

Allen Luis, MD ([00:05](#)):

Hello everyone, and welcome to the American Heart Association's Recurrent Pericarditis podcast series. This is episode six, titled Recurrent Pericarditis, The Role Of IL-1 Receptor Blockade.

Allen Luis, MD ([00:19](#)):

My name is Allen Luis, and I will be the host and moderator for this section. I am the co-director of the pericardial clinic at Mayo Clinic in Rochester, Minnesota. I am also the associate dean for the School of Health Sciences at Mayo Clinic.

Allen Luis, MD ([00:35](#)):

Joining me today are two guests, who are experts in the field of pericarditis, and it is our pleasure to welcome them both here today. My first guest is Dr. Anene Ukaigwe, who completed her cardiology training at Penn State University, at the Hershey Medical Center in Pennsylvania.

Allen Luis, MD ([00:54](#)):

She went on to complete interventional cardiology training at Beth Israel Lanhee Health System in Burlington, Massachusetts, and subsequently followed by subspecialty training in structural cardiology interventions at Minneapolis Heart Institute in Minneapolis.

Allen Luis, MD ([01:11](#)):

Dr. Ukaigwe graduated from medical school at the University of Ibadan, where she graduated with honors. She has special interests in hypertrophic cardiomyopathy, mitral and tricuspid valve diseases, and has had multiple publications and presentations at local and national meetings.

Allen Luis, MD ([01:29](#)):

It's also my pleasure to introduce Dr. Cyrille Cornelio. She is an assistant professor at the Shenandoah University Bernard J Dunn School of Pharmacy, and is a clinical pharmacy specialist at Inova Cardiology Clinic in Fairfax, Virginia.

Allen Luis, MD ([01:48](#)):

She is board certified in cardiology as a pharmacist, and has a practice and research experience in both heart failure, readmission reduction, as well as a special interest in pericarditis. Dr. Cornelio is a member of the American Heart Association Council on Clinical Cardiology, and Clinical Pharmacology Committee.

Allen Luis, MD ([02:09](#)):

Thank you both very much for joining us, and for participating in this podcast, and sharing your expertise with all of us. Through the course of this podcast, we will be talking about off-label indications for some of the IL-1 receptor blockers that we will be discussing.

Allen Luis, MD ([02:25](#)):

And so it is important to note, that some of what this discussion is going to entail is related to off-label use of these medications. I'm going to start by asking Dr. Ukaigwe if she may be able to introduce us to the role of Interleukin 1, or IL-1, in the path of physiology of pericarditis.

Anene Ukaigwe, MD ([02:47](#)):

Thank you very much for that great introduction. So essentially, what happens with pericarditis as a whole is, when we have paracardial injury from whatever etiology; microorganisms, toxins or trauma, this leads to release of Interleukin-1 alpha, that is stored in pericardial cells.

Anene Ukaigwe, MD ([03:06](#)):

Now, along with cytokines and pathogens, this bind to the membrane of the membrane and intercellular receptors or monocytes, and when this binding occurs, it stimulates certain proteins called damage and pathogen activated membrane pattern proteins.

Anene Ukaigwe, MD ([03:22](#)):

Now these proteins, they're called damps and mamps for short. They then cause activation of inflammasomes, and inflammasomes are made up of about three components. Now, a part of those inflammasomes then lead to activation of the downstream processes, that leads to the production of Interleukin-1 beta.

Anene Ukaigwe, MD ([03:45](#)):

Now, that Interleukin-1 beta binds to the same receptor, that Interleukin-1 receptor, and it's this Interleukin-1 beta and the receptor complex that then activates endothelial adhesion molecules, that then facilitates in infiltration of the pericardial by inflammatory cells, and leads to this pericardial inflammation, and damage that leads to pericarditis, that we're aware of.

Anene Ukaigwe, MD ([04:11](#)):

So now, both Interleukin-1 alpha and Interleukin-1 beta bind to the same receptors, and in our bodies, the activity of those receptors are modulated by our own antagonists that we make ourselves. And so, since both Interleukin-1 alpha and Interleukin-1 beta are central to the action, or the initiation and propagation of pericarditis, it makes sense then that trying to target one of those actions will lead to cessation or stopping of pericarditis.

