Janet Kloos, RN, PhD, APRN-CCNS, CCRN (00:06):

Hello and good afternoon. Welcome to the American Heart Association's Recurrent Pericarditis podcast series. This is a part of a series of podcasts, beginning with diagnosis of acute pericarditis, its treatment and complications, recurrent pericarditis, the pathophysiology, cornerstone agents, and late breaking therapies that include IL-1 blockade. Our topic for today is long-term complications of recurrent pericarditis.

(00:41):

I'm Janet Kloos. I'm a clinical nurse specialist at University Hospital Cleveland Medical Center in the cardiac ICU. Next, Dr. Luis will introduce himself.

S. Allen Luis, MD (00:54):

My name is Allen Luis. I am the co-director of the Pericardial Clinic at Mayo Clinic in Rochester, Minnesota. I'm also the associate dean for student and faculty affairs at the School of Health Sciences and the associate chair for education for the Department of Cardiovascular Medicine.

Janet Kloos, RN, PhD, APRN-CCNS, CCRN (01:12):

Joining me today are two guests with expertise in the field of pericarditis. Dr. Brian Hoit is professor at Case Western Reserve School of Medicine. He's the director of cardiology resident and fellowship program and the university hospital system medical director of echocardiography and cardiology.

(01:34):

Dr. Bart Gillombardo is a fellow in cardiovascular medicine at University Hospital Cleveland Medical Center. His undergraduate education was at John Hopkins University. He completed medical education at Northeast Ohio Medical University and his internship and residency in internal medicine was completed at the Cleveland Clinic.

(02:00):

Dr. Gillombardo, I'd like to start the conversation by talking about the long-term complications of recurrent pericarditis. What are they and how frequently do they occur?

C. Barton Gillombardo (02:12):

Thank you for having us. Let me begin with a little background. In approximately 70% of cases, acute pericarditis occurs as a single episode lasting from days to weeks, resolves without significant complication and responds well to the standard treatment regimen of aspirin or NSAIDs and colchicine.

(02:33):

But as you alluded to in your question, there are major complications to be aware of and these include [inaudible 00:02:40] recurrence, pericardial effusion, pericardial tamponade, transient constriction, effusive constrictive pericarditis, and chronic constrictive pericarditis. Now, recurrent pericarditis is defined as new signs and symptoms of pericardial inflammation after a symptom-free interval of four to six weeks, usually occurring within 12 months of the index diagnosis.

(03:05):

As with acute pericarditis, patients typically present with chest pain, which is substernal or left-sided. The pain is pleuritic in nature often radiating to the ridge of the trapezius. In addition to symptoms, there must also be objective evidence of pericardial inflammation, the presence of a pericardial friction rub on physical exam, typical ECG findings, new or worsening pericardial effusion. Lastly, an elevated

high sensitivity C-reactive protein, which may be followed serially after the index diagnosis to monitor for disease activity.

(03:45):

Now, let me take a moment to talk about the related diagnosis of incessant pericarditis because I've seen this label imprecisely used in the community and the distinction is important. Incessant pericarditis is defined as an episode lasting longer than four to six weeks without a period of remission. This can occur during the index diagnosis of acute pericarditis or during any subsequent bout of recurrence, the hallmarks of which are either an inadequate response to treatment or an inability to taper treatment.

(04:19):

We need to be careful regarding this diagnosis because it has serious prognostic implications for the patient. With this background in mind, let's turn our attention back to recurrent pericarditis. Evidence from high quality clinical trials as well as queries of U.S. national claims databases suggests that a single episode of recurrence happens in about a third of cases. Unfortunately when it does occur, it's the gift that keeps on giving and the likelihood of an additional recurrence increases with each subsequent episode.

(04:56):

For example, if the risk of a single recurrence is around 30%, the risk of a second recurrence could be 40%, the risk of a third recurrence even higher than that and so on. Now, some patients may have 10 or more episodes, so this process can really spiral out of control. It is important that we recognize this entity early and initiate the proper treatment because symptoms can be severe with significant quality of life implications for our patients.

