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COMPLEX ISSUES IN THE MANAGEMENT OF PERICARDITIS. IN ANTICIPATION OF THE RELEASE OF UPDATED RECOMMENDATIONS OF THE EUROPEAN SOCIETY OF CARDIOLOGY

With the advent of new diagnostic and therapeutic methods, the management of pericarditis has not become an easier task. The well-studied, but currently rare tuberculosis, bacterial and malignant forms have been joined by pericarditis associated with infection or vaccination against SARS-CoV-2. While 2–3 years ago, cardiologists had to recall the schedule of managing acute viral pericarditis, today its complications are often encountered, including chronic, recurrent, effusive or constrictive pericarditis. The European guidelines were updated 10 years ago and are expected to be issued within the next year. We posed the most pressing questions on the management of pericarditis to the coordinator of the 2015 European Society of Cardiology (ESC) guidelines [1], who will also chair the 2025 ESC guidelines on myocarditis and pericarditis, one of the most cited scientists in the field of inflammatory diseases of the pericardium, Massimo Imazio. He is a Professor in the Department of Cardiology and Anatomy at the University of Turin, runs a school on pericarditis, and has initiated fundamental research of this pathology. We presented his answers with comments of the co-author in the form of a short interview.

Keywords Pericarditis; guidelines; complexities of therapy; colchicine

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– Prior to the publication of data showing that pericarditis was associated with high mortality in patients with COVID-19 [2], there was a perception that myocarditis represented a more serious disease, with pericarditis being underestimated. Was this also the case for you?

– This assertion is indeed accurate. Pericarditis, like myocarditis, has long been a cardiovascular «Cinderella disease», that is, a condition that has been underestimated by the medical community. However, the advent of the COVID-19 pandemic has helped to raise awareness of these fairly common conditions in clinical practice.

– In our practice, there were only a few cases of pericarditis in the context of vaccination with Russian vaccines [3]. How would you assess the prevalence of pericarditis and myocarditis associated with SARS-CoV-2 vaccination in Italy?

– A recent study conducted in Lombardy revealed that the incidence of myocarditis was 9.9 cases per million person-months within the first 28 days after the introduction of vaccines from different manufacturers and 5.2 cases per million person-months in the absence of vaccination. The incidence of pericarditis was 19.5 and 15.9 cases per million person-months, respectively [4].

Comment

In this study, the risk of myocarditis was found to be particularly elevated following the administration of the second dose of the Moderna vaccine (adjusted hazard ratio (HR) 5.5, 95% confidence interval (CI) 3.7–8.1), while it was lower following the first dose of Moderna (adjusted HR 3.5, 95% CI 2.1–6.1) and following the administration of both the first and second doses of the Pfizer-BioNTech vaccine (adjusted HR 1.5, 95% CI 1.1–2.2). The administration of the first and second doses of Moderna was associated with an elevated risk of pericarditis (adjusted HR and 95% CI 1.6, 1.0–2.5 and 2.2, 1.5–3.1, respectively). The authors call for a comparison of these data with the risk of myocarditis and pericarditis following acute COVID-19 disease, which, as shown in a recent cohort study in the United States, are 5.38 and 1.85 times higher, respectively, than in the control group [5]. It is also noteworthy that adenoviral vector-based vaccines did not elevate the risk of pericarditis or myocarditis.

– The most significant point of contention is the question of which form of pericarditis should be classified as idiopathic. In view of the high prevalence of post-COVID-19 cases, the majority of medical centers are lacking the requisite resources to conduct comprehensive diagnostic investigations. Consequently,

we largely adhere to the 2015 guidelines and your work, which provides the definition of idiopathic pericarditis of unidentified origin. Nevertheless, there are those who maintain that secondary causes should be excluded as much as possible and that only orphan cases should be considered idiopathic. Has this issue been the subject of discussion within your medical community?

– Yes, it has. In Italy, the term «idiopathic pericarditis» is used when secondary causes have been excluded within the scope of available diagnostic investigations. It is important to note that in the majority of cases, the therapeutic approach remains largely consistent. The majority of patients are treated with non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine.

– What is the standard of care for patients with pericarditis (both acute and recurrent) in clinical practice in Italy?

– In Italy, the 2015 ESC guidelines are followed. Our scientists made a substantial contribution to the development of these guidelines (I served as the coordinator of the 2015 ESC guidelines and have been appointed as a chairperson of the 2025 ESC guidelines on myocarditis and pericarditis) [1]. NSAIDs in combination with colchicine represent the first-line treatment, with corticosteroids being the second-line treatment. In the event that patients develop corticosteroid-dependent and colchicine-resistant forms, we administer anakinra.

– What is the prevalence of non-inflammatory forms of pericarditis within the context of your clinical practice? In the treatment of such patients, is colchicine administered initially, or are hormones promptly initiated?