Anene Ukaigwe, MD ([04:45](#)):

So that's essentially what leads to the development, the different targets of the different Interleukin-1 based therapies that we use for pericarditis. And in fact, it's even part of this system that Interleukin-1 beta activates Cyclooxygenases, which is a target for NSAIDs and steroids, and one of the inflammasomes that is actually activated by Interleukin-1 alpha is one of the targets for Colchicine that we use, even before we get to the targeted Interleukin, what other targeted Interleukin-1 therapies, that we'll talk further about during this discussion.

Allen Luis, MD ([05:26](#)):

Thank you very much Dr. Ukaigwe. I think that was a great overview, and really gave us a good idea of what the different targets that we see with the different agents that we use, in the treatment of both acute and recurrent pericarditis.

Allen Luis, MD ([05:40](#)):

And I think it's really important to realize for this discussion today, that Interleukin-1 really is quite a central molecule, in terms of mediating the pathophysiology that we see in pericarditis, and it's both the

Interleukin-1 alpha, as well as the Interleukin-1 beta that are important, as well as their receptors in this disease process.

Allen Luis, MD ([06:03](#)):

I might keep asking you a second question here, Dr. Ukaigwe, I was hoping you might be able to tell us a little bit about the usual treatment of recurrent pericarditis, and when we should consider IL-1 receptor blockers, and sort of the treatment paradigm here.

Anene Ukaigwe, MD ([06:18](#)):

So recurrent pericarditis essentially refers to when there's an incidence or recurrence of the same clinical features that define pericarditis, that is chest pain per cardio rub, EKG changes, or paracardial effusion, after there has been a symptom free interval of about at least four to six weeks.

Anene Ukaigwe, MD ([06:38](#)):

And with that, there has to be new evidence of pericardial inflammation, which could be elevation of inflammatory markers, which should be CRP and a reactive protein, erythrocyte mentation rates, or white cell count elevation.

Anene Ukaigwe, MD ([06:54](#)):

But other imaging findings can define pericardial inflammation as seen on CT scan or cardiac MRI. So if any or all of these occur, then the first line therapy is actually starting a non-steroidal, anti-inflammatory agent which includes aspirin and colchicine.

Anene Ukaigwe, MD ([07:12](#)):

Then after this has been tried, do taper the non-steroidal antiinflammatory agent after about two to four weeks, and Colchicine in this scenario should be used for at least six months, and this is a longer duration of therapy as compared to three months that we use for acute pericarditis.

Anene Ukaigwe, MD ([07:29](#)):

Now if this fails to control symptoms, then the second line therapy tends to involve use of steroids, and this is typically low dose steroids, approximately Prednisone 0.2 to 0.5 milligrams per kilogram daily, and that tends to be used for months. The steroids are used in addition to Colchicine as well.

Anene Ukaigwe, MD ([07:51](#)):

And sometimes, if there are other contraindications or other limitations to use of non-steroid anti-inflammatory drugs, this may actually end up being the first line therapy, and it's after there is failure of these two initial first steps, that's where interlocking one inhibition comes in as the third line treatment for recurrent pericarditis, which is only initiated after we've done certain steps to be sure that this patient can tolerate, or medications will be safe in this situation, top of which it will be making sure that there are no infections.

Allen Luis, MD ([08:29](#)):

Thank you for the fantastic overview. I think, really important to recognize that this is not usually our first line therapy, but really one of our later line therapies when our initial therapies fail. But it's

important to keep this in mind, because there are a group of patients who are incredibly difficult to treat with their recurrent pericarditis.

Allen Luis, MD ([08:50](#)):

Nonsteroidal anti-inflammatories are not enough to control their pain, and so we escalate, and some who are on corticosteroids that you just cannot withdraw, and this provides a very valuable strategy to be able to treat your patients effectively.

Allen Luis, MD ([09:04](#)):

So definitely something to keep in mind. Dr. Cornelio, could I please ask you to give us an overview of what IL-1 targeted therapies are available, that we may be able to use in our patients with recurrent pericarditis?

Cyrille K. Cornelio, Pharm.D., BCCP ([09:18](#)):

Thank you. So the two IL-1 blocking agents that we currently have the most evidence in treating recurrent pericarditis, are Anakinra and Rilonacept. So Anakinra is actually a recombinant version of our own native IL-1 receptor antagonist, and it competitively binds to, and blocks the IL-1 receptor.

