Impact of Prior Statin Therapy on 1-year Recurrence and Length of Hospitalization for Acute Idiopathic Pericarditis

William Nseir MD[1,2], Lior Masika MD[3], Adi Sharabi-Nov MD[4], and Raymond Farah MD[2,3]

[1]Department of Internal Medicine A, Padeh Medical Center, Poriya, Israel
[2]Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel
[3]Department of Internal Medicine B, Ziv Medical Center, Safed, Israel
[4]Tel Hai Academic College, Tel Hai, Israel

ABSTRACT **Background:** Statins have anti-inflammatory effects that are independent of their lipid-lowering activity.

Objectives: To examine whether prior statins therapy affects the clinical course of the first episode of acute idiopathic pericarditis (AIP) as the 1-year recurrence and length of hospitalization (LOH).

Methods: This retrospective study included 148 subjects with first episode AIP admitted between the years 2015 and 2019. Data were collected from two hospitals in Northern Israel. We divided the patients in into two groups: 117 those without statins use and 31 those with prior statins use. We compared age, sex, co-morbidities, drugs, laboratory data, 1-year recurrence, and LOH.

Results: The mean age of participants was 43.1 ± 19.4 years. Comparisons between subjects without statins and with prior statins use were made according to age (37.5 ± 16.7 years vs. 64.4 ± 12.7 years, $P < 0.01$), C-reactive protein (50 ± 40 vs. 48 ± 35 mg/dl, $P = 0.9$), LOH (5.4 ± 2.85 vs. 8.03 ± 4.92 days, $P < 0.01$), 1-year recurrence of pericarditis (23 vs. 6 cases, $P = 0.95$), respectively. Multivariate logistic regression analysis revealed that 1-year recurrence (odds ratio [OR] 0.8, 95% confidence interval [95%CI 0 0.6–1.1, $P = 0.41$), was not associated with prior statin use, while LOH (OR 2.56, 95%CI 2.08–2.75, $P = 0.01$) was prolonged with prior statins use in patients with first episode of AID.

Conclusions: Prior statins use in patients with the first episode of AIP did not reduce the 1-year recurrence of pericarditis and prolong the LOH.

IMAJ 2022; 24: 747–751

KEY WORDS: 1-year recurrence, acute idiopathic pericarditis (AIP), length of hospitalization (LOH), statins

Hydroxymethylglutaryl-coenzyme A reductase inhibitors or statins are potent lipid-lowering agents that reduce the risk of cardiovascular events in patients with diabetes mellitus, coronary artery disease, and other causes of atherosclerosis [1]. Although, the therapeutically beneficial effects of statins in these diseases are generally attributed to their cholesterol-lowering action, the results from an increasing number of in vitro and in vivo studies indicate that statins also have anti-inflammatory effects that are independent of their lipid-lowering activity [2-4]. Statins have also been reported to have immunomodulatory, anti-oxidative, and antithrombotic actions [5,6]. Several studies have investigated the effects of statins in patients with bacteremia, sepsis, bacterial pneumonia, psoriasis, rheumatoid arthritis, and bacterial infections such as Helicobacter pylori, and Clostridium difficile [7-12].

Acute pericarditis is an inflammatory disease of the pericardium. Most patients with acute pericarditis have either viral or idiopathic pericarditis. A viral etiology is often presumed, but evidence for this is not often sought due to the expense involved and the time required before the results of laboratory tests are available. The aims of treatment of acute pericarditis are to relieve chest pain and inflammation [13]. Patients with acute pericarditis who have major risk factors associated with poor prognosis, such as high fever, subacute course, evidence of large pericardial effusion, cardiac tamponade and failure to respond within 7 days to non-steroidal anti-inflammatory drugs (NSAID), require hospitalization. Moreover, patients with certain amount of minor risk factors, including pericarditis associated with myocarditis (myopericarditis), immunodepression, trauma, and on oral anticoagulant therapy should be hospitalized. All other patients should be managed as outpatients with empiric anti-inflammatory therapy [14,15].

The mainstay of therapy of acute pericarditis is NSAIDs, although colchicine has been demonstrated as a first-line drug to be added to conventional anti-inflammatory therapies with a first episode of pericarditis or recurrences [14].

Recurrent pericarditis is the most troublesome complication of the disease, occurring in 15% to 50% of cases despite the new drug regimens [15-17]. The optimal management for preventing recurrences has not been established [19].