(05:24):

Now, as I mentioned earlier, the development of pericardial effusion is common. These effusions can become quite large requiring intervention but rarely do so, occurring in maybe 10% of cases. At the extreme end would be progression to pericardial tamponade occurring in even fewer instances, maybe around 4% of cases. Of course, tamponade is acutely life-threatening, requires immediate intervention, and so we as clinicians need to remain vigilant of this possibility.

(06:00):

The last complication worth mentioning is constrictive pericarditis and all of its various subtypes, transient constriction, effusive constriction, and chronic constrictive pericarditis, thankfully only occurring in around 2% of cases. Historically, the risk of developing constriction has been more closely associated with the etiology of pericarditis rather than the number of recurrences. Predisposing factors include purulent pericarditis, TB, malignancy, previous cardiac surgery or trauma.

Janet Kloos, RN, PhD, APRN-CCNS, CCRN (06:33):

I was wanting to ask if there are risk factors. You mentioned several of the complications that can occur, but are there certain risk factors that put a patient at risk for developing any of these complications?

C. Barton Gillombardo (06:50):

Yeah. Sure. Of course. I know I've already mentioned certain types of infection, malignancy, cardiac procedures, et cetera. Other poor prognostic indicators include a history of radiotherapy, advanced renal disease, a sub-acute presentation, persistent fever, large or hemodynamically significant pericardial effusion, preexisting oral anticoagulation therapy, evidence of mild pericarditis.

(07:20):

Now, recurrent pericarditis is an immune-mediated process, so it makes intuitive sense that underlying autoimmune disease might be a risk factor and it is. SOE, rheumatoid arthritis, Sjogren's and others have been implicated.

Janet Kloos, RN, PhD, APRN-CCNS, CCRN (07:36):

Knowing what some of the risk factors are, can you tell us about some precautions to take to prevent or reduce the development of the complications?

C. Barton Gillombardo (07:49):

Well, as a care provider, I'll focus my answer on treatment selection. There is evidence from the COPE trial that corticosteroid use is associated with roughly a fourfold increased rate of recurrence. This finding has been recapitulated in a variety of other settings and it has been hypothesized that the use of, in particular, high-dose steroids may impair clearance of viral particles from within the pericardial space, thus creating the conditions for immune-mediated recurrence, weeks or months down the line.

(08:22):

In summary, steroids should not be your agent of choice. Well, if not steroids, then what agents should we be using? Multiple randomized control trials and subsequent meta-analyses pulling data from around 2000 patients have shown that the addition of colchicine to aspirin or NSAIDs considerably reduces symptom duration and reduces the rate of re-hospitalization as well as the rate of recurrence. Yet despite these findings, the vast majority of patients are undertreated in the community.

(08:56):

One study found that around 40% of patients in the U.S. were discharged with no home-going medications and only 15% of patients were discharged on the standard course of aspirin or NSAIDs times two weeks plus colchicine times three months. What can we as care providers do to prevent complications? There's no mystery here. Make the correct diagnosis, initiate the recommended course of treatment, and then make time to educate our patients regarding the possibility of recurrence, emphasizing the importance of completing a full 90-day course of therapy.

(09:31):

If we do this, the vast majority of our patients would feel better sooner and just have a better overall course. Now, there will still be difficult cases that progress despite excellent adherence to the correct first-line treatment, and we should identify this cohort of patients early because they may benefit from an upfront escalation of therapy, including a prolonged course of steroids or steroid-sparing immunosuppressives like azathioprine or methotrexate.

(10:00):

But the future of this space will likely be dominated by more targeted therapy by which I'm referring to IL-1 directed agents like rilonacept and anakinra. There is an appropriate level of excitement when it comes to these newer agents and truly refractory cases of recurrent pericarditis can be hard to watch and hard to help patients navigate through. The patients are really suffering and now it looks like we may have a path forward for them.

S. Allen Luis, MD (10:30):

Thank you, Dr. Gillombardo. I think that you say something that is very, very important that we all do need to take a note of, which is how do we reduce the risk of these recurrences and these events from recurring? Because it is painful and disturbing and uncomfortable to our patients.