Cyrille K. Cornelio, Pharm.D., BCCP ([09:41](#)):

It's FDA approved for inflammatory conditions like rheumatoid arthritis, but emerging data actually has supported its use in recurrent pericarditis off label. Rilonacept, on the other hand, is an IL-1 trap protein, and what that essentially means is that it serves as a soluble decoy receptor for both IL-1 alpha and IL beta cytokines.

Cyrille K. Cornelio, Pharm.D., BCCP ([10:06](#)):

It actually has been FDA approved since 2008, but in 2021, due to new data, the FDA actually granted its approval for recurrent pericarditis also. So interestingly Rilonacept is the first and only agent of the agents that we'll discuss today that, to date in the United States, has an official labeled indication for this.

Cyrille K. Cornelio, Pharm.D., BCCP ([10:28](#)):

There is a third agent called Canakinumab. It's an IGG-1 human monoclonal antibody that specifically binds to IL-1 beta, so not alpha. However, we don't really have as much data with this agent in pericarditis compared to Anakinra or Rilonacept.

Allen Luis, MD ([10:48](#)):

Thank you very much for that overview, Dr. Cornelio. So it sounds like we have Anakinra and Rilonacept, which sort of blocked both IL-1 alpha and IL-1 beta, and then we have Canakinumab, which really we don't have a lot of data for, and Canakinumab would block IL-1 beta alone without sort of specifically addressing the IL-1 alpha portion of this.

Allen Luis, MD ([11:12](#)):

I'm wondering if Dr. Ukaigwe, if you could please give us an overview of what evidence we have for the use of Anakinra in patients with recurrent pericarditis.

Anene Ukaigwe, MD ([11:24](#)):

So basically, the first use of Anakinra was in the pediatric population inpatients who had recurrent pericarditis. And all of these pediatric population patients in whom this was tried, were all steroid dependent and had evidence of inflammation; that was fever or elevated inflammatory markers.

Anene Ukaigwe, MD ([11:44](#)):

And when subcutaneous and Anakinra was started, it led to the symptoms rapidly disappearing, and normalization of acute phase reactant. And then, because of continued treatment with this Anakinra, it allowed discontinuation or tapering of the steroids.

Anene Ukaigwe, MD ([12:01](#)):

And when these patients were followed up out to six months from the initial time that they were given Anakinra, none of these patients had a relapse. And subsequently again, there was use of this of Anakinra in adult patients who were also Corticosteroid dependent in the treatment of their recurrent pericarditis. And again, this led to marked improvement in their symptoms and inflammatory markers.

Anene Ukaigwe, MD ([12:27](#)):

And based off of these, it's led to the first trial that evaluated the efficacy and safety of Anakinra inpatient for the treatment of recurrent idiopathic pericarditis, called the Air Trip trial.

Anene Ukaigwe, MD ([12:40](#)):

And this was an investigator initiated randomized control, randomized double blind placebo control trial, and basically they were trying to see, it took patients who had recurrent pericarditis, with at least three previous recurrences, had evidence of inflammation as manifested by elevation and see reactive protein, and had demonstrated Colchicine resistance and corticosteroid dependence.

Anene Ukaigwe, MD ([13:05](#)):

So they had failed the second line therapy that we had talked about, and they gave Anakinra at the specified dose of about two milligrams per kilogram per day, up to about a hundred milligrams for two months. And in this trial, all of these patients, about 21, responded to Anakinra with resolution of the pericarditis. And after this, patients were then randomized to continue the Anakinra, or switched to placebo, and tried for about six months, and see if this led to a recurrence.

Anene Ukaigwe, MD ([13:35](#)):

And the primary outcome was to see how many people had a recurrent pericarditis, and how long did it take for people to have recurrent pericarditis. And in following this patient outings, a median of about 14 months, the patient who received placebo, 90% of them actually had recurrence, as opposed to only about 18% of patients in the Anakinra group.