Previously, a clinical randomized trial evaluated the safety and efficacy of the combination of indomethacin and statins compared with indomethacin plus placebo in patients with a first episode of pericarditis [20]. The authors showed that statins and indomethacin treatment in patients with pericarditis was feasible.

The aim of the present study was to assess in a retrospective, observational study if prior statins use could affect the clinical course of first episode of acute idiopathic pericarditis (AIP) presented in 1-year recurrence and length of hospitalization (LOH)

PATIENTS AND METHODS

This retrospective, observational cohort study was conducted at two medical centers: Ziv Medical Center, Safed, which serves the residents of Safed and the upper Galilee and has 320 beds, and Nazareth Hospital EMMS, Nazareth, a primary hospital with 150 beds. The study was approved by the local medical ethics committee of both hospitals. We enrolled consecutive patients with acute pericarditis who admitted to intensive care units and internal medicine departments at Ziv between January 2015 and December 2019, and EMMS from January 2015 and December 2017.

We included patients older than 18 years of age with a diagnosis of first episode of AIP. We excluded patients younger than 18 years, with metastatic disease, chronic renal failure defined as creatinine clearance test < 30 ml/min, history of rheumatoid arthritis, lupus, tuberculosis, inflammatory bowel disease, human immunodeficiency viruses, or recent chest trauma as well as those receiving radiation therapy. Readmission cases due to pericarditis were followed. Demographics, medical history, side and adverse events of drug therapy, and laboratory were collected. Moreover, age, sex, body temperature, blood pressure, and underlying diseases such as diabetes mellitus, hypertension, hyperlipidemia, cardiac diseases (ischemic heart disease, history of myocardial infarction, congestive heart failure, echocardiography, coronary angiography results) were collected. Data on all prescribed chronic drug use, duration, type, and adherence, especially for statins NSAIDs, aspirin, colchicine, and prednisone were recorded. Laboratory data on complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), chemistry, LOH, complications of pericarditis, readmissions because pericarditis, 1-year mortality, and the etiology of pericarditis were also collected. Any covariate in the medical information including laboratory or echocardiography findings that were not noted as present were noted as absent.

The first episode of AIP was diagnosed according to 2015 European Society of Cardiology (ESC) guidelines for the diagnosis and management of pericardial diseases [13]. AIP was diagnosed when at least two of the following criteria were met:

- Clinical presentation of fever, malaise, myalgia, retrosternal/left pericardial chest pain, shortness of breath, and rapid heart rate
- Physical examination finding of friction rub
- Classical electrocardiogram changes (widespread upward concave ST-segment elevation or PR-segment depression)
- Echocardiographic evidence of pericardial effusion
- Elevation of markers of inflammation (i.e., ESR, CRP, and white blood cell count)
- Evidence of pericardial inflammation by an imaging technique especially echocardiography and computed tomography (CT) to exclude malignancy or other causes.

We did not perform coronary angiography or magnetic resonance imaging that was not indicated. All patients were treated according by aspirin/NSAIDs, colchicine, or prednisone [Table 1].

We defined 1-year recurrence of pericarditis as the recurrence of pericarditis after a documented first episode of AIP and a symptom-free interval of 4–6 weeks within one year. Prior statins users were identified as individuals who were taking statins of any dose and any type daily for at least 12 weeks prior the AIP.

STATISTICAL ANALYSIS

Data were analyzed using WinSTAT. A 2-sided $P < 0.05$ was considered statistically significant. Continuous variables were expressed as the mean ± standard deviation. The chi-square test was used to test differences in categorical variables between the subjects with no statins use and prior statins use, and analysis of variance (ANOVA) or the t test was used for comparisons of continuous variables. Multivariate logistic regression analysis was used for identifying predictors of 1-year recurrence of pericarditis and LOH. All variables significantly associated with the outcome on univariate analysis, Spearman correlation ($P < 0.05$) were entered into a logistic regression analysis.

RESULTS

A total of 148 hospitalized adult patients with AIP of first episode were included. Patient data were collected from intensive care units and internal medicine departments from the two hospitals between January 2015 and December 2019.

