KINERET IL-1 PODCAST SERIES • PODCAST TRANSCRIPT

Identifying IL-1–mediated patterns in clinical RA practice

An expert discussion on the role of IL-1 in RA, including the autoinflammatory spectrum of RA, common features of IL-1 involvement in the disease, and when blocking IL-1 may be clinically appropriate.

FEATURED SPEAKERS

01 HOST · ADULT RHEUMATOLOGY
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02 GUEST · INVESTIGATIVE RHEUMATOLOGY
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ABBREVIATIONS USED IN THIS TRANSCRIPT

ACPA = anti-citrullinated protein antibody; **ACR** = American College of Rheumatology; **BD** = twice daily; **CAPS** = cryopyrin-associated periodic syndromes; **CAR T-cell** = chimeric antigen receptor T-cell; **CCP** = cyclic citrullinated peptide; **CRP** = C-reactive protein; **DMARD** = disease-modifying antirheumatic drug; **ESR** = erythrocyte sedimentation rate; **IL-1** = interleukin-1; **IL-6** = interleukin-6; **JAK** = Janus kinase; **MCP** = metacarpophalangeal; **MMF** = mycophenolate mofetil; **NLRP3** = NOD-like receptor protein 3; **PIP** = proximal interphalangeal; **RA** = rheumatoid arthritis; **RMD Open** = Rheumatic and Musculoskeletal Diseases Open; **TNF** = tumour necrosis factor.

TRANSCRIPT

Identifying IL-1–mediated patterns in clinical RA practice

NARRATOR

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DR. HUGUES ALLARD-CHAMARD

Welcome everybody to this podcast on targeting IL-1 in rheumatoid arthritis. I'm Dr. Hugues Allard-Chamard. I'm an adult rheumatologist, working academic centre in Sherbrooke University in Canada. I'm joined today by Dr. McGonagle. Dr. McGonagle, do you want to introduce yourself?

PROF. DENNIS MCGONAGLE

Hello, everyone. Yeah, I'm Dennis McGonagle, an academic rheumatologist, in the University of Leeds and Leeds Teaching Hospitals. And I've had an interest in autoinflammation since the term was coined just before the turn of the millennium.

DR. HUGUES ALLARD-CHAMARD

So, today in our podcast we're going to discuss IL-1 in rheumatoid arthritis. We're going to try to identify the red flags that should make you think about when IL-1 might be a dominant cytokine in the manifestation of the rheumatoid arthritis that you're facing. We're going to discuss how to use IL-1–blocking therapy and discuss a few additional cases of when blocking IL-1 worked or didn't work based on the clinical features that we saw. So, could you tell me a little bit more about where do we position IL-1–blocking therapy if RA is an autoimmune disease?

PROF. DENNIS MCGONAGLE

Okay, yeah, so as you say, 80% of rheumatoid arthritis patients have autoantibodies predating disease. It is well targeted by drugs like rituximab or abatacept, which target the B and T cell axis. But it's also targeted by cytokine blockade including TNF and IL-6. And of course, IL-1 is another cytokine, in fact, the founder cytokine that was initially shown to be associated with rheumatoid arthritis. So, there's a couple of issues here.

The autoimmune variant of RA is thought to be mediated by immune complexes which activate macrophages, and these produce interleukin-1 alpha and beta, and this works in an autocrine fashion to further activate those cells. And this is probably the mechanism whereby IL-1 plays a role in the classical autoimmune variant of rheumatoid.

Now, the innate immune variant of rheumatoid, or the autoinflammatory variant, are those groups that lack autoantibodies, so this immune complex model does not fit. And as we're going to discuss, these groups also make quite a bit of interleukin-1, and it's independent of the immune complex disease, and this is probably, Hugues, where most of our focus is going to be on. And of course, 20–30% of patients with rheumatoid do not respond to existing therapies, and I suppose we need to define which group within that may be particularly responsive to interleukin-1 blockade.

