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Idiopathic recurrent pericarditis – a new orphan autoinflammatory disease? A retrospective analysis of cases of idiopathic recurrent pericarditis and a design of a double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of RPH-104 treatment in patients with idiopathic recurrent pericarditis

Aim	To analyze cases of idiopathic recurrent pericarditis (IRP) in the structure of pericardial diseases of various origins from patient visits to the Multidisciplinary Federal Center.
Material and methods	A retrospective analysis of case records was performed for patients admitted to the V.A. Almazov National Medical Research Center from January 1, 2015 through January 1, 2020 for pericardial effusion of different etiologies.
Results	For the study period, 4 981 new cases of pericardial damage of different etiologies were found. Among these cases, postpericardiotomy syndrome accounted for 4 360 cases and pericarditis for 621 cases. IRP was detected in 34 cases, which amounted to 5.4%. Based on the study data, the estimated IRP prevalence in the Russian Federation can be 1.1 cases per 100 thousand population.
Conclusion	IRP should be regarded as a new autoinflammatory disease, the prevalence of which borders on that of adult Still disease and should be addressed within the concept of orphan diseases. Current knowledge of the pathogenesis and data from recent studies demonstrated a great importance of interleukin-1 blockade as a leading mechanism for achieving remission. This has justified conduction of a randomized clinical study at the Center.

Keywords	Idiopathic recurrent pericarditis; epidemiology; pathogenesis; orphan diseases; autoinflammatory diseases; inflammasome; interleukin-1; clinical study; interleukin-1β blocker
For citation	Myachikova V. Yu., Maslyanskiy A.L., Moiseeva O.M. Idiopathic recurrent pericarditis – a new orphan autoinflammatory disease? A retrospective analysis of cases of idiopathic recurrent pericarditis and a design of a double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of RPH-104 treatment in patients with idiopathic recurrent pericarditis. Kardiologiia. 2021;61(1):72–77. [Russian: Мячикова В. Ю., Маслянский А. Л., Моисеева О. М. Идиопатический рецидивирующий перикардит – новое орфанное аутовоспалительное заболевание? Ретроспективный анализ случаев идиопатического рецидивирующего перикардита и план рандомизированного, плацебо-контролируемого исследования для оценки терапевтической эффективности и безопасности блокатора ИЛ-1 (RPH-104). Кардиология. 2021;61(1):72–77]

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Introduction

Autoinflammatory diseases (AIDs) constitute a large and diverse group of pathologies resulting from a perturbation of the innate immune system (IS) [1]. Regardless of the nosology, all AIDs have several common manifestations: cyclic course (recurrences of different duration, often provoked by non-specific triggers), likely self-limiting course, episodes of febrile fever with duration depending on the nosology, laboratory signs of a systemic inflammatory reaction (neutrophilic leukocytosis) [2]. AID is based on the innate IS pathology leading to a recurrent course of sterile, local, or generalized inflammatory processes, usually triggered by non-specific factors. Some AIDs develop due to the inflammasome activation. Inflammasome is an intracellular compound organelle present in the cells of monocyte series and consisting of inactivated cytosol proteins that gather into a single macromolecular complex in response to the pathological stimulus [3]. The main function of the inflammasome is to trigger an inflammatory response due to a receptor-mediated signal, i.e., one of two types of triggers: pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [4].

The establishment of high clinical efficacy of interleukin-1 (IL-1) blocking agents was a breakthrough in the treatment of AIDs. Several blockers of IL-1 and its receptor (anakinra [5, 6], canakinumab [7, 8], rilonacept [9]) are approved in

ISSN 0022-9040. Kardiologiia. 2021;61(1). DOI: 10.18087/cardio.2021.1.n1475

the world to treat cryopyrin-associated periodic syndromes, TNF-alpha-receptor-associated periodic syndrome, hyperimmunoglobulin D syndrome, familial Mediterranean fever, adult Still's disease, systemic-onset juvenile idiopathic arthritis and Kawasaki disease [10–12]. It should be noted that the list of diseases is growing steadily [13].

The high clinical efficacy of IL-1 blockers in the treatment of AIDs pathogenetically associated with inflammasome activation created a perception of IL-1 driven diseases [14]. For example, one of the authors of this concept proposes the ex juvantibus diagnostic use of short-acting IL-1 blockers (anakinra) as the final stage of diagnosis verification in complicated cases [15].

Due to their low morbidity and prevalence, most AIDs are included in the international registries of rare diseases [16]. In this sense, idiopathic recurrent pericarditis (IRP), listed in the Orphanet rare disease nomenclature (ORPHAcode: 251307) in Systemic and Rheumatic Diseases in Adults and Children [17] is no exception. However, the rare status of this pathology is determined by the low prevalence of a specific disease in the population [18]. While in the European Union, the threshold prevalence for rare diseases is fewer than 5 cases per 10,000 people, the World Health Organization defines it as 6.5–10 cases per 10,000 people, while in the United States, a disease is only considered rare when it affects less than one in 200,000 citizens.