CLINICAL CHARACTERISTICS OF STUDY POPULATION

The mean age of all study group was 43.1 ± 19.4 years; 117 were male (79%). Of 148 study subjects 21 (14.2%) presented with diabetes, 36 (24.3%) with hypertension, 45 (30.4%) with dyslipidemia, and 19 (12.8%) with ischemic heart disease. In addition, 64 (43.2%) were smokers. Patients were treated for AIP mainly by aspirin and NSAIDs with the addition of prednisone or colchicine. In 87 patients (58.8%) aspirin therapy was initiated, 58 patients (39.2%) received NSAIDs, colchicine was added in 44 patients (29.7%), and for 18 (12.2%) prednisone therapy was administered. Some 31 patients (21%) were chronic statins users (a period of more than 3 months of statins therapy).

Table 1. Demographic and clinical characteristics of 148 hospitalized patients for first episode of acute idiopathic pericarditis

Demographic and clinical characteristics	
Age, years (mean ± standard deviation)	43.1 ± 19.4
Sex (male, n (%)	117 (79.0)
Diabetes mellitus, n (%)	21 (14.2)
Hypertension, n (%)	36 (24.3)
Smoking history, n (%)	64 (43.2)
Dyslipidemia, n (%)	45 (30.4)
Ischemic heart disease, n (%)	19 (12.8)
At least two risk factors for IHD, n (%)	63 (42.6)
Three or more risk factors for IHD, n (%)	41 (27.7)
Aspirin initiation for pericarditis, n (%)	87 (58.8)
Prednisone initiation for pericarditis, n (%)	18 (12.2)
NSAIDs initiation for pericarditis, n (%)	58 (39.2)
Colchicine initiation for pericarditis, n (%)	44 (29.7)
Chronic statin use, n (%)	31 (21.0)
No pericardial effusion, n (%)	85 (57.0)
Mild pericardial effusion, n (%)	27 (18.2)
Moderate pericardial effusion, n (%)	19 (12.8)
Severe pericardial effusion, n (%)	17 (11.5)
Pericardiocenthesis, n (%)	15 (10.1)
One-year recurrence of pericarditis, n (%)	29 (19.6)
Length of hospitalization stay (days, mean ± standard deviation)	6.0 ± 3.6
One-year mortality, n (%)	1 (0.7)

IHD = ischemic heart disease, NSAID = nonsteroidal anti-inflammatory drugs

Simvastatin was the most common statin used by the study patients (simvastatin: 17, atorvastatin: 13, and one patient was on rosuvastatin). According to the results of repeated cardiac echography studies, we classified our cases of pericarditis according to the amount of pericardial effusion in four groups: no pericardial effusion 85 (57%), mild 27 (18.2%), moderate 19 (12.8%), and severe 17 (11.5%). Pericardiocentesis was performed in 15 patients (10.1%) the cause was idiopathic. One-year recurrence of AIP was observed in 29 subjects (19.6%). Mean LOH was 6.04 ± 3.56 days. One patient died within one year [Table 1]. Most of causes AIP were due to idiopathic (88/148, 59.46%) and viral infection (60/148, 40.54%), no other causes were identified.

COMPARISON BETWEEN THE TWO GROUPS OF NO STATINS AND STATINS USERS

There were significant differences between the two groups in age, male sex, and co-morbidities. Patients who were receiving statins were older and more often of male sex, diabetic, hypertensive, and with dyslipidemia. No significant differences seen concerning the mean CRP, mean ESR, type of drug therapy of AIP (aspirin, prednisone, NSAID, colchicine). The LOH of statins users was longer than those who did not use statins (8.03 ± 4.92 days versus 5.4 ± 2.85 days, $P < 0.01$) respectively. No significant difference was seen concerning the 1-year recurrence of pericarditis of first episode between subjects of no statins users and statins users, 23 patients (19.6%) vs. 6 patients (19.3%), $P = 0.95$, respectively [Table 2].

Table 2. Demographic and clinical characteristics: comparison between the two groups of prior statin use and no statin use