PROF. DENNIS MCGONAGLE

Since interleukin-1 was first defined (it was the first biological target in inflammatory arthritis), a lot has happened in the world, hasn't it? Including the realization that systemic release of IL-1 from the joints into the circulation is likely to be a key factor in systemic manifestations that accompany rheumatoid. Top of the list which was the accelerated risk of atherosclerotic disease and cardiovascular death. And, of course, fast forward to you know, 2020 approximately. We now have studies showing that blocking IL-1 in subjects with atherosclerosis and raised CRPs reduces the risk of cardiovascular disease. So, the IL-1 pathway cuts across both the local and systemic aspects of rheumatoid in the autoimmune and innate immune or autoinflammatory variant, including joint destruction and comorbidities.

So, having said that, I'd like to ask you, okay, so how do we identify patients who would potentially benefit from IL-1 blockade and what are the signs and symptoms that lead you in your investigational path towards the IL-1–responsive patient?

DR. HUGUES ALLARD-CHAMARD

Yeah, so I think there are several cues that can make us think about IL-1–mediated manifestation. So, I think that there is two different category. There are the signs, and there is also the failure to treatment that sometimes after a few trials you can have a good sense that it's probably not the adaptive immune system that is triggering most of what you're seeing. There are probably other paths, not only IL-1, but then already you have an idea that could be something else that is not adaptive.

For the other manifestation, we do have patients that present with a lot of palindromic manifestation. I think palindromic manifestation, anything that appears within 24 to 48 hours and disappears as quick, is probably not autoimmune. The adaptive immune system, to be activated, it takes a week, so anything that is really more rapid and disappears really rapidly is probably not manifestation that we see often with adaptive immune system.

There is also other rheumatoid arthritis that presents with additional manifestations. I call them RA plus, so RA plus additional features. Patients with a lot of night sweat, fever that comes and goes with RA that you don't have any other explanation, are things that should make you think about a strong innate component to the manifestation that you're seeing. I would also add too that leukocytic vasculitis, that could be seen, is roughly seen in 5% of RA patients. But when you have these manifestations, usually it's treated with colchicine, and colchicine is only impacting neutrophils. So it's not targeting the adaptive immune system, so it's something that really is targeting your innate immune system, and it highlights the fact that you have strong innate immune system activation underneath. There are other manifestations like mouth sores. It's often, it's hard because most of our patients do have methotrexate at some point. There are always confounding factors. But when it's one of the main features, presenting feature, it's something to think of. And I would say patients that present with recurrent serositis. We do have a phenotype of seropositive RA patients that are poorly treated for years and that go on developing serositis. I'm not talking about these patients. These are long-going RA; it's probably immune complex–mediated. But we have patients that present early on in their course with recurrent serositis. These patients, it's very rare that they are seropositive, and for these patients, I think it's one of the red flags that we should think about a strong IL-1, or at least innate immune system activation.

So, I think for me, these are the main things. I would say there are some things that are a little bit more blurry. Often these patients have a lot of fatigue, asthenia, and that is a little bit more than what I see with the other patients. And sometimes they tend to present with very high CRP and ESR. I would say I have them with above 100, 150, and that is a feature that we don't often see with purely adaptive innate immune system activation. It has not as much noise when it presents as when you have a strong innate immune system activation.

PROF. DENNIS MCGONAGLE

Yeah. I wanted to ask you, the palindromic attacks of arthritis that come on pretty quickly, by the time they get to see a doctor, it may be gone. And I think the mobile phone era and the ability to take a picture has helped us. And I want to ask you, do you put much emphasis on joint erythema that accompanies the transient or, you know, the palindromic swelling? Because that further adds to the neutrophilic story. Like it looks like a cellulitis and some of these people get diagnosed and treated with intravenous antibiotics initially. So, do you put much weight on that joint erythema aspect of the palindromic attacks?