(10:48):

I think as you highlighted very importantly, there is a vast underutilization of colchicine, and colchicine, as you clearly indicated, has been used time and time again and been shown to reduce the recurrence risk following an acute episode of pericarditis. So I think it's really important to emphasize to everyone treating these patients with pericarditis regarding the importance of use of colchicine and an adequate duration of colchicine therapy.

(11:15):

In addition to this, I think it's widely important that we note that it is really, really important that we treat each episode fully. It's not sufficient to have a mild reduction in the person's pain, but really what you're trying to do with your additional therapy in conjunction with your colchicine, be it nonsteroidal or be it steroid or be it a steroid-sparing agent, is really to ensure that your patient is pain-free and that the inflammation has resolved.

(11:43):

You may need inflammatory markers to show that these have normalized before you deescalate your therapy. Thank you for highlighting that.

Janet Kloos, RN, PhD, APRN-CCNS, CCRN (11:53):

Dr. Gillombardo, you previously mentioned the complication of constrictive pericarditis. Could you tell us about the clinical findings of constrictive pericarditis?

C. Barton Gillombardo (12:06):

Sure. Constrictive pericarditis is the end stage of an inflammatory process involving the pericardium in which you essentially have scar formation with fibrosis and adhesions forming between the visceral and parietal pericardium. The pericardial sac becomes thick and stiff, ultimately impacting chamber filling and overall cardiac performance among other things.

(12:33):

The abnormal rigid pericardium does not allow for increased venous return to the right side of the heart, and so patients with constriction present with signs and symptoms of right-sided heart failure. They have elevated jugular venous pressure on physical exam along with lower extremity edema, abdominal distension, early satiety, passive hepatic congestion, SIDs, anasarca. Advanced cases can present with cardiac cachexia, diffuse muscle wasting, profound fatigue.

(13:09):

I'll end my remarks with two classic physical exam findings associated with constriction. The first is a pericardial knock, which is an early diastolic sound best heard at the left sternal border or apex and corresponds to an early abrupt cessation of ventricular filling.

(13:28):

The second is Kussmaul's sign, in which the expected inspiratory collapse of neck veins is replaced by increased distension. Kussmaul's sign is not specific for constriction and can be seen in other cardiac disease states, but it is not a feature of pericardial tamponade and can be helpful in distinguishing between the two, particularly when you're at call in the hospital at night by yourself as a first or second-year fellow.

Janet Kloos, RN, PhD, APRN-CCNS, CCRN (14:00):

Well, thank you Dr. Gillombardo for this excellent discussion and we'll move into asking Dr. Hoit some questions. Dr. Hoit, what is transient constrictive pericarditis and how is it different to the traditional fibrotic constrictive pericarditis?

Brian Hoit, MD (14:24):

Janet, thank you for the kind invitation this afternoon. Now, a subset of patients who present with constrictive pericarditis undergo spontaneous resolution or response to medical therapy and is referred to as transient constrictive pericarditis. In a review of 212 patients with echo findings of constriction, 17% had follow-up studies showing resolution at an interval ranging from two months to two years. Some degree of effusion was common in these cases.

(14:56):

The most common cause of transient constrictive pericarditis was post-injury pericarditis, responsible for a quarter of cases, infection, idiopathic, collagen vascular disease, trauma and malignancy accounted for the remainder. Five patients had resolution of constriction without any specific therapy. This syndrome may overlap with another variant of constrictive pericarditis, namely effusive constrictive pericarditis.

(15:24):

The chief distinctions being its transient or reversible nature and the more advanced constrictive findings in effusive constrictive pericarditis. However, as a practical matter, the diagnosis of transient constrictive pericarditis can only be made in retrospect. Cases that do not reverse either spontaneously or after a trial of anti-inflammatory therapy are best classified as either chronic constrictive pericarditis or effusive constrictive pericarditis depending on the presence or absence of effusion and the degree of chronicity.

(16:00):

Cardiac magnetic resonance or CMR imaging specifically the degree of late gadolinium enhancement of the pericardium appears to be a promising way to identify patients with transient constrictive pericarditis who may have reversal or spontaneous resolution of the process. There is thicker and more intense late gadolinium in patients with transient constriction than in those that ultimately develop chronic fibrotic constrictive pericarditis.

