

Pain Management in Gout – An Interview With Lawrence Edwards, MD

Transcript

Meghna Rao (Host): September 2021 is Pain Awareness Month. It's also Arthritis Awareness Month. So today, we're discussing how clinicians and rheumatologists can approach pain and its management in patients with gout.

I'm Meghna Rao the senior editor of *Rheumatology Advisor*, one of the Haymarket Medical network's digital publications that focuses on the latest news and research and rheumatology to inform clinical practices.

I'm speaking today with Dr Lawrence Edwards, professor of medicine in the Division of Rheumatology and Clinical Immunology, as well as program director and vice chairman of the Department of Medicine at the University of Florida. Dr Edwards is also the chairman of the Gout Education Society.

Hello, Dr Edwards, and thank you for joining me for this very important conversation today.

Lawrence Edwards, MD (Guest): It's my pleasure to be here, Meghna.

Meghna: In 2008, you and your colleagues had published an article about pain management in gout. Can you tell us about the evolution of pain management over the years? What changes have you seen during the course of your practice?

Dr Edwards: Well, I do go back a ways, so it's pretty much the history of therapies for gout. Surprisingly, although over the past couple of decades there has been a great deal of understanding about the mechanisms of inflammation and the genetics behind the accumulation of uric acid in the body, there hasn't been a great deal of progress in new therapies for the management of pain.

Pain is the hallmark of gout, and so, it's surprising that there have been more therapies. Back in 2008, we had the standards that are still the standards today. We have the nonsteroidal anti-inflammatory drugs [(NSAID)], such as ibuprofen and naproxen, and a host of others that can be used. We have colchicine that actually goes back a millennia or two, and we have corticosteroids. We have all of those today. If you look at the [American College of Rheumatology] (ACR) 2020 gout management recommendations, those are still main core of how we approach this disease.

There has been some work on the mechanisms of pain and inflammation in gout and they all revolve around the [NLRP3] inflammasome and the production of interleukin (IL)-1 and some other pro-inflammatory cytokines. So, there is new information on how to block that, and even though a number of us use IL-1 inhibitors for acute gout situations, predominantly in the

hospital or in the emergency department, the others are the more standard therapies.

Meghna: Dr Edwards, from a research perspective, what has been learned about the mechanisms and pathways of inflammation and pain in patients with gout that are important and that can be applied to clinical practice?

Dr Edwards: The mechanisms of inflammation in gout are a little bit different than the inflammation of a lot of other rheumatic diseases. This intimately involves the innate immune system, with the ultimate production of IL-1 and IL-18 as the main “gasoline” that gets poured on the “fire” of gout.

We have learned a lot about how crystals exert this effect, of how they stimulate the resident macrophages within the synovium by simply touching the cell surface, especially where there is toll-like receptors that begin the process of increased production of proteins that are going to aid the inflammatory process.

We also know that a very important part of the process is the crystals actually getting engulfed into the white blood cells, into the macrophages, and they trigger a whole coming-together of preexisting cytoplasmic proteins to form a complex that will ultimately be important in modifying the enzymes that are being stimulated to allow IL-1 data to be produced in its final form, so it can be transported.

So, there is a lot of detail in that that has been worked out by some excellent investigators, and the benefits are that we know now [w]hat that mechanism is. There's been other great research that's [happened] about NET science, [ie], neutrophil extracellular traps, and that's the other side of the coin, which is how the inflammatory mechanisms shut down because gout is characterized by this very peculiar, acute pain – [f]rom no pain to maximum pain in an 8- to 10-hour period of time. [T]here isn't another condition in rheumatology where you have that kind of abruptness to the onset of it, and that severity of pain. And the hallmarks are that it comes on – usually at an opportune time – but it will last for anywhere from 4 or 5 days up to 7 to 10 days, 2 weeks, and then shut itself off. So, it's a self-remitting process. [A] lot of attention is being given to what is it that shuts the inflammatory process down.