Anene Ukaigwe, MD ([13:58](#)):

And the time to recurrence for the patients who were receiving placebo was about 72 days, and could not be accurately calculated for those with Anakinra for the small size. And so, based off of this study, you found that the Anakinra was definitely efficacious in people who had recurrent pericarditis, and the side effect profile that was reported in this study was essentially only, for the most part of about 95% of people who had skin reactions, and there were transient elevations in liver function tests, and there was

somebody who had hyper [inaudible 00:14:35] reactivation infection, but no patient permanently discontinued the drug, which again is a marker of the fact that this is, in addition to being very efficacious, is actually relatively safe.

Anene Ukaigwe, MD ([14:46](#)):

Now, after that trial, there was actually an international registry of Anakinra for pericarditis, and this again was to look at the real world efficacy and safety of Anakinra for patients who, again, were steroid dependent, and Colchicine resistant with respect to their acute pericarditis.

Anene Ukaigwe, MD ([15:06](#)):

And they collected these patients with the aim of getting a primary outcome on pericarditis recurrence rates after treatment. They also looked at other outcomes like ED visits, hospitalizations, who continued to use steroids, and were there any adverse events. And this was actually a really large study that included about 224 patients, of most of which, about three quarters had an idiopathic etiology of pericarditis.

Anene Ukaigwe, MD ([15:30](#)):

They followed these patients with a median of about 17 months, and almost all of these patients had elevated inflammatory markers. Now, when they followed them out to six months, using the same regimen that we had described, pericarditis recurrences were reduced sixfold if patients were on Anakinra, emergency room visits were decreased elevenfold if the patients were on Anakinra.

Anene Ukaigwe, MD ([15:53](#)):

Hospitalizations were decreased sevenfold if the patients were on Anakinra, and corticosteroid use also significantly reduced. And in fact, in this real world experience, the skin reaction rate was much lower than it was in the initial trial, only about 40%, and even less, about 3%, ended up discontinuing the medication, in 224 patients. Again, mirroring the results of the trial, that this is a very efficacious drug, that is also very safe. Thank you.

Allen Luis, MD ([16:26](#)):

Thank you very much for that. I think that was a great and comprehensive overview. I think, really, the basis of Anakinra in recurrent pericarditis is sort of initially based off that Air Trip study that Doctor Ukaigwe mentioned, where they randomized patients to either Anakinra or no Anakinra, and the Anakinra group really did very, very well.

Allen Luis, MD ([16:50](#)):

And that sort of forms the basis for the very widespread use of Anakinra, particularly in the non-US centers, where that really is quite a predominant, has quite a predominant role in the treatment of recurrent pericarditis.

Allen Luis, MD ([17:06](#)):

Dr. Cornelio, could I please ask you if you would be able to describe for us the dosing, and sort of pharmacokinetic profile of Anakinra?

Cyrille K. Cornelio, Pharm.D., BCCP ([17:14](#)):

Sure. So Anakinra is dosed at 100 milligrams subcutaneously daily in adult, and then the pediatric population can be dosed at two milligrams per kilogram daily. In terms of pharmacokinetics, it's time to peak is around three to seven hours, and patients can actually expect to see symptom improvement within hours to days, which is actually pretty impressive.

Cyrille K. Cornelio, Pharm.D., BCCP ([17:38](#)):

It does have a short elimination half life. It actually is the shortest of the three agents that I had mentioned earlier, its half life is four to six hours. This can be particularly beneficial, especially in cases where we may need to discontinue the medication promptly, in the event of, let's say, a severe intolerance, or maybe a serious infection.

Cyrille K. Cornelio, Pharm.D., BCCP ([18:02](#)):

Finally, when it comes to clearance of Anakinra, that is actually altered with declining kidney function, and so for patients with severe renal impairment and end stage renal disease, we should consider every other day dosing as opposed to daily dosing with Anakinra.

Allen Luis, MD ([18:22](#)):

Sounds great. And can I please ask you, as well, what safety concerns should the healthcare professionals or patients have, in the patients that we do put on Anakinra?

Cyrille K. Cornelio, Pharm.D., BCCP ([18:35](#)):

Yeah, so as mentioned earlier, the most common adverse effect is injection site reactions. However, again, as mentioned, these do tend to be mild and transient and self-limiting. And in fact, in the Air Trip trial, these reactions actually disappeared after about a month.