Janet Kloos, RN, PhD, APRN-CCNS, CCRN (16:29):

Dr. Hoit, how do you identify and differentiate transient constrictive pericarditis from fibrotic constrictive pericarditis? How does this influence your therapy?

Brian Hoit, MD (16:44):

Patients with ongoing signs and symptoms of constrictive pericarditis, evidence of late gadolinium enhancement on CMR and elevated C-reactive protein are treated similarly to patients with recurrent pericarditis, with the addition of corticosteroids and IL-1 blockers as necessary. Interleukin-1 inhibition has been shown to be beneficial in patients with a high risk of constrictive pericarditis, namely glucocorticoid dependent, colchicine resistant recurrent or incessant pericarditis.

(17:17):

Patients with marked improvement in signs and symptoms of constrictive pericarditis and resolution of inflammation on CMR following initial treatment can typically be weaned from therapy and avoid

surgical intervention. Pericardiectomy is the only definitive treatment option for patients with chronic constrictive pericarditis who have persistent and prominent symptoms.

(17:41):

Patients with markers of chronic constrictive pericarditis should undergo earlier surgical intervention. Diuretic therapy is used only as a temporizing measure and for patients who are not candidates for surgery.

Janet Kloos, RN, PhD, APRN-CCNS, CCRN (17:58):

Well, you've talked about some of the testing that needs to be done and that is able to help differentiate, but are there other diagnostic or laboratory tests needed to make the diagnosis of constrictive pericarditis? Can you relate those diagnostic findings to the pathophysiology?

Brian Hoit, MD (18:21):

Yes, those are great questions. The critical pathophysiologic features of constrictive pericarditis, which are largely responsible for the physical exam, hemodynamic and imaging findings are elevated venous pressure, greatly enhanced ventricular interaction or interdependence, and a dissociation of intracardiac and intrathoracic pressures.

(18:45):

All patients with suspected constrictive pericarditis should undergo initial evaluation with electrocardiography, chest radiography and echocardiography. Subsequent evaluation may include one or more types of cross-sectional imaging such as computed tomography or CMR. An invasive hemodynamic evaluation depending upon the diagnostic quality of the initial echocardiogram and a relevant history.

(19:15):

The diagnosis of constrictive pericarditis is usually made using echocardiography in patients with history and physical findings that result in a high clinical suspicion. While there is no single diagnostic echocardiographic variable, the following imaging signs typically in combination are highly suggestive of constrictive pericarditis.

(19:37):

These include respiration-related ventricular septal shift or shudder, exploratory diastolic hepatic vein velocities and variation in mitral inflow velocities, all of which results from the heightened ventricular interaction and the dissociation of intracardiac and intrathoracic pressures.

(19:57):

Other signs are preserved or elevated early diastolic mitral annular tissue velocity, and a reversal of the normal lateral to medial mitral annular ratio that is greater than one, a result of tethering of the lateral myocardium by the pericardium and a compensatory increase in medial filling velocity. Finally, a dilated inferior vena cava is seen due to elevated right atrial pressures.

Janet Kloos, RN, PhD, APRN-CCNS, CCRN (20:23):

Thank you for that excellent discussion. Continuing on one of the differential diagnoses for constrictive pericarditis is a restrictive cardiomyopathy. What clinical features and investigations may distinguish these etiologies and allow you to confirm the diagnosis of constrictive pericarditis?

Brian Hoit, MD (20:48):

Yeah. Janet, that's another great question. Constrictive pericarditis is the result of scarring and a consequent loss of normal elasticity of the pericardial sac. This leads to impairment of ventricular filling in mid and late diastole, and as a result, the majority of ventricular filling occurs rapidly in early diastole. In contrast, restrictive cardiomyopathy is characterized by a non-dilated stiff ventricle resulting in severe diastolic dysfunction with normal or near-normal systolic function and restrictive filling.

(21:23):

Similar to constrictive clear pericarditis. Both patients with constrictive pericarditis and restrictive cardiomyopathy have elevated left and right-sided filling pressures often of equal magnitude. However, because of their markedly different treatments, differentiating between the two conditions is critical. In some patients, the correct diagnosis may be readily suggested from the history or routine diagnostic testing.