In the Russian Federation, the incidence of diseases considered rare is not more than 10 cases per 10,000 people. This definition is regulated by Article 44 of Federal Law No. 323 FZ «On Fundamental Healthcare Principles in the Russian Federation». Although many pathologies meet this criterion, only a few are included in the «24 Rare Specific Diseases» list. If a disease is registered as rare, patient records must be maintained involving expensive therapy and the obligatory search for new effective treatments. While the State Register of Diseases also concedes these goals, its relevance increases sharply when high-efficacy treatment methods are introduced into real-world practice.

Although idiopathic recurrent pericarditis is increasingly regarded as a rare autoinflammatory disease, its nomenclature, place in the international classification of diseases and definition was not altered following the new concept of pathogenesis.

The ESC definition of IRP is closely related to the concept of acute pericarditis and strict association with a light (asymptomatic) interval, which should be no less than 4 weeks [19]. However, this approach involves the risk of missing a second exacerbation of the disease within a month, due to mistaking it for part of the first episode. Since patients were selected based on the results of clinical investigations in the first clinical trial evaluating the efficacy of colchicine in preventing recurrent pericarditis (CORE-1 (2005–2011)), time to the onset of exacerbation was not considered [20]. The use of a time interval as the mandatory criterion for the diagnosis of IRP was first mentioned in the CORP-2 trial (2014), in which these parameters were used as patient selection criteria; here, the light period was equal to 6 weeks, which was not subject to change even following a more detailed study of the IRP pathogenesis [21]. Given recent insights about the pathogenesis of IRP and the role of autoinflammation in its development, it is the duration of exacerbation that becomes important rather than the duration of the asymptomatic period, which is in any case reflected in the criteria of other autoinflammatory diseases [19]. Thus, a contemporary definition of IPR can include the following statement: idiopathic recurrent pericarditis is a rare, sporadic autoinflammatory disease involving serous membranes (mainly the pericardium) in the pathological process. By regarding IRP as an AID, it becomes possible to abandon the interpretation of this pathology as a complication of acute pericarditis, as previously described by some authors [19]. The recurrent course involves the specific chronic nature of the autoinflammatory process from a pathophysiological point of view, bringing IRP closer to other AIDs that are closely associated with inflammasome activation [22].

In terms of IRP epidemiology, it should be pointed out that different variants of pericarditis account for 0.1% of all hospital admissions for chest pain. According to the ESC, recurrent pericarditis occurs within 18 months after the first episode in 20–30% of cases. According to Italian researchers, the prevalence of acute pericarditis is 27.7 per 100,000 people in the EU [19]. However, according to other estimations, the number of patients with IPR does not exceed 5.4–8.1 per 100,000 people in the EU. Meanwhile, in Russia, the prevalence of IPR in the population is unknown, since it is not possible to determine the number of patients having such a rare disease in the absence of a unified database. However, it is possible to calculate the estimated number of patients by using the annual hospitalization rate [23], percentage of hospitalization for chest pain accounting for pericarditis [19] and proportion of IRP accounting for the total pericarditis morbidity rate.

In order to analyze all exudative pericarditis cases within the incidence of visits to the multidisciplinary federal center and clarify the actual frequency of IRP, we performed a retrospective study.

Material and methods

All cases of hospitalization with pericardial effusion of various origin in patients over 18 years old were analyzed in a single medical database of the Almazov National Medical Research Center from January 1, 2015 to January 1, 2020. Heart transplant recipients were excluded from the study.

Patients were divided into 13 groups based on the cause of pericardial injury. The study was carried out following the Declaration of Helsinki.

Results

Retrospective analysis of more than 6,000 cases over the specified period revealed 4,981 new cases of pericardial injury of different origin, including 4,360 cases of post-pericardiotomy syndrome (PPS). Pericarditis accounted for 621 cases. The structure of different pericarditis origins is presented in Table 1.