DR. HUGUES ALLARD-CHAMARD

Yes, I would say I do. So, if there is erythema, it's one point in the right direction for something IL-1–mediated. If you don't have it, you can have like palindromic arthritis with Whipple and Crohn's disease and other, but usually these palindromic attacks are not as swollen. They are not as intense as the ones I have in my mind when I think about RA with a strong innate immune activation. So, for me, this is definitively something that I would put value on. If I have that, definitively I would think about something that is highly IL-1 and neutrophilic in its presentation.

PROF. DENNIS MCGONAGLE

And just to pick up on that again, so this innate immune type of rheumatoid, the 20% in the antibody-negative group might be more likely to have this presentation. But it's also true that in early RA that some ACPA-positive disease starts out with a palindromic pattern. This is very interesting, isn't it? Then they seem to settle down to a more typical, you know, chronic rheumatoid pattern.

DR. HUGUES ALLARD-CHAMARD

Maybe there is also some, I mean the immune system, it's communicating the innate versus adaptive immune. Maybe there are some arthritis that at their presentation are more IL-1–innate driven and with time they settle to something that is more autoimmune.

PROF. DENNIS MCGONAGLE

The other interesting thing you pointed out there was the serositis. And, of course, serositis is a key feature of rheumatoid, including pleurisy and pericarditis. But outside of the rheumatoid worldview, idiopathic serositis manifesting as pericarditis is incredibly IL-1–dependent, isn't it? And that's empirically derived from treating pericarditis with IL-1–blocking strategies as well, right?

DR. HUGUES ALLARD-CHAMARD

Yes, and this is something we often do even in Canada. When we have these manifestations, it is something that we keep on our list for very refractory cases. Definitively, we venture there.

PROF. DENNIS MCGONAGLE

So, you covered a lot of ground there. So, what would, just to summarize the red flags that might indicate an IL-1–associated or even dependent disease?

DR. HUGUES ALLARD-CHAMARD

So, for me, the red flag would be very high CRP at presentation, patients that have some fever during the process, recurrent serositis, palindromic arthritis, would be the top things. There is also leukocytoclastic vasculitis that could be meaning that you have some predominant innate immune activation. So, for me, these are the top things that I will keep in my mind.

PROF. DENNIS MCGONAGLE

Very good, and it's very interesting, as you say, that before the 1960s that this type of rheumatoid arthritis you just described, it was all lumped in as rheumatoid, but afterwards people realized that there's a bit of an overlap, isn't there? Between the rheumatoid phenotype and the Still's phenotype, the adult Still's phenotype, and it's something we may not be able to clearly discern in the real world. It can be a bit of a gray area in my experience.

DR. HUGUES ALLARD-CHAMARD

Definitively, I agree. I see the same in my practice.

PROF. DENNIS MCGONAGLE

Yes.

DR. HUGUES ALLARD-CHAMARD

So, now that we've described the red flags that could make us think about IL-1–mediated manifestation in RA, can you tell me a little bit more about how IL-1 contributes to local inflammation and joint destruction?

PROF. DENNIS MCGONAGLE

Yeah, no, thank you. So obviously the major producer of IL-1 is macrophages, and as you know, macrophages are major cells in the inflamed synovium, being abundant in the lining layer hyperplasia, and also in the subsynovium. And obviously macrophage numbers correlate with the risk of erosion. This was worked on in the 90s by the late Barry Bresnihan who was, you know, at the forefront of the IL-1 revolution. And of course every cell in the joint expresses the IL-1 type I receptor, so that leads to a plethora of outcomes, including activation of fibroblasts to make metalloproteases to contribute to pannus and tissue invasion, the activation of osteoclast precursors to help drive erosion formation, the activation of endothelium to lead to vasodilation and angiogenesis, and prostaglandin E2 and nitric oxide production. So there's a plethora of cell types in the joint that are affected that then contributes to the disease phenotype and, as you rightly say, we've already mentioned that IL-1 systemically escaping goes to places like the brain where it triggers the fever response and hence one of its original names as endogenous pyrogen, before it got the designation as interleukin-1 alpha and beta.

