Christiaan Scott:

Good day everyone. My name is Chris Scott. I'm a pediatric rheumatologist from Canada and I'm joined by Dr. Raphaella Stander who's a general pediatrician from Cape Town. We're both members of the International Clinical Council for FOP, and we're very happy to be able to talk to you today about the diagnosis and management of FOP. This talk is supported by an educational grant from Ipsen Biopharmaceuticals and our conflict of interest declarations is there for you to see.

So I'll start us off by talking about how one goes about diagnosing fibrodysplasia ossificans progressiva. So what would you do if you saw this girl aged four years old who comes into your office with a two-month history of this very tender, painful lump over her left scapula? The lump is progressively increasing in size. It's also getting more tender, and it's also started affecting the mobility of her spine. When you do some initial investigations, because you've probably never seen a lump like this before, her CRP is 24, her full blood count is normal. Her CK is normal, indicating no evidence of muscle inflammation, and her LDH is normal. The question you should ask yourself is, would I do a biopsy in this context?

When you do the x-rays, you notice that there are areas of extra bone formation. Here you can see that demonstrated approximating her humerus, and you can also see that she has a very short first toe with a toe situated in a valgus position. Other further x-rays reveal this lattice network of heterotopic bone, actual bone that's formed in the wrong place. And here you can see how on the slide on the right, the humerus is tethered to the thorax with a bridge of bone that is what renders her arms immobile. So I wouldn't blame you if you didn't know about fibrodysplasia ossificans progressiva and you decided that you might want to consider a biopsy. This is certainly the root that many children with FOP go.

Unfortunately, though it is the wrong route and biopsies in FOP are completely contraindicated. So why are biopsies contraindicated? Surely one would want to know what's going on in an infant like this with lumps on the back or a child like this with lumps on the back of her scalp. Well, the reason is that biopsies can be potentially extremely harmful in the context of FOP. And our first rule in medicine is to first do no harm. So fibrodysplasia ossificans progressiva advances to the extent where it encases the body in a heterotopic skeleton of additional bone that's formed in the area where muscle formerly used to be. And the point about the biopsy is that it is harmful. The diagnosis of FOP is extremely straightforward.

It's very, very easy, and if you misdiagnose it and you start to consider doing biopsies, it can be extremely harmful. And here's the key to the diagnosis. The first toe, as you saw on that x-ray of our first patient is usually abnormal in FOP. You can see various examples. These are from a handbook called the Tin Soldiers Diagnostic Handbook showing various children of various ages with abnormal first digits in their feet. Thumbs incidentally are also slightly can be shortened and malformed as well. But the most obvious finding is toes that are shortened, often lacking a joint and immobile, and they're usually in valgus. And you can see various degrees of that present on this slide.

If you see a child with lumps on the back and toes that are in valgus and that are shortened, you can make the diagnosis of FOP. So much so that if you consider this slide on the right, which is a copy of a textbook that is a collection of medical oddities that was published somewhere in the 1800s that shows a textbook of a man, the ossified man as they call him on the text, and you can see there a man with FOP. And the reason we know it's FOP, even though this description comes from 1875 or something, is the fact that the toes are manifestly abnormal on the very accurately drawn medical images. So again, why do we not biopsy FOP? Well, as you've seen, FOP forms in muscle and it forms when muscle is injured and needs to be replaced.

And what happens is if one damages the muscle, such as by doing an incision with a scalpel in the area of interest, the healing doesn't occur in the normal fashion and muscle is not replaced by muscle, but muscle is in fact then replaced by bone. And here you can see how a bony bridge like that would form between the humerus and the thorax. So biopsy is absolutely contraindicated. Other forms of muscle injury are also contraindicated because they can accelerate this process of ossification and lead to normal muscle becoming replaced by bone. This is especially important in the context of mandibular blocks or intramuscular injections. Here you can see how a mandibular block would affect the mass of the muscle, and what it does is it locks the jaw closed forever. The jaw will never open again once that muscle turns into bone.

