioprine, have also been previously suggested [1].

In this article, we will discuss new emerging therapies for recurrent pericarditis.

INTERLEUKIN-1 ANTAGONISTS

Interleukin-1 (IL-1) is a family of cytokines involved in both acute and chronic inflammation. IL-1 β was found to be associated with autoimmune conditions, and is therefore used as a therapeutic target. IL-1 antagonists, such as anakinra, are used to treat autoimmune and autoinflammatory conditions such as familial Mediterranean fever [7].

Treatment with anakinra was previously tested in relatively small samples, but the results seemed promising. The treatment resulted in complete remission in corticosteroid-dependent patients and enabled discontinuation of corticosteroid treatment [8]. Another study reached similar conclusions, with complete and relatively fast remission (within a few days) [9]. An interventional double-blind placebo-controlled trial from Italy demonstrated significant reduction in pericarditis recurrence in colchicine-resistant and corticosteroid-dependent patients [10]. Similar results were also seen in case reports, in both children [11] and adults [12].

A review conducted in 2016 by Lazaros et al. [13] reported that C-reactive protein (CRP) levels were normalized within an average of 7.1 days, and corticosteroids were discontinued within 62 days.

It is important to note that discontinuation of anakinra leads to relapses in many cases, and therefore it seems that anakinra should be used as a long-term treatment [8,9]. The length of the treatment protocol is still unknown.

The recommended dose is 1–2 mg/kg daily, up to 100 mg/daily in adults, for several months. It is not yet determined whether tapering down is needed [14]. Adverse effects described are injection

site reaction in up to 44% of patients [13]. Other rare adverse effects include transaminases elevation [9,10], herpes zoster, and optic neuropathy [10].

INTRAVENOUS IMMUNOGLOBULINS

Intravenous immunoglobulins (IVIG) are comprised of pooled immunoglobulin G (IgG) antibodies from serum of thousands of donors. Although initially intended for treatment of immunocompromised patients, discovery of its immunomodulatory effects led to its use in different autoimmune and autoinflammatory conditions [15].

In recent years, evidence has accumulated regarding the beneficial role of IVIG in the treatment of refractory recurrent pericarditis. Early evidence from case reports show efficacy and safety of high-dose IVIG treatment for recurrent pericarditis attributed to different etiologies [16,17]. A small scale retrospective trial conducted in patients with no documented autoimmune diseases concluded that IVIG was effective in recurrent pericarditis treatment, with no major side effects documented [18]. A recent review of all published cases reported 73.3% of patients treated with one cycle of IVIG (400–500 mg/kg/day for 5 consecutive days) did not have recurrent episodes, and only 16.6% still needed corticosteroid treatment at the end of the follow-up period [19].

The recommended dose for IVIG is 400–500 mg/kg daily for 5 days, with no tapering needed [14]. The adverse effects that are described include headaches, which were documented in 3% of subjects [19], as well as flushing, chills, tachycardia, nausea, fatigue, and hypotension [20].

The major disadvantage of IL-1 antagonists and IVIG therapies is their high cost and their methods of administration.

Anakinra is injected subcutaneously, while IVIG is infused, usually in a hospital setting. Currently, these agents serve as a fourth-line of treatment, after different combinations of aspirin, NSAID, and colchicine [14]. This recommendation is classified as class IIB [1].

CONCLUSIONS

Recurrent idiopathic pericarditis seems to be both of autoimmune and autoinflammatory nature. Studies on treatments with new immunomodulatory agents, such as IL-1 antagonists and IVIG, show preliminary yet promising results and would probably change future prevention strategies of the disease and reduce the need for pericardiectomy.

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Capsule

A small-molecule inhibitor of the ubiquitin activating enzyme for cancer treatment

The ubiquitin–proteasome system (UPS) comprises a network of enzymes that is responsible for maintaining cellular protein homeostasis. The therapeutic potential of this pathway has been validated by the clinical successes of a number of UPS modulators, including proteasome inhibitors and immunomodulatory imide drugs (IMiDs). **Hyer** and collaborators identified TAK-243 (formerly known as MLN7243) as a potent, mechanism-based small-molecule inhibitor of the ubiquitin activating enzyme (UAE), the primary mammalian E1 enzyme that regulates the ubiquitin conjugation cascade. TAK-243 treatment caused depletion

of cellular ubiquitin conjugates, resulting in disruption of signaling events, induction of proteotoxic stress, and impairment of cell cycle progression and DNA damage repair pathways. TAK-243 treatment caused death of cancer cells and, in primary human xenograft studies, demonstrated antitumor activity at tolerated doses. Due to its specificity and potency, TAK-243 allows for interrogation of ubiquitin biology and for assessment of UAE inhibition as a new approach for cancer treatment.

Nature Med 2018; 24: 186

Eitan Israeli

“The unreal is more powerful than the real, because nothing is as perfect as you can imagine it, because it's only intangible ideas, concepts, beliefs, fantasies that last. Stone crumbles, wood rots. People, well, they die. But things as fragile as a thought, a dream, a legend, they can go on and on”

Chuck Palahniuk (born 1962) American novelist and freelance journalist