– In Italy, approximately 80% of patients with pericarditis present with an inflammatory phenotype. Our treatment approach remains consistent regardless of whether the phenotype is inflammatory or non-inflammatory.

Comment

The term «non-inflammatory phenotype» is used to describe cases of pericarditis or rheumatological diseases that occur without the presence of humoral inflammatory activity. In many cases, this is a chronic form of pericarditis or a recurrent exacerbation of the disease. Such patients are often misdiagnosed and are managed with a diagnosis of «psychogenic pain.» Although it is estimated that C-reactive protein (CRP) negative pericarditis accounts for approximately 22% of cases even in the acute pericarditis population, this can also be attributed to early blood sampling or previous anti-inflammatory therapy in this group [6].

– The patient presented with a newly identified pericardial effusion, with no evidence of inflammatory activity according

to the results of the blood tests and magnetic resonance imaging (MRI). No obvious secondary causes for the effusion were identified. Would you consider administering colchicine or adopting a watchful waiting approach?

– In patients with simple hydropericardium without documented inflammation, the administration of anti-inflammatory therapy is typically ineffective. In the event of suspected pericarditis, however, we will try this therapeutic approach.

Comment

The current diagnostic criteria for pericarditis require the presence of two or more of the following: chest pain, abnormal electrocardiographic findings, pericardial effusion, and pericardial rub. Confirmation may be conducted through laboratory or multimodal procedures. However, if the fundamental criteria are satisfied, these supplementary approaches are optional [1].

– A further significant challenge is the choice of appropriate treatment for patients with rheumatological diagnoses who have achieved clinical and laboratory remission of the underlying disease in response to targeted therapy, but who present with clinical and echocardiographic evidence of pericarditis. It is understandable that rheumatologists are reluctant to incorporate colchicine into therapeutic regimen in numerous cases. How do you achieve a mutually acceptable compromise?

– If it is deemed that the episode is related to the underlying disease, the baseline treatment is increased; conversely, if it is determined that pericarditis is not related to the systemic disease, it is treated as «idiopathic pericarditis.»

Comment

Statistical data indicates that patients with immunoinflammatory diseases exhibit pericardial lesions in 5 to 80% of cases, with the prevalence varying depending on the principal diagnosis [7].

– How often can pericarditis without an identifiable effusion be diagnosed by echocardiography? Do sonographers employ the term «hyperechoic» when describing fibrinous pericarditis?

– Our data indicate that «dry» pericarditis is present in 40–50% of cases [8]. The term «hyperechoic» is frequently employed by sonographers to describe this phenomenon. Sometimes these findings correlate with signs of pericardial inflammation, particularly pericardial edema.

– How often an MRI is required to confirm pericarditis? Approximately what percentage of cases involve the performance of an MRI in conjunction with an echocardiogram? Is it always T mapping?



Лечение острого и рецидивирующего перикардита с контролем дозировки (1 мг с риской)



ЕВРОПЕЙСКОЕ ОБЩЕСТВО КАРДИОЛОГОВ (ESC) РЕКОМЕНДУЕТ КОЛХИЦИН В КАЧЕСТВЕ ПРЕПАРАТА 1-Й ЛИНИИ ПРИ ТЕРАПИИ ПЕРИКАРДИТОВ В СОЧЕТАНИИ С АСК или НПВП ^{1,2,3,4,5}

- Колхицин в сочетании с АСК достоверно снижает на 33,3% частоту рецидивов острого перикардита по сравнению с монотерапией АСК (11,7%)⁶
- Колхицин в сочетании с АСК достоверно купирует симптомы рецидивирующего перикардита в течении $17,2 \pm 12,2$ мес.⁷
- Колхицин в комбинации с АСК или НПВС на 78% предотвращает риск возникновения будущих эпизодов перикардита по сравнению с сочетанием АСК или НПВС с плацебо⁸