So, all of that is new stuff and I'm sure that we will learn a lot more from the NETosis-type of research that will help.

There [are] other new things that are being investigated by other scientists. [Dr] Bob Terkeltaub out on the [US] west coast has been looking at A and P kinase as another important intermediary control mechanism within this production of pro-inflammatory cytokines, and there might be a reward at the end of that research as well.

So, good things are happening.

Meghna: Would you be able to also summarize some of the pharmacologic treatments that are specifically targeted at reducing pain in patients with gout? And, a brief note about their safety in gout would also be valuable.

Dr Edwards: The classic ones, again, are the [NSAIDs], which are kind of nonspecific anti-inflammatory approaches, nothing peculiar to gout or pseudogout or in the inflammatory arthritis that use them. [NSAIDs] predominantly work by inhibiting the cyclooxygenase pathway in one form or the other.

What we do know is that you need full doses of anti-inflammatory medications, and we need it promptly. So, more importantly than which of these drugs we use, it seems to have to do a lot with the timing. If a patient has their anti-inflammatory therapies available to them, then whenever the attacks come on they can start up the regimen right away. And if they do that in the first few hours, they are going to actually do a great deal as far as deterring the full-blown gout flare, and they might get by with a little bit of limping around for a day, and then it resolves rather than being incapacitated for 3 to 5 days and a slow regression after that. So, yeah, so the [NSAIDs] are kind of nonspecific.

Colchicine, like I say, has been around for thousands of years. Originally, it was thought by Hippocrates that it had its benefit by just making everybody sick and throwing up and somehow the diarrhea and the throwing up purged the body. Well, that's simply not the case. But there are mechanisms that we have thought about for a long time.

There's evidence that [colchicine] has other activities that are more specific to gout and crystalline arthritis, in general, and that is its ability to, kind of, disrupt this whole NLRP3 inflammasome production, as well as the interactions of the crystals with the toll-like receptors. So, there [are] more specific mechanisms there.

The other standard therapy of glucocorticoids, which again, is pretty nonspecific; all of [the] rheumatologic diseases or at least the inflammatory arthritides respond to one degree or another to that.

The newest drug on the market right now is the IL-1 inhibitor group; anakinra is the one that is most often used, and it is effective because it inhibits the release of IL-1, and therefore, prevents [the] stimulation of leukocyte migration into the cells. So, it's a pretty important new discovery, and one that is used frequently in the hospitals because of its rapid onset of action.

Finally, there are some experimental forms of [caspases] that block that whole pathway. So, it's something on the horizon that a few companies are looking at and have drug development and something in the pipeline maybe for the next 3 or 4 years.

But again, the important thing for clinicians to remember about all of this is that you are really trying to nip this inflammatory process in the bud, so the earlier the patient can get on these anti-inflammatory drugs, the more successful they are going to be. And evolved out of that, is this concept of pill-in-a-pocket, so that whatever it is that you're going to give them, they should have it available to them and start taking it right away.

If you're 12 to 24 hours out since the pain started and you are trying to [s]top the pain, [i]t's a much bigger fight. And if you're waiting a couple of days, most anything you throw at it isn't going to be helpful, with the exception of anakinra.

Meghna: So, while we're still on the topic of therapeutic options, some patients with gout may not be able to tolerate treatment with NSAIDs for reasons including allergies and gastrointestinal bleeding. What would you suggest for these patients to manage acute pain, and would you be able to review some mitigation strategies to limit the side effect from these drugs as well?

Dr Edwards: One of the problems with treating gout is that there's so many comorbid metabolic [d]iseases that are coupled with gout, including diabetes, kidney disease, fatty liver disease, hypertriglyceridemia, hyperlipidemia in general, and hypertension. And all of those have a number of reasons for not taking any of the anti-inflammatory drugs I've mentioned, particularly nonsteroidal [drugs] in the setting of chronic kidney disease, steroids in the setting of diabetes, colchicine in the setting of significant liver disease or kidney disease. So, it's an art form, if you will!