Intramuscular injections can have the same effect by causing muscle inflammation and muscle injury and starting a process of ossification that can lock a hip into place. And there are many people with FOP who as infants, when they were given their immunizations developed their first signs of FOP by developing ossification in their quadriceps muscles from immunizations that have gone intramuscularly. So you can take a child who's previously able to eat, lock their jaw forever and render them with a mouth that is closed and therefore restricting their diet and their ability to enjoy food. Or you can take a child who was previously running or just learning to walk and render them wheelchair bound for the rest of their lives.

Why does this happen? Well, in FOP, the embryonal skeleton formation is emulated and the body is trying to replace muscle with bone in terms of virtually trying to build a brand new skeleton. And what it does is it builds this new skeleton in a embryonic pattern, starting at the back and the top of the head moving downwards and outwards just as the human embryonic skeleton would be formed. This is because the human skeleton development is driven by bone morphogenic proteins or BMPs. And the BMPs help to regulate the polarity of the embryo, and they also help to schedule the building of the skeleton in a specific way. The mutation that's responsible for FOPs in the ACVR1 or ALK2 receptor and this receptor regulates BMP activity and a missense mutation of the ACVR1 receptor causes FOP.

How does this work? Well, normally a normal ACVR1 receptor responds to binding with the BMP ligand by sending signals to the nucleus and which result in endochondral and ossification genes being activated and expressed. Activin A is a molecule that's related to inflammation, and in a normal BMP receptor, this molecule regulates inflammation through the same pathway. When the gene is mutated or the receptor protein is therefore abnormal and the ACVR1 becomes hyper-responsive to BMP but also starts inappropriately responding to Activin A. And so what you get when inflammation or damage is stimulated, you get this baseline leaking of BMP that's always present, and then the Activin A, which is there to be involved in the immune function, starts to stimulate bone production and endochondral ossification genes, just in the same way that BMP would.

It's been shown that people with FOP have at baseline a pro-inflammatory state, they're more inclined to respond with an excessive immune response to pathogen-associated molecular patterns and damage-associated molecular patterns. And this inflammatory pathway plays a role in driving endochondral ossification and heterotopic bone formation. So the key to the diagnosis of FOP is to look at the toes. And here you can see two neonates. This is from a paper which describes children born to parents with FOP. Incidentally, it can be inherited and it's autosomally dominantly inherited.

But to show you the power of being able to make the diagnosis at birth and these two infants born to parents who had FOP, you can see that on the left one, child was born with toes that are in valgus and that are shortened. And the other child was born with toes that appeared normal. And the child on the left with the abnormal toes was diagnosed as having fibrodysplasia ossificans, and the other child did not have this condition. I'm going to switch now and let Raphaella tell you about some of the cases that she's dealt with that illustrate some of the management issues in FOP. Over to you Raph.

Raphaella Stander:

Thanks, Chris. So this case actually begins with something every child and sometimes adults do, a simple fall. But in FOP, even a small fall can change everything. So this is patient A. She wasn't climbing, running or doing anything dangerous. She was simply walking on a smooth surface when her shoe sort of knocked something and she tripped. She was actually at the hospital getting a wheelchair fitting, so not in any abnormal environment or anything like that. But because her arms were locked, she couldn't protect herself when she fell. And what would've been a minor fall for someone else ended up being a head injury with a fracture to her orbit.

And this is the reality in FOP. So individuals are prone to fracture of both normal and the heterotopic bone, and this risk is increased by multiple factors, immobility, sometimes chronic steroid use, certain drugs like palovarotene, which we will come back to a little bit later. And just to discuss the management in this patient. So like Chris said, first, do no harm. So this injury was managed non-operatively. We opted for close monitoring given that there was stability of the fracture, the size of the fracture, and that there weren't any associated complications. And in her case, the outcome was actually excellent, it healed with no evidence of new heterotopic ossification.