Clinical factors	No statin use (n=117)	Prior statins use (n=31)	*P* value
Age, years (mean ± SD)	37.5 ± 16.7	64.4 ± 12.7	< 0.001
Male sex (%)	97 (82.9)	20 (64.5)	0.036
Diabetes (%)	9 (7.7)	12 (38.7)	< 0.001
Hypertension (%)	17 (14.5)	19 (61.3)	< 0.001
Smoking (%)	50 (42.7)	14 (45.0)	0.80
Dyslipidemia (%)	16 (13.7)	29 (93.5)	< 0.001
Ischemic heart disease (%)	9 (7.7)	10 (32.0)	< 0.001
Aspirin initiation (%)	66 (56.4)	21 (67.7)	0.25
Prednisone initiation (%)	14 (12.0)	4 (13.0)	0.88
NSAIDs initiation (%)	49 (41.9)	9 (29.0)	0.19
Colchicine (%)	33 (28.2)	11 (35.4)	0.43
Chronic statin use (%)	–	31 (21.0)	–
Simvastatin 40 mg	–	17 (55.0)	–
Atorvastatin 20 mg	–	13 (13.6)	–
Rosuvastatin 10 mg	–	1 (3.2)	–
Side effects of drugs (%)			
Epigastric pain	17 (14.5)	4 (12.9)	0.52
Nausea	10 (8.5)	3 (9.7)	0.46
Myalgia	18 (15.3)	6 (19.3)	0.25
Diarrhea	16 (13.7)	4 (12.9)	0.49
CRP, mg/dl (mean ± SD)	50 ± 40	48 ± 35	0.9
ESR, mm/hour (mean ± SD)	40± 20	3.4 ± 28	0.32
Lymphocyte cells/µl (mean ± SD)	1.64 ± 0.66	1.74 ± 0.75	0.483
Length of hospitalization (mean ± SD) in days	5.4 ± 2.9	8.0 ± 4.9	< 0.01
1-year recurrence of pericarditis (%)	23 (19.6)	6 (19.3)	0.95

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, NSAID = nonsteroidal anti-inflammatory drugs, SD = standard deviation

Table 3. Demographic and clinical characteristics of a sample of 18 patients with and without prior statin use, matched in age ± 5 years and sex

Clinical factors	No statin use (n=18)	Prior statin use (n=18)	*P* value
Age, years (mean ± SD)	55.8 ± 4.5	55.4 ±3.1	0.31
Male sex (%)	16 (88.8)	16 (88.8)	1
Diabetes (%)	6 (33.3)	2 (11)	0.25
Hypertension (%)	12 (66.6)	6 (33.3)	0.15
Smoking history (%)	8 (44.4)	8 (44.4)	1
Dyslipidemia (%)	4 (22.2)	18 (100)	< 0.001
Ischemic heart disease (%)	0 (0)	8 (44.4)	0.02
Aspirin initiation (%)	16 (88.8)	12 (66.6)	0.25
Prednisone initiation (%)	14 (77.7)	17 (100)	0.13
NSAIDs initiation (%)	0 (0)	4 (22.2)	0.13
Colchicine (%)	4 (22.2	8 (44.4)	0.31
CRP, mg/dl (mean ± SD)	78.5 ± 60	21.5 ± 30	0.003
ESR, mm/hour (mean ± SD)	56.7 ± 18	45.6 ± 12	0.27
Lymphocyte cells/μl (mean ± SD)	1.81 ± 0.9	1.85 ± 0.59	0.20
Length of hospitalization (mean ± SD) days	4.4 ± 1	8.7 ± 1.4	< 0.001
1-year recurrence of pericarditis (%)	3 (33.3)	4 (44.4)	0.94

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, NSAIDs = nonsteroidal anti-inflammatory drugs, SD = standard deviation

COMPARISON BETWEEN THE TWO GROUPS OF NO STATINS AND STATINS USERS OF A SAMPLE OF 36 SUBJECTS MATCHED IN AGE ± 5 YEARS AND SEX

As expected, statin users were older and with more co-morbidities in comparison with no statin users. Therefore, in order to prevent any statistical bias, we compared between two groups of no statins and statins users of a sample of 36 subjects matched in age ± 5 years and sex [Table 3]. We found a significant differences between the two groups in term of: CRP levels were higher among the no statins users from that of prior statins users ($P = 0.003$), and the LOH of statins users was longer than those who did not use statins (8.7 ± 1.4 days versus 4.4 ± 1 days, $P < 0.001$) respectively. We did not find any significant differences in term of: co-morbidities(excluding the dyslipidemia, subjects with prior statin use in general suffer from dyslipidemia),drug therapy for AIP, mean ESR, mean lymphocyte, and 1-year recurrence of pericarditis.