And in those patients, what you can do, and a lot of us do, is [c]ombine these 3 drugs. For instance, nonsteroidal [drugs] and colchicine in lower doses if the person is intolerant to the colchicine or if you're having to start on a low dose of it because of kidney disease, and a lower dose of the nonsteroidal [drugs] because of kidney disease or a history of peptic ulcer disease, and you might get through with that. Or you could have a combination of steroids and colchicine. Again, lower doses for the [patients with diabetes]; even a short 6- or 7-day course of steroids dramatically raises the blood glucoses in a lot of these [patients with diabetes]. It doesn't just irritate their endocrinologists when you do that, but it probably does have some effects on the overall health of the patient and we should be conscious of those.

Anakinra, again, in the hospital is good even for patients with kidney disease, diabetes, or liver disease, and [it] is usually given as a [subcutaneous] injection daily, and it usually only takes 1 or 2 injections before the flare is resolving.

Meghna: Recent studies have indicated high opioid prescription rates and opioid overuse in the emergency department to treat pain from gout flares. Do you believe there is a role for chronic opioid use in the management of gout pain, Dr Edwards?

Dr Edwards: Yeah, I've seen studies where they, kind of, monitored the therapies that patients have gotten coming out of [emergency rooms] (ERs), and other urgent-care places, and as many as [one]-third of the patients being treated for gout have been placed on an opioid analgesic. You know, this is inflammatory pain, it's not mechanical pain, and really would respond much better to the anti-inflammatory therapies we've been talking about. I personally remember a couple of episodes where the patient was really just writhing in pain in the emergency department, and so, a little bit of intervention [j]ust to calm them down; it has some effects other than just the pure analgesia that might be helpful in that particular setting.

But most patients, if we promise them that we're going to be doing an intra-articular injection and they're going to start feeling better in a half an hour or so, can forgo that kind of opioid or narcotic therapies.

Yeah, long-term, I don't think it has any role whatsoever; it shouldn't be used.

Meghna: Pivoting to a slightly different angle, clinical trials are using patient-reported outcomes or PROs as secondary outcomes to measure and assess pain, function, and quality of life in patients with gout, right? Can you provide further insight on the importance of PROs as study endpoints in gout?

Dr Edwards: It's very important. The trouble is documenting the evolution of pain in these various clinical trials. Gout is not a predictable – or gout flares are not predictable by and large – and so it's very hard to get a clinic visit in the middle of a flare, and so, we rely heavily on the [h]istory that the patients are giving us surrounding that. But, again, it's difficult.

Clinical trials that do this, they use tablets or some sort of electronic recording device, so in the throes of the pain they can register on some sort of scale – and there's multiple pain scales, not just 1 to 10 – how they're doing at any given point following the onset of their symptoms and how that's affected by the medication that they have been given to block it. Always a little imprecise, but I think it's the best that can be done now.

Meghna: Seeing the importance of collaboration between specialties, what methods can rheumatologist adopt in conjunction with other health care professionals, such as emergency departments, pain specialists, or primary care physicians, in the management of painful gout?

Dr Edwards: Well, we try and do as much education as possible. A group of us have developed an educational website, the Gout Education Society at www.gouteducation.org, and there is a professional side to that; it was originally designed for patient information, so that they know what good gout care is supposed to look like and then compare that to what their own practitioner [or] health care provider is giving them. About 8 years ago, we set off on a professional side that [h]as updated research information on best

approaches, comments on gout guidelines from various sources, and that's something that's there.

But I always use the opportunity in the emergency department to talk to them about exactly what's appropriate and inappropriate for gout. Ignoring it is, unfortunately, common and I always make the point that that is the worst of all approaches. That what we mentioned before about opioids is pain, is not pain [*sic*]. There are various types of pain and they respond differently and not everybody needs opioids. And certainly, gout is one of those conditions that has better therapeutic approaches.