And this case illustrates that even a simple fall is never really that simple in FOP. Which brings me onto my next slide, which is the key to FOP prevention. And when it comes to preventing falls in FOP, we focus on three key things. So here you can see a little boy with a helmet. So that is protective gear. And these we like to use when kids are learning to walk or they're unstable. The next thing is environmental safety, so optimizing flooring and surrounds and reducing the risk of slipping or falling. And then thirdly, stability support. So making sure they have proper shoes, walking aids when needed. And like I said, because in FOP, prevention really is protection, which brings me on to my next slide.

And that's just discussing fracture management in FOP. So the principles remain the same for all trauma care, but in FOP you need to think about every single step. And like Chris said, first, do no harm. So let's walk through what this would look like. So first we would stabilize. I mean, trauma principles. So gentle handling always. I remember airway neck precautions. And just to reiterate that we can't be doing IM injections for analgesia and mandibular blocks. Imaging is essential, so x-rays, if we need to use CT, MRI, ultrasound, and just don't forget airway neck precautions. And then we move on to conservative care.

So like our case illustrated, you want to prevent surgery and doing invasive things. So immobilize cast, but just make sure that those areas you are casting are protected from trauma. So padding, checking the skin. And then sometimes we recommend steroids and these can be given at two milligrams per kg and usually started within the first 24 hours of the fracture. We usually use steroids if there's lots of inflammation and swelling to try dampen down the inflammatory response.

Okay, we can move on to the next slide. Analgesia remains the same, just remember not to use intramuscular injections. And then surgery once again, only if it's life or limb saving. So you never want to try and remove HO or go into their bone, because you're just going to trigger a flare or new bone formation. Follow up is the usual six weeks. And if you look at the evidence, most fractures heal within the first six weeks and 97% have healed with union with only 7 to 10% who actually develop flares or new HO formation. And the golden rule here really is to avoid surgery at all costs unless it's life-saving. Okay, we can move on.

So fractures are one part of the story, but in terms of long-term health in FOP, it also really depends on nutrition. So there are nutritional challenges due to them being immobile. There's, like Chris said, chronic inflammation and often feeding issues. If their jaw is locked, it's difficult to get solids in. So iron deficiency is something we commonly see and we usually just say clinical vigilance is important. So monitoring your full blood count or CBC and iron studies if they're symptomatic, ensuring a diet is rich in

iron rich foods. And then we sometimes supplement with iron, vitamin D, calcium, all important things for bone health. And I'm going to hand over to Chris for the next case.

Chris Scott:

Thanks, Raphaella. So I'll present a case of a man who actually required surgery in FOP. And before I go into that slide, Raphaella's made a clear point that one should avoid surgery at all costs. Surgery potentially harms an injured muscle and therefore it can cause an exacerbation of FOP and new ossification. But that's only part of the story. The other dangerous part of surgery, as Raphaella's also mentioned, is the anesthetic. So while we're presenting a case of a patient going to surgery in FOP, I would like to be clear that this is really a last resort for anyone with FOP. So the reason this young man had to go for surgery was because he had a late diagnosis of FOP and he had severe jaw ossification.

And as a result of these two factors, he had a mouth that would never open and he was unable to do good dental hygiene. So his teeth became were poorly tended to by virtue of the fact that he couldn't open his mouth. And he therefore developed quite severe dental disease and gum disease with multiple caries, multiple dental abscesses. And when he was eventually diagnosed and put into care and connected with an international FOP dental expert and a South African FOP dental expert, it was decided that he required dental surgery to remove all of these teeth, which were causing him great discomfort but also placed him at great risk for complications of dental abscesses and so on.

The surgery was extremely complicated and here you can see why. His spine was completely rigidly fixed. You can see there that his neck and spine are completely encased in bone and this makes flexion or extension of his neck impossible. You can also see that his chest is severely restricted. This is one of the major complications of FOP, that the chest becomes constricted by this excessive bone having replaced muscle and the chest wall is no longer able to expand in the way that it should do and one ends up with quite severe restrictive lung disease. So with a combination of severe lung disease, a mouth that won't open, a neck that won't bend, this young man had to go for the fairly simple procedure of a dentectomy in someone without FOP, became extremely complex procedure for someone with FOP.