PREDICTORS FOR 1-YEAR RECURRENCE OF PERICARDITIS AND LOH

Multivariate logistic regression analysis was used for identifying predictors of 1-year recurrence of pericarditis and LOH. After adjustment for differences in baseline characteristics, multivariate logistic regression analysis revealed that prior use of statins (odds ratio [OR] 0.8, 95% confidence interval [95%CI] 0.6-1.1, $P = 0.41$ was not associated with 1-year recurrence in patients with first episode of AIP [Table 4]. Prior statins use OR 2.56, 95%CI 2.08-2.75, $P = 0.01$, prolonged the LOH of patients with AIP of first episode [Table 4].

DISCUSSION

With this observational study, we showed that prior statins use in patients with first episode of AIP did not reduce the 1-year recurrence and even prolong the LOH.

Statins as pleiotropic agents have been used in different inflammatory diseases as adjuvant therapy. A previous randomized clinical trial (RCT) evaluated the safety and efficacy of the combination of indomethacin and statins compared with indomethacin plus placebo in 55 consecutive patients with a first episode of pericarditis [20]. The authors showed that statins and indomethacin treatment in patients with pericarditis was feasible, with a significant reduction in inflammatory markers and in hospitalization time. No studies have evaluated the anti-inflammatory effect of statins in acute pericarditis in over a decade.

Recurrence of pericarditis is one of the most common complications of AIP affecting one-third of patients after a first attack of pericarditis [21]. Traditional therapy of recurrences is based mainly on anti-inflammatory therapies with colchicine as adjuvant [15]. Recently, immunotherapies have been considered in the treatment of idiopathic recurrent pericarditis in adult populations [22]. Our study showed that prior statins use in patients with first episode of AIP and during their illness did not reduce the 1-year recurrence. There is a need for randomized clinical trials with a large number of patients to assess the clinical outcome of statins in AIP.

In our study, we also examined the effect of prior statin use in patients with first episode of AIP on the LOH. Our results showed a contrary result from the previous RCT concerning the LOH [20]. Although, in the previous RCT the outcome of LOH was not statistically significant but had a trend toward some significance results. It is difficult to compare the two studies because they differ in term of study population regarding the demographic, clinical characteristics and type of pericarditis therapy. The mean age of the patients with statins therapy in our study was older than the patients who received statin in the RCT. Moreover, patients with prior statins therapy in our study had more cardiovascular diseases. According to our results, it seems that prior statins use prolongs the LOH in patients with first episode of AIP [Table 4]. The cause of longer hospitalization time was due to pericarditis itself and not due to complication of co-morbidities. There is a need for more studies to assess the effect of statins on LOH in AIP.

Table 4. Multivariate logistic regression analysis of 1 year of first episode of acute idiopathic pericarditis

Predictors	Odds ratio	95% confidance interval	*P* value	Odds ratio	95% confidance interval	*P* value
	1-year recurrence of first episode of acute idiopathic pericarditis			Length of hospitalization		
Age (years)	0.54	0.01–1.8	0.58	0.62	0.01–1.8	0.58
Hypertension	0.7	0.39–1.04	0.48			
Chronic statin use	0.8	0.6–1.1	0.41			
NSAIDs	1.3	1.1–1.5	0.01			
Prednisone	1.01	0.9–1.2	0.31			
More than 3 risk factors for IHD				0.05	0.31–0.7	0.50

NSAIDs = nonsteroidal anti-inflammatory drugs, IHD= ischemic heart disease

LIMITATIONS

The small number of patients with prior statins use compared to the number of patients without statin use (almost 4 times more) created two unequal groups and is considered a limitation. Moreover, subjects who used statins were older and with more co-morbidities than those with no statins. Therefore, to prevent any statistical bias, we compared two groups of no statins and statins users of a sample of 36 subjects (18 subjects in each group) matched in age ± 5 years, sex, diabetes, hypertension, and smoking history [Table 3]. We found the same results in all study group. The LOH of statins users was longer than those who did not use statins and no significant difference was seen concerning the 1-year recurrence of pericarditis with first episode between subjects of no statins users and statins users. Our patients have received different therapies of diverse durations, which may affect the outcome of our study and was difficult to introduce the duration of drug therapy in final analysis.

CONCLUSIONS

Prior statins use in patients with first episode of AIP and during the episode receiving traditional therapy for pericarditis did not reduce 1-year recurrence and prolong the LOH stay. There is a need for more studies, especially randomized clinical trials with large number of patients, to assess the clinical and therapeutic effects of prior statins use in AIP.