Table 1. Structure of pericardial injuries in patients hospitalized from January 1, 2015 to January 1, 2020 in the Almazov National Medical Research Center

Parameters	n
Total number of patients, n	4981
PPS (early- and late-onset, recurrent), n	4360
Pericardial injury of different origin, n (%)	621 (100)
Hemopericardium, n (%)	113 (18.2)
Hydropericardium, n (%)	224 (36)
Early post-radiation pericarditis, n (%)	5 (0.8)
Constrictive pericarditis, n (%)	14 (2.3)
Pericardial metastases and primary pericardial malignancy, n (%)	63 (10)
Benign pericardial mass, n (%)	30 (4.8)
Idiopathic recurrent pericarditis, n (%)	34 (5.4)
Pericarditis associated with rheumatic disease, n (%)	112 (18)
Drug-induced pericardial injuries, n (%)	5 (0.8)
Chronic pericarditis, n (%)	14 (2.3)
Specific pericarditis, n (%)	7 (1.1)

PPS – post-pericardiotomy syndrome

Discussion

Admissions to the Almazov National Medical Research Center for IRP accounted for 5% of pericardial injuries (n=34). Such a low prevalence may be due to several factors:

1. The application of an integrated and multidisciplinary approach, identifying the origin of pericarditis to be other than IRP, which is known to be an exception.
2. Exclusion of patients with PPS following open-heart surgery, including its recurrences, from the analysis, since the contribution of humoral (acquired) immunity is considered to be a key factor of this disease. In other words, unlike IRP, PPS develops mainly as an autoimmune response, in which a failure of the primary immunity (autoinflammation) is considered to constitute the main pathogenic mechanism. Moreover, hospitalization was required for cardiac surgery, while early- or late-onset PPS was the result of such an intervention, not its cause.
3. The idea that, under the new concept, the development of IPR is associated with autoinflammation, in which almost all diseases appear to be rare.

Let us try to project the data on the general adult population. As of 2016, the total number of hospitalizations was 29,351,395, while the Russian population was estimated at 146,544,710 people. On this basis, the calculated number of patients with pericardial injuries was 29,351. Therefore, using the data obtained from the analysis of all hospital admissions for pericardial injuries in Russia, the number of patients with IRP (5.4%) should be about 1,585. Thus, the estimated prevalence of IPR would be 1.1 cases per 100,000 people of the Russian population. However, such an estimated prevalence cannot be considered to be true; such a fact could only be obtained by creating a national Russian register. Nevertheless, these data can inform further study of the disease and determine the need to include IPR in the Rare Disease Group in the Russian Federation.

In order to exclude other known causes of pericarditis from rheumatic diseases, IRP diagnosis requires a differential search: diffuse connective tissue disorders, vasculitis, inflammatory arthropathies and other AIDs. Given the similarity of symptoms (both clinical and laboratory), adult Still's disease (which is characterized, like IRP, by neutrophilic leukocytosis), a significant increase in acute phase indicators, including ferritin, should be initially excluded from all non-monogenic AIDs [24]. It should be noted that the existing classification criteria for IRP and adult Still's disease often do not permit the final differential diagnosis if Stiller's disease involves pericarditis [25]. Three monogenic AIDs manifesting as recurrent pericarditis should be excluded first: Mediterranean fever, TNF-alpha mutation-associated periodic syndrome and mevalonate kinase deficiency associated periodic syndrome. While these diseases can be ruled out using genetic tests, any failure to perform an adequate differential search will lead to an overestimation of the prevalence of IPR in the general population.

Like other APRs, the treatment of IRP is based on anti-inflammatory therapy. The commonly used combination of NSAIDs and colchicine produces good results in some cases [19]. However, this strategy has certain limitations: according to current guidelines, any attempt to cancel the therapy can be made only within 6 months from the beginning of therapy, which in most cases results in a recurrence requiring the therapy to be resumed. Long-term NSAID therapy is associated with an inevitable

ISSN 0022-9040. Kardiologiia. 2021;61(1). DOI: 10.18087/cardio.2021.1.n1475

increase in the rate of cardiovascular and gastrointestinal complications [26]. The long-term administration of colchicine is also associated with the development of gastrointestinal side effects, limiting the use of this group of drugs [27]. Absolute contraindications associated with kidney dysfunction typically occur. In 20–30% of cases, the detection of colchicine resistance requires long-term therapy with medium- and high-dose glucocorticoids, resulting in steroid-dependence and -resistance associated with cardiovascular complications, infections, osteoporosis, electrolyte disorders, steroid diabetes and secondary Cushing's syndrome [28].