Anesthesia is not to be undertaken lightly in someone with FOP. It's to be avoided at all costs. And if it needs to be done, needs to be done in consultation with anesthetists who are aware of FOP, know the complications and know the basic principles of FOP anesthesia management. Anesthesiologists like this are available all over the world through the ICC. You can reach us. And this is what we did in fact with this patient in South Africa. He was fortunate enough to have an anesthetist who had worked on FOP before and this was going to be the second case. But in this man, the case was much more complicated.

On that slide, on the top right, you can see the anesthetist doing an awake fiber optic intubation. It was not necessarily very comfortable for the patient, but two anesthetists with fiber optic endoscopic expertise were involved and you can see anesthetic assistance involved as well. The other part that you can see just peeking out at the back is a man in the green surgical uniform with a mask. There were two ENT surgeons on standby. Should the fiber optic intubation fail and the airway become compromised, two ENT surgeons were on standby to perform a tracheostomy as an emergency, already scrubbed and ready to go when the anesthetic was initiated.

The dentectomy itself, you can see the extracted teeth lying on the table next to the operating, next to the patient. That was performed by maxillofacial surgeons, all of whom had been instructed in the care of FOP and knew to minimize trauma and muscle injury and bone injury to other parts as much as possible. So it was very carefully and meticulously done. All his teeth were eventually removed and he was extremely happy with the result of this. So the key concerns in FOP anesthesia relate to the immobility of the spine, the inability to open up the airway once a patient is sedated. Therefore, the use of fiber optic nasal intubation is important, again, avoiding intramuscular injections.

And also in the case of FOP, surgery in FOP, reduce that inflammatory component that surgery necessarily involves, we often treat patients with prednisone before surgery. The FOP anesthesia guidelines are available on the International Clinical Council website. Over to you Raph.

Raphaella Stander:

Thanks, Chris. So sometimes FOP doesn't reveal itself through those dramatic lumps and bumps that we saw in the first picture. Sometimes it's the quiet subtle signs that tell the whole story. You can see in this picture this young boy wasn't even our patient. He was attending clinic with his father when we noticed that he had subtle neck stiffness and when we looked at his big toes, they were malformed, and together these actually tell the story of FOP before the disease declares itself dramatically. So often in FOP, the subtle signs speak loudly. We can move on. So what did we learn from patient B Junior? His case shows us how critical it is to diagnose it early and what difference preventative steps can actually make.

So early detection is often subtle, like we saw, the neck stiffness, the malformed toes, and then you confirm the diagnosis, like Chris said, by clinical signs. So those malformed toes, the neck stiffness, and together with genetic testing, we can confirm the diagnosis. So we can test for that ACVR1 gene mutation. And because there's no cure at the moment, prevention is everything. So avoiding trauma, avoiding unnecessary dental procedures, IM injections, subcutaneous injections, these are the keys to managing FOP in young patients. So this story really reminds us that by early diagnosis, how important it is. Because his father was already diagnosed with FOP, it was easier for us to recognize the disease earlier in his son. Just a reminder to look for the subtle signs.

Chris Scott:

So at this point, I'm sure you're all wondering how else does one manage FOP and what can be done about the ossification itself? And I'm going to introduce the ICC treatment guidelines. I've mentioned the ICC several times. This is an international council of 21 international members who come from all parts of the world, from various subspecialties and disciplines, from dentists to dermatologists to rheumatologists, orthopedic surgeons, geneticists and endocrinologists. The ICC was set up as a voice for people with FOP and to better advise the FOP community on the management of FOP as well as issues such as running clinical trials and so on, and evaluating new therapies.