Correspondence

Dr. W. Nseir
Dept. of Internal Medicine A, Padeh Medical Center, Poriya 15208, Israel
Phone: (972-4) 665-2685
Fax: (972-4) 665-2929
email: wnseir@poria.health.gov.il

References

1. National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation* 1994; 89: 1333-45.
2. Weitz-Schmidt G. Statins as anti-inflammatory agents: *Trends Pharmol Sci* 2002; 23: 482-6.
3. Bu DX, Griffin G, Lichtman AH. Mechanisms for the anti-inflammatory effects of statins. *Curr Opin Lipidol* 2011; 22: 165-70.
4. Diomede L, Albani D, Sottocorno M, et.al. In vivo anti-inflammatory effect of statins is mediated by nonsterol mevalonate products. *Arterioscler Thromb Vasc biol* 2001; 21: 1327-32.
5. Halcox JP, Deanfield JE. Beyond the laboratory: clinical implications for statin pleiotropy. *Circulation* 2004; 109: 1142-8.
6. Sakabe K, Fukuda N, Wakayama K, Nada T, Shinohara H, Tamura Y. Lipid-altering changes and pleiotropic effects of atorvastatin in patients with hypercholesterolemia. *Am J Cardiology* 2004; 94: 497-500.
7. Nseir W, Khateeb J, Abu-Elheja O, Bishara J, Assy N. The impact of prior long-term versus short-term statin use on the mortality of bacteraemic patients. *Infection* 2012; 40: 41-8.
8. Dublin S, Jackson ML, Nelson JC, Weiss NS, Larson EB, Jackson LA. Statin use and risk of community acquired pneumonia in older people: population based case-control study. *BMJ* 2009; 338: b2137.
9. Chodick G, Weitzman D, Shalev V, Weil C, Amital H. Adherence to statins and the risk of psoriasis: a population-based cohort study. *Br J Dermatol* 2015; 173480-7.
10. Chodick G, Amital H, Shalem Y, et al. Persistence with statins and onset of rheumatoid arthritis: a population-based cohort study. *Plos Med* 2010; 7 (9): e1000336
11. Nseir W, Diab H, Mahamid M, et al. Randomized clinical trial: simvastatin as adjuvant therapy improves significantly the Helicobacter pylori eradication rate-a placebo-controlled study. *Aliment Pharmacol Ther* 2012; 36: 231-8.
12. Nseir W, Bishara J, Mograbi J, et al. Do statins against the development of Clostridium difficile-associated diarrhea? *J Antimicrob Chemother* 2013; 68: 1889-93.
13. Imazio M, Gaita F. Diagnosis and treatment of pericarditis. *Heart* 2015; 101: 1159-68.
14. Spodick DH. Acute pericarditis: current concepts and practice. *JAMA* 2003; 289: 1150-3.
15. Adler Y, Charron P, Imazio M, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases. *Eur Heart J* 2015; 36: 2921-64.
16. Schifferdecker B, Spodick DH. Nonsteroidal anti-inflammatory drugs in the treatment of pericarditis. *Cardiol Rev* 2003; 11: 211-7.
17. Imazio M, Bobbo M, Cecchi E, et al. Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (Colchicine for REcurrent pericarditis) trial. *Arch Intern Med* 2005; 165: 1987-91.
18. Imazio M, Brucato A, Cemin R, et al. Colchicine for recurrent pericarditis (CORP): a randomized trial. *Ann Intern Med* 2011; 155: 409-14.
19. Imazio M, Belli R, Brucato A, et al. Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicenter, double-blind, placebo-controlled, randomized trial. *Lancet* 2014; 383: 2232-7.
20. Di Pasquale P, Cannizzaro S, Fasullo S, et al. Combination of indomethacin and statin compared with indomethacin and placebo in patients with a first episode of acute pericarditis: preliminary findings. *Clin Sci* (Lond) 2007; 113: 443-8.
21. Soler-Soler J, Sagrista-Sauleda J, Pennanyer-Miralda G. Relapsing pericarditis. *Heart* 2004; 90: 1364-8.
22. Imazio M, Battaglia A, Gaido L, Gaita F. Recurrent pericarditis. *Rev Med Interne* 2017; 38: 307-11.
23. Schwier NC, Hale GM, Davies ML. Treatment of Adults with Idiopathic Recurrent Pericarditis: Novel Use of Immunotherapy. *Pharmacotherapy* 2017; 37: 305-18.