So the corollaries of this effect of macrophage predominant–derived IL-1 alpha and beta, and its multiplicity of effector cells, is that when you block IL-1, you then have this corresponding numerous effects, including the reduction of migration of inflammatory cells to the joint, reduced diapedesis of cells, reduced inflammation, reduced damage, reduced osteoclastic activity. And, of course, anakinra, the interleukin-1 receptor antagonist, blocks both interleukin-1 alpha and beta via its antagonism of the interleukin-1 type I receptor. And this basically accounts for the efficacy that is well reported of anakinra going back to the 1990s when data from over 1800 patients, including those treated with methotrexate, that shows efficacy in rheumatoid arthritis, including swollen, tender joints, improved physical function, as expected, reduction in the acute phase response, and in patient's and physician's global physical assessment.

So, this is a sort of an overview encompassing this key role of this foundational cytokine in the joint and how its antagonism has been beneficial in the treatment of rheumatoid. And not just the autoimmune variant where the original trials were predominantly done on the autoimmune variant, where there was efficacy but it was obviously slightly lower than the TNF agents, but I think what you and I are talking [about] is this seronegative or sometimes seropositive autoinflammatory group is where the IL-1 antagonism has come into its own. And to me, who was involved in the original Phase 3 trials in Dublin of anakinra in the classic rheumatoid factor, this was pre-ACPA era where most people are rheumatoid factor positive, when I saw the impact of anakinra in the autoinflammatory space, including autoinflammatory RA, it quite surprised me what this amazing, this extra benefit that was evident in the autoinflammatory phenotype of RA. It was quite remarkable.

PROF. DENNIS MCGONAGLE

I was just going to ask you about, okay, so, cycling of treatment and the heterogeneity of RA from autoimmune to innate immune, and cycling of treatment in patients failing therapy. And it just reminded me of a case report in *Annals of Rheumatic Disease* last month of CAR T-cell, CD19 CAR T-cell therapy for refractory rheumatoid. And the patient that was reported in this study from Tel Aviv in Israel had failed all biological classes, including anakinra, before they had a CAR T-cell therapy. When would you consider, you know, using anakinra instead of one of the other five mechanisms like a JAK, a TNF, IL-6, abatacept, and B cell depletion strategy. When would you consider using it, or would you just use everything you can get your hands on when the patient is proving to be recalcitrant, as in that case report in *Annals* recently?

DR. HUGUES ALLARD-CHAMARD

Well, I think there are two ways of seeing it. I think the easy one is when everything fails, then you have another mechanism of action, but this is not how I try to use it, so.

PROF. DENNIS MCGONAGLE

Same here.

DR. HUGUES ALLARD-CHAMARD

So, what I try to do is, I try to see the phenotype of rheumatoid arthritis that I have in front of me, and I try to think, based on the red flag that we discussed, do I have a phenotype that is more IL-1–driven or innate immune system–driven or adaptive immune system–driven. And based on that, I will often try to go first with anti-TNF. I think it's something that we commonly will use. But if, with my anti-TNF, I still have these red flag manifestations that are not vanishing, I still have the fever, I still have the palindromic arthritis, I still have serositis that are not controlled. Well first, we always reconsider for alternative diagnostic. I think it's important to do not spiral down into a diagnostic that might not be exact. But if I'm pretty sure of what I'm seeing, then with these manifestations, instead of keeping anakinra for a last line or very further down the line, I will try to bring it as a second line or something like that to at least try it and see if I have some response, 'cause usually I feel that anakinra response for these autoinflammatory manifestation is very quick. You don't need to wait for three months to say, oh, it's working or not.

PROF. DENNIS MCGONAGLE

Yes.