Cyrille K. Cornelio, Pharm.D., BCCP ([18:52](#)):

So that's actually pretty reassuring. In terms of counseling points for this, we want to make sure that we're telling our patients to rotate injection sites. Using topical steroids or antihistamines can actually help. And then maybe even applying cold compress. It is stored in the refrigerator, so allowing it to warm to room temperature before injecting can also help with this too.

Cyrille K. Cornelio, Pharm.D., BCCP ([19:13](#)):

Some other concerns. Because of its mechanism, it can also potentially suppress the immune system, making patients potentially more prone to serious infections, though relatively, compared to injection site reactions, it's a little more rare. However, we do want to make sure that a patient doesn't have an active infection before starting it.

Cyrille K. Cornelio, Pharm.D., BCCP ([19:36](#)):

We should also be making sure to get appropriate baseline testing. So baseline TB, TB testing, as this medication can lead to reactivation of latent tuberculosis. Neutropenia is rare, but also can occur, so it's recommended to actually get a CBC with differential at baseline, and then monthly for the first three months of therapy, and then maybe quarterly up to one year, as kind of listed in the package insert.

Cyrille K. Cornelio, Pharm.D., BCCP ([20:06](#)):

Anakinra is also actually produced using an e-coli bacteria expression system, so it's contraindicated in patients who also have hypersensitivities to other similar e-coli derived proteins. In terms of drug interactions, they should not be used with tumor necrosis factor, or TNF blocking agents.

Cyrille K. Cornelio, Pharm.D., BCCP ([20:26](#)):

And these agents are typically used for inflammatory conditions like rheumatoid arthritis, and some examples of these agents would include Infliximab, Etanercept and Adalimumab. That's pretty much it. So there's several factors. It's kind of like a laundry list of screening that we do have to do.

Cyrille K. Cornelio, Pharm.D., BCCP ([20:44](#)):

And so it might be beneficial for health systems and providers to maybe build these into their workflows, baseline testing in their clinical decision supports, to help kind of make sure that we're checking our boxes before starting Anakinra.

Allen Luis, MD ([20:58](#)):

That sounds great. So quite a list of things to check on. I think really important to remember the risk of recurrent or reactivating infections that you may or may not know of.

Allen Luis, MD ([21:11](#)):

So particularly screening for tuberculosis, HIV, Hepatitis B and Hepatitis C, along with all those other things that Dr. Cornelio highlighted here. My next question is, I'm going to shift gears a little bit. We've spoken a lot about Anakinra, and we've heard about Riloncept as well. So, Dr. Ukaigwe, do you mind telling us a little bit about Riloncept? What is the evidence for Riloncept in patients with recurrent pericarditis?

Anene Ukaigwe, MD ([21:39](#)):

Riloncept, just like Dr. Cornelio had mentioned, basically acts as a trap, and binds Interleukin-1 alpha, and stops them from attaching to their receptor. And this drug was actually tested in a trial called Rhapsody trial, and in this study, they had patients who it was a multicenter double blind event driven study, and they took patients with recurrent pericarditis, as again evidenced by symptoms and systemic inflammation, and then had them receive Riloncept for about 12 weeks.

Anene Ukaigwe, MD ([22:16](#)):

And this is typically as a loading dose on the first day, and then followed by about half of that dose every week. Then after all the patients who received this therapy actually had a clinical response, that is, the symptoms resolved, and their inflammatory markers resolved, and then they were now randomized one to one, either to continuing Riloncept, or continuing with placebo, similar to what happened in the Air Trip trial.

Anene Ukaigwe, MD ([22:41](#)):

And the primary efficacy was, how long does it take for the first pericarditis recurrence to happen? And essentially, during this period, in the Riloncept group, only 7% of the patients had a pericarditis recurrence. That's about two in thirty.

Anene Ukaigwe, MD ([22:57](#)):

However, the patients in the recurrence group, about three quarters of them had recurrent infection, recurrent and pericarditis, I mean, as the first. Then the time that it took to recurrent in pericarditis in patients in the placebo group was about 8.6 weeks. And due to small numbers, again, it could not be accurate estimated comparably in the Rilonacept group.

Anene Ukaigwe, MD ([23:20](#)):

Again, from a safety perspective, about 13% of patients had adverse events that ended up leading to discontinuation of the Rilonacept therapy, and most of these were injection site reactions, and upper respiratory tract infections.