(21:51):

In others, however, this differentiation cannot be diagnosed before biopsy or even after surgical exploration. Findings that can aid in distinguishing the two conditions include the history which may provide helpful clues such as prior pericarditis or a systemic disease predisposing the constrictive pericarditis or a cause of restrictive cardiomyopathy such as amyloidosis.

(22:18):

The vast majority of patients with both constrictive pericarditis and restrictive cardiomyopathy display elevated jugular venous pressure making this physical finding less helpful in distinguishing the two conditions. The electrocardiogram may be helpful for example, depolarization abnormalities, pathologic Q waves or impaired atrial-ventricular conduction strongly favor restrictive cardiomyopathy.

(22:46):

Several small observational studies have suggested that BNP levels in patients with restrictive cardiomyopathy are significantly higher than those in patients with constriction. A normal value, that is a BNP less than a hundred picograms per mill, essentially excludes restrictive cardiomyopathy. Calcification of the pericardium strongly suggests constrictive pericarditis, whereas cardiomegaly on chest radiography is more prominent in restrictive cardiomyopathy.

(23:18):

On pericardial imaging, increased thickness or calcification of the pericardium favors the diagnosis of constrictive pericarditis, but increased pericardial thickness is not present in all patients. Thickening of the ventricular wall and septum, abnormal myocardial texture and to a lesser extent, mitral or tricuspid regurgitation all favor the diagnosis of restrictive cardiomyopathy.

(23:45):

Spectral and tissue Doppler echocardiography and strain echocardiography can provide other helpful clues. Mirror image discordance between peak RV and LV systolic pressures during inspiration is another sign of increased ventricular interdependence. During peak inspiration an increase in RV pressure occurs when LV pressure is lowest.

(24:10):

Discordance is arguably the most useful hemodynamic sign at cardiac catheterization in distinguishing constrictive pericarditis from restrictive cardiomyopathy.

Janet Kloos, RN, PhD, APRN-CCNS, CCRN (24:25):

Thank you so much for helping us determine what the differential testing might be and the findings might be. Can you please talk to us about the treatment regimen for each of the complications?

Brian Hoit, MD (24:41):

Sure. For most patients with recurrent pericarditis, combination therapy with colchicine plus either an NSAID or aspirin is sufficient. The duration of therapy is guided by resolution of symptoms and normalization of inflammatory markers. Colchicine is given for six months. For patients with persistent symptoms on or contraindications to colchicine plus NSAIDs or aspirin therapy, glucocorticoid therapy using moderate initial dosing followed by a slow taper is recommended.

(25:17):

For patients with recurrent pericarditis and persistent symptoms despite the addition of NSAIDs or aspirin, treatment is based upon whether an inflammatory phenotype is present. An inflammatory phenotype is characterized by the presence of one or more signs of inflammation, that is, fever, elevated C-reactive protein, white count or sedimentation rate, pericardial late gadolinium enhancement on CMR, or pericardial contrast enhancement on CT.

(25:49):

For patients with an inflammatory phenotype and Interleukin-1 inhibitor, rilonacept or anakinra, appears very effective. Patients presenting without any of these signs of inflammation have a non-inflammatory phenotype. In this setting, the potential benefits and risks of immune therapy and of pericardiectomy as an alternative should be discussed with the patient. Options include intravenous immunoglobulin preferred for patients with an autoimmune disorder and azathioprine for others.

(26:23):

Pericardiectomy is an option for all patients with recurrent pericarditis after failure of medical regimens, including NSAIDs or aspirin, colchicine, glucocorticoids and Interleukin-1 inhibition. The treatment of cardiac tamponade, which occurs in 1 to 2%, is pericardiocentesis. For treatment of effusive constrictive pericarditis, medical therapy should be directed at the underlying cause whenever possible.

(26:51):

In cases with clear evidence of pericardial inflammation, a trial of anti-inflammatory regimen is warranted. Pericardiocentesis alone may produce at least a temporary relief of symptoms and pericardiectomy should be reserved for those with refractory symptoms or clinical evidence of chronic constrictive pericarditis, and when undertaken, the pericardium should be removed completely including the visceral pericardium.