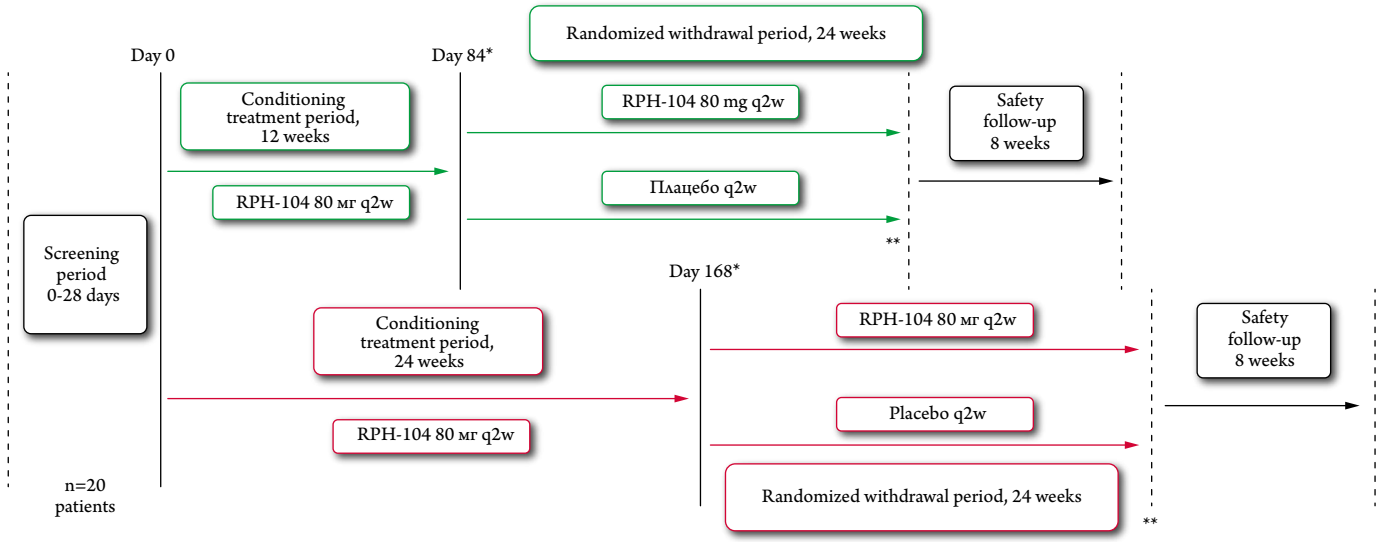
These obstacles can be overcome using anti-cytokine therapy recently introduced into clinical practice. In 2015, the AIRTRIP clinical trial (randomized, double-blind, placebo-controlled, multi-center, medication-withdrawal study to evaluate the efficacy, tolerability and safety of anakinra in adults and children with idiopathic recurrent pericarditis) was completed. This confirmed the efficacy and safety of the IRP treatment, justifying its inclusion in the AIDs group [29]. In June 2020, the third phase of the RHAPSODY trial (global, multi-center, double-blind, placebo-controlled and randomized withdrawal study with open-label extension to assess the efficacy and safety of rilonacept treatment in subjects with recurrent pericarditis) was completed. At that point, it was envisaged that approval of rilonacept indication for IRP would be granted in the United States at the end of 2020 [13].

This predetermined the development of the Russian IL-1β blocker RPH-104 and the carrying out of similar clinical studies in IRP patients in Russia. The developed molecule is a recombinant heterodimer hybrid protein that selectively binds and inactivates IL-1β, whose molecular weight at almost half that of the relevant analog implies better penetration into tissues. After all necessary in vitro and in vivo preclinical trials of the drug had been carried out, the clinical trial phase began.

The design comprises a double-blind, randomized, placebo-controlled 60-week clinical trial to assess the efficacy and safety of RPH-10480 mg administered subcutaneously twice-weekly to patients with IRP. The clinical trial consists of two parts: the initial period to unify the treatment (cancellation of colchicine and/or NSAIDs, cancellation of GCs), induction of clinical and laboratory remission using only the investigational drug, and the period of randomized cancellation. It should be noted that patients randomized to the placebo group who experience recurrent pericarditis had the opportunity to restart the treatment before the completion of this period. After the end of the randomized cancellation period, patients will be asked to continue participating in the open-label trial to evaluate the long-term safety and efficacy of RPH-104 for 50 more

ISSN 0022-9040. Kardiologiia. 2021;61(1). DOI: 10.18087/cardio.2021.1.n1475

Figure 1. Study design



*, randomization; **, transition into an open-label long-term study of RPH-104 safety and efficacy subject to patient's consent, 50 weeks.
Day 0 – the first administration of RPH-104; q2W, once every two weeks.
–> – previous treatment with NSAIDs and/or colchicine (monotherapy or combination).
–> – previous therapy with GCs (monotherapy or combination with NSAIDs and/or colchicine).

weeks. Patients who do not consent to further participation will continue to be monitored until the program is complete (Figure 1).

The study's primary endpoint is time (number of days) to recurrence within 24 weeks after randomization during the use of RPH-104 compared to placebo in patients with IRP. The trial started at the end of January 2020 in the Almazov National Medical Research Center. The national approval of the first Russian biological drug for IRP is expected following the trial.

The clinical trial was registered on ClinicalTrials.gov under the identification number NCT04692766.

No conflict of interest is reported.

The article was received on 24/11/2020

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