Anene Ukaigwe, MD ([23:40](#)):

And so, basically, on the basis of this trial, like Dr. Cornelio had mentioned, this Rilonacept is approved for use for recurrent pericarditis by the FDA as of March, 2021, and is one of the therapies that we should have in our armament to treat patients who are steroid dependent, and culture and resistant to current pericarditis.

Allen Luis, MD ([24:08](#)):

Thank you very much for that. So I guess it sounds like both Rilonacept and Anakinra are pretty equally effective, when you look at the separate randomized control trials. So Dr. Cornelio, could you please run us through how does Rilonacept differ from Anakinra?

Cyrille K. Cornelio, Pharm.D., BCCP ([24:27](#)):

Yes, certainly. So, there are differences in the mechanism of actions between the two, as I mentioned earlier. The other glaring difference is the dosing administration, for one. So just kind of to summarize that dose, Rilonacept actually requires a 320 milligram loading dose, and that actually has to be administered under supervision of a healthcare provider, and that pediatric loading dose would be 4.4 milligrams per kilogram.

Cyrille K. Cornelio, Pharm.D., BCCP ([24:52](#)):

Now, one week after that loading dose, the patient can begin to self administer their maintenance regimen of 160 milligrams every week. And then that pediatric kind of equivalent weight based dosing would be 2.2 milligram per kilo every week.

Cyrille K. Cornelio, Pharm.D., BCCP ([25:08](#)):

So, that's kind of that first step, is that the dosing and the dosing frequency, and you could probably kind of correlate that to its half life. So it actually does have a longer half life than Anakinra, seven days. And I think that it's also worth mentioning, just kind of thinking of, how do we coach our patients, and advocate for our patients, is that the need for this in depth patient education.

Cyrille K. Cornelio, Pharm.D., BCCP ([25:34](#)):

So kind of going into this a little bit, is that Anakinra is actually only supplied, or actually supplied as prefilled syringes, whereas Rilonacept is actually not, it's supplied as a vial, that requires the patient to actually use sterile water to then inject into the vial, to mix it up into a readily injectable solution.

Cyrille K. Cornelio, Pharm.D., BCCP ([25:57](#)):

And so, we need to make sure that our patients and caregivers do spend some time with us, to make sure that they're comfortable with handling sharps and syringes, with proper aseptic technique. So those are the major glaring differences that stand out.

Allen Luis, MD ([26:13](#)):

Thanks a lot for that. Do you think Dr. Cornelio, you could possibly run us through the pharmacokinetic properties of Rilonacept, since we already spoke about the pharmacokinetic properties of Anakinra?

Cyrille K. Cornelio, Pharm.D., BCCP ([26:23](#)):

So other than that half life of seven days, study state concentrations in pericarditis with Rilonacept have been achieved within two weeks. And then the other main pharmacokinetic parameter to talk about, is that onset. And so in the Rhapsody trial, the meantime to see reactive protein normalization was one week, and then that was accompanied by a rapid resolution of symptoms, within the first five days, actually.

Cyrille K. Cornelio, Pharm.D., BCCP ([26:51](#)):

So again, pretty remarkable, and keeping in mind that's actually just after one dose, after the first loading dose. And then, finally, just to kind of summarize and parallel with Anakinra, at this time there's not really any pharmacokinetic data in patients with renal and hepatic impairment as it relates to Rilonacept.

Allen Luis, MD ([27:11](#)):

Thank you very much for that. I might turn it back to Dr. Ukaigwe, and ask her to describe the safety profile of Rilonacept.

Anene Ukaigwe, MD ([27:20](#)):

Rilonacept was, the deceptive profile was initially tested in a phase two clinical trial, and similar to the other Interleukin-1 inhibitor, the side effects, issues or concerns that could arise from this are all similar. So the most common side effect is skin reactions. And it was more common, there was more commonly reported with Anakinra.

Anene Ukaigwe, MD ([27:45](#)):

It certainly happened to about 60% of the people who received Rilonacept, and part of the reason that's proposed for the difference, is the fact that Anakinra is a daily injection, whereas Rilonacept is a weekly injection. This is actually the most, one of the most common, and most distressing side effects that could happen from this.