There are people still that use old, high-doses of colchicine even though that's been shown not to be any more effective than the newer low-dose colchicine regimens, and so, we instruct them on that. It's just a matter of recognizing that relatively few of the patients [with gout] cared for in the United States are being cared for by rheumatologists. There's almost an equal number that are being cared for by nephrologists, for instance, and then, the lion's share is being taken care of by primary care doctors. So, I always offer to see them in my own clinic – my own gout clinic – and get them on the right pathway to being overall improved.

You need to remember that the treatment of gout is, first and foremost, has to do with lowering uric acid levels to a point that these flares aren't going to keep coming back, and to get away from the idea that treating gout is just going from flare to flare and trying to knock the inflammation out as quickly as possible. That's an approach taken by probably the majority of treating physicians in this country, and it's just wrong because over time and during the periods of time between the painful flares, the disease is actually progressing unbeknownst to the patients. So [t]hey are accumulating more and more uric acid and the ultimate management of that is going to be harder and harder as time goes on [and] the disease in that process is ignored.

So yeah, we try and make them see the light as far as what modern recommendations are, and it works. I think, locally, here at the University [of Florida], I see a fraction of what I would have called “mismanagement” just 10 years ago, and it's because we keep hammering the same message home.

Meghna: We've spoken a little bit about how rheumatologists can be informed and stay up-to-date, but how can rheumatologists inform their patients about managing pain and gout? Topics on gout seem to be riddled in misinformation. Secondly, can you describe any effective strategies for self-management during a painful episode of acute gout flare?

Dr Edwards: Yeah, there are a lot of bad sources of information on the internet, and if you start looking around, a whole lot of it has to do with food and things to avoid, and here's the perfect diet for you. All of that is not very helpful, truly. There are, of course, non-[US Food and Drug Administration] (FDA) approved therapies that also take up a lot of space on the internet. So yeah, to find a good sites – the one that I mentioned before of the Gout

Education Society, gouteducation.org, is important; the Arthritis Foundation has a good website that we help them with.

And I think that it is important we encourage patients to take our outline of what good management is to their primary care doctors if they feel like they are not being treated well, and if the doctor is recalcitrant to looking at their gout as a serious disease, then we also list on our website the names and phone numbers of more than 800 private practice rheumatologists around the country that do abide by the ACR [g]out guidelines. And so, I think that's one thing that they can do.

As far as somebody with an acute, painful joint right now, it's [w]hatever has helped them in the past whether that's colchicine, nonsteroidal [drugs], or corticosteroids, they should have those on hand in the house at all times.

Other people that things do, certainly, mobilization is important. Most patients with gout flares, if they are occurring in the lower extremities are not going to be out walking – Hippocrates called it the “unwalkable disease” – so rest. Ice is promoted by a number of people. There are relatively few studies on its real efficacy, but some of my patients have used it and have felt pretty good. The problem is how you apply it can be touchy; [m]ost patients with gout don't want anything put on their swollen, red, angry joint, and even a bag of ice is painful. Some of my patients have put ice in a bucket of water and then just kind of put their foot in that and found that they got some relief.

Meghna: Wonderful advice. And lastly, I'm going to bother you with one last question, Dr Edwards, what can clinicians, especially rheumatologists, take away from this conversation we've had in light of Pain Awareness and Arthritis Awareness Month?

Dr Edwards: Well, I hope they would take away that gout isn't just pain. It is the hallmark of the disease and it is the most excruciating pain that rheumatologists will probably see. It needs to be approached, it needs to be approached quickly and decisively, with good doses of anti-inflammatory medications and the patient that is in your office or in the hospital on the anakinra would be a great approach to that.

But then, to remember that gout isn't just the painful flares, it's the underlying disease, metabolic disease process of accumulating too much uric acid and those forming crystals and the crystals causing bony destruction, so that what we are trying to prevent over the next decade or two of this person's life is for them becoming [incapacitated] because of a disease that was very treatable in its early stages.

Meghna: That's great advice, and with that thought, I thank you for your time and wonderful insight you provided today.

Dr Edwards: Okay, my pleasure. Thank you.