DR. HUGUES ALLARD-CHAMARD

Usually, fever will break rapidly. So, for me, there is a kind of window where you can try it. You can see if it's going to work or not, and I try to use it a little bit early on when I have the manifestations that are compatible with a component of autoinflammation.

PROF. DENNIS MCGONAGLE

Yes.

DR. HUGUES ALLARD-CHAMARD

It makes you be a little bit more confident that the manifestations that you're seeing were mediated by the innate immune system. If it's totally not working, that's probably mediated by something else and then you should consider that there might be other pathophysiology that is involved in the manifestation that you're seeing. Like serositis, it could be mediated by immune complex. This is what we see probably in lupus or things like that.

PROF. DENNIS MCGONAGLE

I wanted to ask you, the other issue is the conversation we're having when expert panels make guidelines, they don't ever talk about this continuum of the autoinflammatory rheumatoid to the autoimmune. Yet anakinra is still in the mix, right? It's recognized by expert panels as, you know, as a treatment option, but obviously recognized at the population level not to be as potent as the, say, the anti-TNFs.

DR. HUGUES ALLARD-CHAMARD

Yeah, I don't think it's recognized enough, and I think there should be some advocacy for these patients for them to have anakinra tried earlier in their course, so they don't have to fail every mechanism of action before we find something that we had a clue that it would be working early on. It's not the same when you have a mild RA, when you have no clue that there is something specific happening, then I think we kind of have to go to trial and error and cycle through our mechanisms, and just don't give something that would not be optimal based on comorbidities. But for the patient who had some hints that something might be working better, then we should emphasize that it should probably be tried earlier.

PROF. DENNIS MCGONAGLE

Okay, here, good theoretical stuff there. Can you give us an example of a case that illustrates the comments you're making?

DR. HUGUES ALLARD-CHAMARD

Yeah, so one of the cases that we saw in Sherbrooke that for me was very interesting, so it's a 44-year-old male who presented at the age of 35 roughly with episodic night sweat, fever. He had some erythematous rash and bilateral synovitis of the small joint that was very suggestive of RA, but it did have this erythematous component that we discussed earlier. When we've done all his investigations, the CRP was very high. He was negative for rheumatoid factor and CCP and the skin biopsy had some feature of urticarial vasculitis, but we didn't make much at this point of that manifestation. So, he was treated and we followed him over decade, and he had multiple episodes of these synovitis and rash. And we tried to treat him as we do with conventional rheumatoid arthritis, so he was treated with methotrexate first, etanercept was tried, and then we added tocilizumab, and he was always suboptimally controlled. And I would add to that he had what I would call a poor response to prednisone. So, you know, if you give high enough dose, everything will respond to prednisone.

PROF. DENNIS MCGONAGLE

Yeah.

DR. HUGUES ALLARD-CHAMARD

So, what I'm saying is usually in my experience, rheumatoid arthritis when they are on 10 milligrams of prednisone, most of them will respond nicely or at least improve. You don't need this, 30 milligrams, to break rheumatoid arthritis, but for that patient he needed this higher dose. And because he was not responding as we would expect and because he had this urticarial vasculitis that was becoming more and more dominant with time, we decided to consult with immunology who made the very bright move to send him to genetics. And he had a panel that was done and he had a mutation that was pathogenic in NLRP3, which is consistent with a diagnostic of CAPS, but he's not a young child manifesting with all the classical feature of CAPS. It's something that was a little bit muffled in its presentation. Older age, he didn't have the deafness that could be associated, he didn't have anything else but RA, rash, some fever, and the palindromic arthritis that was very erythematous in its presentation. So, we brought the sample to the lab because we were very curious to see if it was something that was germline or somatically acquired. It was not somatically acquired, it was germline, it was just late bloomer, if you will. In his blood, he was producing upon stimulation way more IL-1 beta than in healthy control, so I think that was very interesting for us.