Anene Ukaigwe, MD ([28:06](#)):

And the fortunate thing, and this is one of the conversations to have with patients before we initiate this therapy, is that it usually tends to resolve, it's typically transient, and oral histamines and topical corticosteroids can be used for the treatment of this side effect.

Anene Ukaigwe, MD ([28:23](#)):

Now the other things that, the next common side effects that can happen with Rilonacept, is actually upper respiratory tracts infections. And usually when this happens, it tends not to be due to

opportunistic pathogens. And for the most part, those reactions are being mild, mild infections, and it happened in Riloncept phase two clinical trial only about 16% of the time.

Anene Ukaigwe, MD ([28:50](#)):

The other things that happen in order of decreasing frequency, will be arthralgias and myalgias, and again, these are reversible. About 4% of the patients have elevations in their transaminitis, which is why we get liver function test at baseline, and during follow up. And it rarely ends up resulting in hepatitis, and resolves when this therapy is discontinued.

Anene Ukaigwe, MD ([29:11](#)):

Patients can also have neutropenia and leukopenia, and in up to 8% of patients who are receiving Riloncept, they could have elevation or distortion in their non fasting lipid panel. But even though, in this situation, none of the patients have ever been reported to require any statins or medications to specifically treat this, any results when the medications have been discontinued.

Anene Ukaigwe, MD ([29:40](#)):

Just like Dr. Cornelius has said, before any of these therapies are initiated, we need to be sure that there's no underlying infection, malignancy, or latent tuberculosis that could be flared up with the initiation of this immunomodulating agent. And that's one of the key things to ensure, that this medication continues to remain safe, while we get the benefit of its efficacy.

Allen Luis, MD ([30:06](#)):

That sounds great. So, you're thinking of similar things with Riloncept and Anakinra, in terms of safety profile. And so, really watching out for malignancy and infection particularly. Often we start these agents, because we're looking to get people off corticosteroids, or to get them off their nonsteroidal anti-inflammatories, or to get them off other therapy. And so Dr. Cornelio, could I ask you, once you start an IL-1 receptor blocker, how do you taper the rest of the therapy that they're on?

Cyrille K. Cornelio, Pharm.D., BCCP ([30:37](#)):

Yeah, sure. So thank you. There still needs to be more data had with the optimal, I guess, tapering schedule. But if we look at the data, for example with Anakinra, after patients start to respond well by that first week of therapy, we can then start to taper off.

Cyrille K. Cornelio, Pharm.D., BCCP ([30:54](#)):

So you are kind of assessing for symptoms, and trending even CRP if you can, and then you can start to taper off those background therapies. And if we look at the Air Trip trial, [inaudible 00:31:05] were tapered off within about two weeks, while steroids required at least a six week taper.

Cyrille K. Cornelio, Pharm.D., BCCP ([31:11](#)):

And then, in terms of that duration of therapy, within Anakinra, typically that can last anywhere between six to twelve months, but can potentially be extended if clinical status permits that, or is necessary for it to be extended. After treatment with Anakinra, ideally this should be tapered over at least a three month period.

Cyrille K. Cornelio, Pharm.D., BCCP ([31:30](#)):

I mean, that all comes from that data from the registry that Dr. Ukaigwe mentioned earlier, where a longer taper duration, particularly longer than three months, was associated with less recurrences.

Cyrille K. Cornelio, Pharm.D., BCCP ([31:42](#)):

For Riloncept, if we look at the Rhapsody trial, about one week after starting therapy, we can start to, again, to wean off background therapies. And in the Rhapsody trial, that was done over an average about eight weeks. Now, when it comes to tapering Riloncept, after it's treatment course of around nine months, but again can be extended longer, that's kind of a tough question to answer.

Cyrille K. Cornelio, Pharm.D., BCCP ([32:06](#)):

In terms of tapering Riloncept, 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 Riloncept, though keeping in mind that it does, again, have a longer half life.

Cyrille K. Cornelio, Pharm.D., BCCP ([32:23](#)):

So we may be able to get away with a slightly attenuated taper schedule. But again, that's something that may hopefully be answered with future registry data from resonance studies. So the registry of the natural history of recurrent pericarditis in pediatric and adult patients.

Allen Luis, MD ([32:41](#)):

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.