1. Adler Y., Charron P., Imazio M., Badano L., Barón-Esquivias G., Bogaert J., Brucato A., Gueret P., Klingel K., Lionis C., Maisch B., Mayosi B., Pavie A., Ristic A.D., Sabaté Tenas M., Seferovic P., Swedberg K., Tomkowski W. ESC Scientific Document Group. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: the task force for the diagnosis and management of pericardial diseases of the European Society of Cardiology (ESC). Eur Heart J 2015; 36(42): 2921–2964, <https://doi.org/10.1093/eurheartj/ehv318>. 2. Клинические рекомендации МЗРФ «Перикардиты»–2022, 145 с. 3. Imazio M., Gribaudo E., Gaita F. Recurrent pericarditis. Prog Cardiovasc Dis 2017; 59(4): 360–368, <https://doi.org/10.1016/j.pcad.2016.10.001>. 18. 4. Ismail T. F. Acute pericarditis: update on diagnosis and management. Clin Med (Lond) 2020; 20(1): 48–51, <https://doi.org/10.7861/clinmed.cme.20.1.4>. 5. Tuck B.C., Townsley M. M. Clinical update in pericardial diseases. J Cardiothorac Vasc Anesth 2019; 33(1): 184–199, <https://doi.org/10.1053/j.jvca.2018.04.003>. 6. Massimo Imazio, Marco Bobbio, Enrico Cecchi, Daniela Demarie, Brunella Demichelis, Franco Pomari, Mauro Moratti, Gianni Gaschino, Massimo Giammaria, Aldo Ghisio, Riccardo Belli, Rita Trinchero Colchicine in addition to conventional therapy for acute pericarditis: results of the COLchicine for acute PERicarditis (COPE) trial 005 Sep 27;112(13):2012–6. 7. Massimo Imazio, MD; Marco Bobbio, MD; Enrico Cecchi, MD; et al Colchicine as First-Choice Therapy for Recurrent Pericarditis Results of the CORE (Colchicine for REcurrent pericarditis) Trial 2005;165(17):1987–1991. 8. Massimo Imazio, Riccardo Belli, Antonio Brucato, Roberto Cemin, Stefania Ferrua, Federico Beqaraj, Daniela Demarie, Silvia Ferro, Davide Forno, Silvia Maestroni, Davide Cumetti, Ferdinando Varbella, Rita Trinchero, David H Spodick, Yehuda Adler Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicentre, double-blind, placebo-controlled, randomised trial 2014 Jun 28;383(9936):2232–7.

– In Italy, as in many other European countries, access to MRI is limited. MRI is employed in complex or atypical cases with uncertain diagnoses, accounting for approximately 15% of patients with pericarditis at our cardiac center. In such instances, mapping is not necessary for the differential diagnosis. At our medical center, such an opportunity exists, yet it is utilized for the assessment of the myocardium.

– *Do you use blood tests for interleukin (IL) – 1, IL1 receptor, or IL-18 in the treatment of pericarditis? If you do, please specify the cases in which you do so. Do you investigate other cytokines or inflammatory factors in addition to CRP and erythrocyte sedimentation rate (ESR)?*

– At present, the measurement of interleukins in clinical practice is not accepted, not established, not recommended, and not practiced. In clinical practice, the use of C-reactive protein, ESR, and serum amyloid-A is standard practice.

– *It would be interesting to know whether there is a significant number of general practitioners and cardiologists who are reluctant to prescribe colchicine, and instead defer this authority exclusively to rheumatologists.*

– Colchicine is currently employed with greater frequency by cardiologists, and in Italy it has been approved for the indication «pericarditis» and is provided by the National Health System.

– *What is the procedure for patients with idiopathic pericarditis in Italy with regard to the use of IL-1 inhibitors? Is the drug approved by the relevant regulatory authority? If it is prescribed off label, is a specialized consultation required, or is it prescribed in the same manner as colchicine?*

– In Italy, anakinra can be provided by the National Health System in accordance with a special law (Law 648), which permits the off-label use of a drug with proven efficacy and no alternative options. This is applicable to patients who are dependent on corticosteroids and resistant to colchicine.

– *Do you have experience prescribing colchicine to patients with extracardiac tumors and symptomatic pericarditis?*

– For such patients, a combination of steroids and colchicine may be prescribed as palliative therapy to prevent or limit recurrent cardiac tamponade.

– *Does polyserositis associated with chemotherapy necessitate active management or it can be safely left to resolve spontaneously?*

– These cases may be symptomatic. I recommend treatment for such patients in cases of pericarditis.

– *In the 2021 guidelines for the prevention of cardiovascular diseases, colchicine is classified as a class 2b drug. Are*

there many patients in your practice who receive it for the management of coronary heart disease (CHD)? What kind of patients are these?

– This was a very modest recommendation. The drug in question is usually used in cases of class I or IIa indications. I consider these guidelines to be erroneous. In the United States, however, colchicine has been approved by the FDA for the same indications. In Italy, colchicine is prescribed off-label for the prevention of cardiovascular events, particularly in patients with recurrent events despite the adequate control of common risk factors. It is our hope that colchicine will be approved for this indication in the near future, thereby increasing the likelihood of its being prescribed in accordance with the approved indication. In clinical trials (LoDoCo-2 [9] and COLCOT [10]), colchicine was administered to all patients in conjunction with standard anti-inflammatory therapy, irrespective of CRP levels.