So, we decided to add at this point anakinra to kind of bring down the IL-1–mediated component of the disease, and in the beginning he was also on methotrexate, but with the diagnostic of NLRP3–mediated autoinflammatory syndrome that was the possible explanation, we decided to remove methotrexate and then the arthritis came right back. So, we had to reconsider that it was probably rheumatoid arthritis that was kind of enhanced with more IL-1 production because of a pathogenic mutation NLRP3, so he was put back on methotrexate concomitantly with anakinra and we were able to achieve remission for that patient. We've been following him and he's doing good, but it's not a very old story, so we're roughly two years in the dual therapy but it seems to control the arthritis and all the systemic manifestations. So that was a very interesting case for me. It was a late bloomer but he had a lot of these red flags that we discussed that we should have thought that there was something more in the innate immune system lingering underneath the surface.

PROF. DENNIS MCGONAGLE

And you sometimes think of myelodysplasia there when this sort of thing happens as well as a somatic mutation. But we've actually had a case similar to yours. It was actually the similar phenotype, predominant arthritis, but the patient was also ACPA-positive, and we carried on the methotrexate to control the sort of classic autoimmune rheumatoid component, and the patient also had a germline NLRP3 mutation. And this was published as part of a case series on rheumatoid by my colleague and I, Sinisa Savic, in *RMD Open* about 6 years ago. So yeah, very interesting but rare phenotype that one, but definitely on the radar, yeah.

So, yeah, thanks for that very interesting case with rheumatoid and autoinflammation overlaps, but not everybody with a classic autoinflammatory phenotype responds to interleukin-1 blockade. And could you share with us some examples, please, Hugues?

DR. HUGUES ALLARD-CHAMARD

Yes, we have other cases where I think we thought we were doing the right thing and then we obviously were not doing it. So, I have another case. It's a lady that I met, in her 40s. She was probably 41, and she had longstanding rheumatoid arthritis that was diagnosed probably 10 years ago, and her evolution was really marked by high fever, CRP that were rising up to 300, 400, when she was in the flare and very erythematous rash that was almost covering her all arm and legs. So, very intense rush, fever, arthritis. She was kept on prednisone because she failed a lot of mechanisms of action. So, she had failed anti-TNFs, she had failed anti-IL-6 therapy. And when I met her, because she was having such fever, high CRP, and the arthritis that was very invalidating, I thought, "Oh, maybe this patient is IL-1–mediated condition." And she was doing so poorly that we had to hospitalize her, and we wanted to rule out at this point other lymphoma, infection, and anything that could have triggered the most recent flare of arthritis. All investigations that were done per hospitalization were negative.

DR. HUGUES ALLARD-CHAMARD

So I said, "Okay, let's try anakinra for that patient," and that patient had literally zero response to it, so I was a little bit puzzled by what was happening with that patient not responding to anakinra despite these features that seem very autoinflammatory in the presentation. So, we were puzzled, so we performed a cytokine panel. So, we have access to these in Canada and basically, it's a little bit hard to interpret the cytokine panel, but what I could tell you is there was no innate immune system that seems to be activated in her. It was all T cell–mediated condition, so all T cell–stimulating cytokines were up and cytokines that are produced by T cells were also all up. Not all, but tons were up.

PROF. DENNIS MCGONAGLE

Wow.

DR. HUGUES ALLARD-CHAMARD

So, for that patient that (well, and I didn't mention, but she was rheumatoid factor and CCP-positive), so for that patient we say, okay, that's RA that failed all mechanisms of action plus also failed anakinra; so we decided to empirically started her on MMF to try to control the T cell hyperactivation. Abatacept has already failed in the past, so we decided to go down that path. And I would say, surprisingly for us, we were able to calm most of the inflammation and decrease the prednisone, so right now she's still on 5 milligrams of prednisone. We're trying to remove that but she's very reluctant for us to completely eliminate the prednisone because she's, for the first time in a very long time, doing very good. And we kept her on MMF. We still think it's rheumatoid arthritis, although it's a little bit rare that we have to go to MMF for rheumatoid arthritis. Usually, it's not super good with the joints feature.