Allen Luis, MD ([32:56](#)):

And sometimes, I think the important things are an adequate duration of therapy, and then sort of figuring out whether we should taper or not. And as we heard about with Anakinra, there is some data to suggest that tapering may be beneficial. And with Riloncept, we really don't have that data, and it had just hasn't been locked into thus far, but definitely an area for more information on the horizon.

Allen Luis, MD ([33:23](#)):

I was wondering if, Dr. Ukaigwe, you could cover the advantages of utilizing IL-1 inhibitors for us?

Anene Ukaigwe, MD ([33:30](#)):

I think to... 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 the chest pain that just wouldn't go away.

Anene Ukaigwe, MD ([33:50](#)):

And so it's imperative for us, and for the wellbeing of the patients, to help control the symptoms. Now, the medical therapies that we have, NSET and Colchicine and steroids, are excellent drugs, but they do have their limitations.

Anene Ukaigwe, MD ([34:07](#)):

And for instance, using steroids for long periods of time, leads to several side effects that go all the way from neuropsychiatric, to bones, to even an increased risk of GI bleeding. And in any inflammatory disease, anywhere that we use steroids for long term, we always have a steroid sparing therapy specifically for that reason. And the same should apply to recurrent pericarditis, we should have a steroid sparing strategy.

Anene Ukaigwe, MD ([34:34](#)):

And while other steroid sparing strategies have been tried [inaudible 00:34:38] and IVIHE, 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.

Anene Ukaigwe, MD ([34:55](#)):

The second thing, for instance, is that you don't need renal dose adjustment, 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, and we can't use NCETs when people have renal failure.

Anene Ukaigwe, MD ([35:09](#)):

So having an option for treating this patient, and getting this disease, this condition controlled, is one of the other advantages that I see from this. And 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.

Anene Ukaigwe, MD ([35:34](#)):

So these are some of the benefits from getting 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.

Allen Luis, MD ([35:57](#)):

Thank you very much for that. And so 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.

Allen Luis, MD ([36:14](#)):

Dr. Cornelio, could I please give you the job of telling us about the disadvantages of using an IL-1 receptor blocker?

Cyrille K. Cornelio, Pharm.D., BCCP ([36:22](#)):

Yes. So other than the injection site reactions, which again are self-limiting, the one thing that we have to discuss is the cost, unfortunately. So, 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.

Cyrille K. Cornelio, Pharm.D., BCCP ([36:40](#)):

So, it's imperative to really understand the cost reduction strategies that we can use, make sure that we're advocating for our patients, understanding that there is going to be hurdles, and upfront work that we might have to do with the insurance company that need to be completed.

Cyrille K. Cornelio, Pharm.D., BCCP ([36:56](#)):

Pharmaceutical companies for both Anakinra and Rilonacept do have programs that allow patients and providers to help navigate the costs and the logistics. For example, Anakinra does have a co-pay program for commercially insured patients, and a patient assistance program as well, for eligible patients. And then Rilonacept also has a medication access and support program as well.

Cyrille K. Cornelio, Pharm.D., BCCP ([37:22](#)):

So 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.

Cyrille K. Cornelio, Pharm.D., BCCP ([37:35](#)):

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 taping schedule, particularly with Rilonacept.

Cyrille K. Cornelio, Pharm.D., BCCP ([37:48](#)):

We don't have a lot of experience again with Anakinra, but also we're not really completely sure of the role of IL-1 blockade after that first recurrence, and the absence of systemic inflammation. So in the absence of elevated CRP. So there's some investigational questions there that really do need to still be answered.

Allen Luis, MD ([38:09](#)):

Thank you very much, Dr. Cornelio, and I'm very glad you brought up the cost issue, because the reality is that this isn't... Both of these agents that we've discussed, and all the IL-1 receptor blockers are incredibly expensive agents.

Allen Luis, MD ([38:23](#)):

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. So thank you for bringing that up.

Allen Luis, MD ([38:44](#)):

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.

Allen Luis, MD ([39:04](#)):

This podcast series on recurrent pericarditis is supported by an education grant from [inaudible 00:39:10] Pharmaceuticals. And for more educational opportunities, please visit the American Heart Association's website at learn.heart.org. Thank you all very much.