Janet Kloos, RN, PhD, APRN-CCNS, CCRN (27:21):

Well, thank you so much Dr. Hoit, for your thorough and enlightening discussion about testing, treatment for recurrent pericarditis complications. Dr. Luis, would you please give a summary of some of the important points that both Dr. Gillombardo and Dr. Hoit have provided for us?

S. Allen Luis, MD (27:42):

Thank you very much Dr. Kloos, and thank you very much, Dr. Gillombardo and Dr. Hoit for an excellent discussion on this topic. I think through what we've heard from here, it's very clear that the acute episode of pericarditis and each recurrence need to be treated optimally. They need to treat those episodes in their entirety and ensure that the inflammation has completely gone away.

(28:05):

This will reduce the risk of recurrence in the longer term and initial therapy should always include colchicine except where there is a strong contraindication to treatment with colchicine. I think we have heard from Dr. Hoit and Dr. Gillombardo that constrictive pericarditis can occur in these patients, but we may have a variety of different flavors to the constrictive physiology that testing may illustrate.

(28:32):

More commonly what we see is an inflammatory type of constrictive physiology, so-called transient constrictive pericarditis or effusive constrictive pericarditis that's really inflammatory-driven. In these patients, it's important to give them anti-inflammatory therapies and see whether you can cause resolution of the transient features that you see of constriction and spare the person from having surgery in the longer term if possible through resolution of the inflammation.

(29:04):

In rare cases, patients go on to develop a fibrotic pericarditis, and as Dr. Gillombardo indicated, it tends not to be related to the number of inflammatory episodes that the patient has had, but rather the etiology of the pericarditis. We see it more commonly in those etiologies Dr. Gillombardo really illustrated quite well. I'd particularly draw your attention to the purulent types of pericarditis and the tuberculous kinds of pericarditis that are far more associated with constriction in the longer term.

(29:35):

These patients that have this traditional type of fibrotic, constrictive pericarditis, the true constrictive pericarditis rather than the inflammation-related constrictive physiology, these patients would need to be treated with surgical pericardiectomy.

Janet Kloos, RN, PhD, APRN-CCNS, CCRN (29:50):

Well, thank you Dr. Luis, and thank all of you for joining us and participating in this episode, Long-Term Complications of Recurrent Pericarditis. This podcast series on pericardial disease is supported by an educational grant from Kiniksa Pharmaceuticals. The views and opinions in this podcast are those of the speakers and reflect the synthesis of science.

(30:16):

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Dr. Cornelio (41:36):

... can be extended longer. That's a tough question to answer in terms of tapering rilonacept but there aren't really any specific recommendations described in the literature. If we take a look at the registry data that we have with anakinra, again, we could potentially extrapolate that three-month approach to rilonacept, though keeping in mind that it does again have a longer half-life, so we may be able to get away with a slightly attenuated taper schedule.

(42:08):

Again, that's something that may hopefully be answered with future registry data from the RESONANCE study, so the registry of the natural history of recurrent pericarditis in pediatric and adult patients.

S. Allen Luis, MD (42:26):

No, that sounds great. There is a lot of uncertainty regarding optimal duration of IL-1 receptor blocker therapy and really there is going to be an area of future study and to try to figure out when we can get

people off these therapies. Sometimes I think the important things are an adequate duration of therapy and then figuring out whether we should taper or not.

(42:55):

As we heard about with anakinra, there is some data to suggest that tapering may be beneficial and with rilonacept we really don't have that data and it just hasn't been looked into thus far, but definitely an area for more information on the horizon. I was wondering if, Dr. Ukaigwe, you could cover the advantages of utilizing IL-1 inhibitors for us.

Dr. Ukaigwe (43:21):

Okay. I think just as a little background for the advantages, recurrent pericarditis is very distressing. While it's not life-threatening, it's very distressing. It leads to lots of emergency room visits, lots of lost hours, lots of anxiety about what's going on with a chest pain that just wouldn't go away. So it's imperative for us and for the wellbeing of the patients to help control the symptoms.