Comment

The LoDoCo-2 study (n = 5522) included patients with chronic stable CHD (84% of whom had a previous history of acute coronary syndrome [ACS]) who were treated with colchicine 0.5 mg/day versus placebo. The follow-up period lasted 29 months. Consequently, the primary endpoint (cardiovascular death, myocardial infarction, ischemic stroke, or coronary revascularization due to ischemia) in the colchicine group was observed to occur 31% less frequently. In the COLCOT study (n = 4745), colchicine was administered to patients within 30 days of myocardial infarction (MI) in conjunction with standard optimal therapy. At the 23-month follow-up point, a 50% reduction in the risk of acute coronary syndrome, a 76% reduction in the risk of cerebral stroke, a 16% reduction in the risk of cardiovascular death, and a 17% reduction in the risk of recurrent myocardial infarction were observed in comparison with the placebo group. A cost-benefit analysis conducted after 20 years of observation revealed that the incorporation of colchicine into the standard treatment regimen resulted in a 47% reduction in total costs per patient and an increase in quality-of-life-adjusted life expectancy from 1.30 to 1.34. A further reduction in costs per patient per lifetime was achieved, amounting to a 69% decrease [11].

– *When may an update to the guidelines for the treatment of pericarditis be anticipated?*

– It is anticipated that the ESC Guidelines will be updated in 2025. The development of the guidelines is currently underway. Once they have been published, I will be available to discuss the topic.

Conclusion

The interview revealed a consensus regarding the significance of pericarditis as a clinical problem and the challenges associated with its management in contemporary medical practice. We would like to express our gratitude to Mr. Imazio for his contributions to elevating the status of this «Cinderella disease» to a nosology worthy of attention. Furthermore, we would like to acknowledge his

efforts in developing structured diagnostic and therapeutic approaches to this condition.

Interviewer Z.N. Sukmarova

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REFERENCES

1. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). *European Heart Journal*. 2015;36(42):2921–64. DOI: 10.1093/eurheartj/ehv318
2. Li P, Shi A, Lu X, Li C, Cai P, Teng C et al. Incidence and Impact of Acute Pericarditis in Hospitalized Patients With COVID-19. *Journal of the American Heart Association*. 2023;12(20):e028970. DOI: 10.1161/JAHA.122.028970
3. Sukmarova Z.N., Ovchinnikov Yu.V., Gudima G.O., Ibragimova F.M., Afonina O.V., Machkalyan K.E. Hyperechogenic signal from the pericardium after vaccination against SARS-CoV-2. *Infectious diseases*. 2021;19(4):43–50. [Russian: Сукмарова З.Н., Овчинников Ю.В., Гудима Г.О., Ибрагимова Ф.М., Афонина О.В., Мачкалян К.Э. Усиление эхо-сигнала от перикарда у реципиентов вакцин против SARS-CoV-2. *Инфекционные болезни*. 2021;19(4):43–50]. DOI: 10.20953/1729-9225-2021-4-43-50
4. Corrao G, Franchi M, Cereda D, Bortolan F, Leoni O, Vignati E et al. Increased risk of myocarditis and pericarditis and reduced likelihood of severe clinical outcomes associated with COVID-19 vaccination: a cohort study in Lombardy, Italy. *BMC Infectious Diseases*. 2022;22(1):844. DOI: 10.1186/s12879-022-07823-3
5. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nature Medicine*. 2022;28(3):583–90. DOI: 10.1038/s41591-022-01689-3
6. Imazio M, Brucato A, Maestroni S, Cumetti D, Dominelli A, Natale G et al. Prevalence of C-Reactive Protein Elevation and Time Course of Normalization in Acute Pericarditis: Implications for the Diagnosis, Therapy, and Prognosis of Pericarditis. *Circulation*. 2011;123(10):1092–7. DOI: 10.1161/CIRCULATIONAHA.110.986372
7. Imazio M. Pericardial involvement in systemic inflammatory diseases. *Heart*. 2011;97(22):1882–92. DOI: 10.1136/heartjnl-2011-300054
8. Imazio M, Demichelis B, Parrini I, Giuggia M, Cecchi E, Gaschino G et al. Day-hospital treatment of acute pericarditis: a management program for outpatient therapy. *Journal of the American College of Cardiology*. 2004;43(6):1042–6. DOI: 10.1016/j.jacc.2003.09.055
9. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease. *Journal of the American College of Cardiology*. 2013;61(4):404–10. DOI: 10.1016/j.jacc.2012.10.027
10. Tardif J-C, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *New England Journal of Medicine*. 2019;381(26):2497–505. DOI: 10.1056/NEJMoa1912388
11. Samuel M, Tardif J-C, Khairy P, Roubille F, Waters DD, Grégoire JC et al. Cost-effectiveness of low-dose colchicine after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT). *European Heart Journal - Quality of Care and Clinical Outcomes*. 2021;7(5):486–95. DOI: 10.1093/ehjqcco/qcaa045