PROF. DENNIS MCGONAGLE

That's right.

DR. HUGUES ALLARD-CHAMARD

It's a little bit better with the extra-articular feature.

PROF. DENNIS MCGONAGLE

Yeah.

DR. HUGUES ALLARD-CHAMARD

For her, it seems to be doing both, given that she has some cortisone on board.

PROF. DENNIS MCGONAGLE

Very interesting case. Now, you mentioned steroids there. So, I had this guy that came along to our joint autoinflammatory clinic, and he was in his 40s and he had recurrent palindromic attacks of MCP and PIP synovitis. And he was only in his 40s and, you know, all his antibodies were negative, and we tried to diagnose gout and it wasn't successful, and it wasn't pseudogout, and it wasn't streptococcal throat, so he had no obvious underlying infections or serious illness. The only thing that controlled him is, as you say, if you give enough steroids, you can usually control things. So, the guy was on 30 milligrams of steroid a day mostly. Colchicine didn't work. He met our ACR criteria for RA because, you know, some of the disease hung around. It became, you know, attacks lasted several weeks. So, we went through the usual DMARDs, which did not work, and at this stage he, after a couple of years of this uncertainty as well, he'd had so much steroid that he, man in his 40s, he twisted his ankle at his daughter's wedding and fractured his ankle. So, after that I thought, "Okay, well, enough of this." So, as you say, he was controlled on high-dose steroids, but we tapered the steroids and put him on to anakinra, 100 milligrams a day maintenance and that did the trick for three or four years, then we had to up the dose to 100 milligrams BD. So that's another example of this, a fairly straightforward autoinflammatory rheumatoid pattern that can be controlled on high-dose steroids, but it's, yeah, it's a problem. So, I was interested in your comments. What do you think of that sort of case?

DR. HUGUES ALLARD-CHAMARD

Yeah, no, I think it's very interesting, and the fact that we need a lot of steroid to control rheumatoid arthritis is probably... We didn't mention it as a red flag, but it's probably something that should make us a little bit worried that there is something else underneath because if you need 30 milligrams to control RA, there is a strong activation of your immune system, innate or adaptive. But it's fairly uncommon with classical RA that you need that high dose to control anything.

PROF. DENNIS MCGONAGLE

Absolutely.

DR. HUGUES ALLARD-CHAMARD

So, it's probably an additional flag for me. I would add it on the list I gave.

PROF. DENNIS MCGONAGLE

No, yeah, absolutely. I would like to emphasize that I didn't use 30 milligrams every day for two years. I would start on 30 and try and taper, then things would flare up again.

Hugues, that that was really great. So, just to summarize this podcast we've done together. We first talked about the heterogeneity of rheumatoid arthritis from autoimmune to autoinflammatory mechanisms. And then we talked about the role of interleukin-1 in both the autoimmune, but the particularly strong role it appears to have in the autoinflammatory mechanisms. And we discussed the key role of macrophages in IL-1 production and the multiplicity of effects of the IL-1 cytokine that lead to all the manifestations of joint destruction. And then we talked about the value of anakinra in therapy of rheumatoid arthritis and particularly the autoinflammatory flavors. And then you and I discussed three interesting cases. Two of them responded very well to anakinra therapy. So, with that, I'd like to thank you for this most edifying discussion around autoinflammation, rheumatoid arthritis mechanisms, and therapy. Thank you.

DR. HUGUES ALLARD-CHAMARD

Thank you so much.

NARRATOR

Thank you to our speakers for providing their insights on RA. Briefly about Sobi. Sobi is a biopharmaceutical company headquartered in Stockholm, Sweden. Sobi's main focus is on therapies in the fields of hematology and immunology and deliver treatments to patients in more than 70 countries all over the world.

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