(43:55):

Now, the medical therapies that we have, NSAIDs and colchicine and steroids are excellent drugs, but they do have their limitations. For instance, like using steroids for long periods of time leads to several side effects that go all the way from neuropsychiatric to bones to even increased risk of GI bleeding. In any inflammatory disease, anywhere that we use steroids for long term, we always have a steroid-sparing therapy specifically for that reason.

(44:25):

The same should apply to recurrent pericarditis. We should have a steroid-sparing strategy. While other steroid-sparing strategies have been tried like azathioprine and IVIG, it's important and it's nice and it's helpful to have a medication that's Interleukin-1 inhibition that has relative safety and it's also very efficacious and specifically tried and tested for this indication.

(44:56):

The second thing, for instance is that you don't need renal dose adjustments for rilonacept for instance. That's the one that is approved for use in the United States and we do need that when we give colchicine. We can't use NSAIDs when people have renal failure, so having an option for treating this patient and getting this condition controlled is one of the other advantages that I see from this.

(45:21):

Then third is there's at least in... Not anakinra, but the one that's approved for use in the United States, rilonacept, the fact that it's just a once-daily dosing is actually helpful or fits into most people's lifestyle than having to continuously give injections. These are some of the benefits from Interleukin-1 inhibition that we can have targeted immunomodulation that is focused on the pathophysiology of recurrent pericarditis and minimizes the impact of this immunomodulation to the rest to systemic functions.

S. Allen Luis, MD (46:02):

Thank you very much for that. Yeah. I completely agree that the big advantage here is these patients often are on corticosteroids and it really does give us the advantage or the option of having a steroid-sparing agent in recurrent pericarditis. Dr. Cornelio, could I please give you the job of telling us about the disadvantages of using an IL-1 receptor blocker?

Dr. Cornelio (46:28):

Yes. Other than the injection site reactions, which again are self-limiting, the one thing that we have to discuss is the cost, unfortunately. These medications are expensive and the cost can be burdensome, especially if you have treatment durations that go on for even almost a year in some patients.

(46:49):

It's imperative to really understand that the cost reduction strategies that we can use, make sure that we're advocating for our patients, understanding that there's going to be hurdles and upfront work that we might have to do with the insurance company that need to be completed. The pharmaceutical companies for both anakinra and rilonacept do have programs that allow patients and providers to help navigate the costs and the logistics.

(47:19):

For example, anakinra does have a copay program for commercially-insured patients and a patient assistance program as well for eligible patients. Then rilonacept also has a medication access and support program as well. The costs are there, but with a good pharmacy team and a good case management team and providers, we could advocate for our patients to hopefully get these medications at a reduced cost.

(47:49):

I guess the other disadvantage is less so at a disadvantage of the medication, but more so as you were alluding to earlier, those gaps in literature, we're not really sure of the optimal tapering schedule, particularly with rilonacept. We don't have a lot of experience again with canakinumab, but also we're not really completely sure of the role of IL-1 blockade after I guess that first recurrence and the absence of systemic inflammation, so in the absence of elevated CRP. There are some investigational questions there that really do need to still be answered.

S. Allen Luis, MD (48:29):

Thank you very much, Dr. Cornelio, and I'm very glad you brought up the cost issue because the reality is that both of these agents that we've discussed and all the IL-1 receptor blockers are incredibly expensive agents. We're talking about tens of thousands of dollars. We're talking about insurance coverage, co-pay programs, so cost is definitely the biggest issue here that one needs to be very aware of and keep in the front of one's mind. Thank you for bringing that up.

(49:05):

I'd like to take this opportunity to thank both Dr. Ukaigwe and Dr. Cornelio. I'd like to thank all of you for joining us and participating in episode six of our series on recurrent pericarditis, focusing on the role of IL-1 receptor blockade in the treatment of recurrent pericarditis.

(49:26):

This podcast series on recurrent pericarditis is supported by an education grant from Kiniksa Pharmaceuticals. For more educational opportunities, please visit the American Heart Association's website at learn.heart.org. Thank you all very much.