So the ICC, clinical guidelines for treatment considerations for FOP were put together by this group as well as seven consultants. And it was a Delphi exercise where more than 2,900 papers were reviewed and we ended up with the management guidelines of 150 pages. These guidelines have recommendations for the treatments of FOP. They talk about the medicines used in FOP and they also give instruction on emergency care of FOP in various contexts. Here you can see all the topics that are covered and you can see we only touched on one or two of them, but there are many aspects of FOP care that the need to be addressed and all of the evidence that is available is summarized in these guidelines for all of these topics that you see here.

I'll just show you some examples. FOP is characterized by flare-ups. These flare-ups are when the muscle is injured and start or sometimes spontaneously happen, and where the muscle is starting its transformation into bone. There's increased blood flow, angiogenesis, then chondrogenesis, and eventually then the formation of healthy bone. We have different guidelines depending on where the flare-ups happen. For instance, if they're happening on the back of the chest where they happen very frequently, they can be very prolonged. But they usually, after the early years, these flare-ups are in areas where limitation of the spine is already present.

And so they don't always have an increased functional risk of damage. In the context of these flare-ups that happen specifically on the back and the chest, we advise using nonsteroidal anti-inflammatory drugs to reduce the swelling and pain and perhaps to mitigate against some of the inflammatory component that's driving the process. But we suggest avoiding narcotic analgesia because these can be so long-lived, the risks of prolonged exposure to narcotic analgesia is higher than the benefit of using them. And sometimes we use steroids.

But again, because of the prolonged nature of these, we do not advocate for long-term steroids use in people with FOP because we know that while it can reduce swelling and pain to some extent, it doesn't actually reduce the eventual ossification that happens. And so it's use is limited to symptomatic treatment and perhaps reducing the initial inflammatory insult as much as possible.

Flare-ups in the throat and mouth area can be critical. Sub-mandibular flare-ups can lead to obstruction of the airway. They can be very difficult to distinguish from dental complications of FOP such as dental abscesses. Imaging can be really useful to tease these two things apart. But for these flare-ups and for flare-ups in this area, we advise prednisone as early as possible really to try and reduce the swelling and therefore the risk of airway obstruction. We advise a pill in pocket approach where people are issued with prednisone tablets or syrup and have it at home so that when a flare-up starts, which is inevitably in the middle of the night or on a long weekend, these tablets or syrups are available. We then give prednisone for up to four days to try and reduce the swelling of these.

Scalp flare-ups in infants are very common, but they are of usually very low clinical significance and can just be observed. Just a reminder that using non-steroidal drugs and steroids together obviously is a risk for the gastric mucosa and we usually advocate using PPIs for this as well. Intramuscular injections or live vaccines or vaccines that cause a profound inflammatory response such as the intranasal flu vaccine, which can sometimes cause inflammation of muscle are all to be avoided. And this is a broad topic with many factors to consider, but there are excellent guidelines for immunizations in the ICC treatment guidelines.

And there are also other resources such as this talk from the International FOP Association, which deals specifically with immunization in children with FOP. So in general we encourage subcutaneous vaccination of killed vaccines.

Hearing is another component that is often overlooked and is an important part of FOP by various mechanisms such as disorders of the ossification of the muscles and tissues in the ear as well as neurological problems can result in hearing loss. It's very common, it's essential to screen children with FOP yearly to manage their hearing loss. And here you can see a youngster with a hearing aid.

Incidentally, we did a project in South Africa where we had an international FOP meeting for people from all over Africa. We had nearly 30 or 35 individuals attend the meeting of various ages and we had audiologists test every person who attended the hearing and without fail, every single patient with FOP had hearing loss and the majority of them would've qualified for hearing aids. So those are just some examples of the, as Raphaella has identified, some of the preventative things one can do. Respiratory health is another important component as is dental health, and these are all covered in the FOP treatment guidelines.

But I still imagine many of you want to know what can be done about therapy for this. Well, we are in the era where the first approved medication for FOP was registered just recently, palovarotene has been registered in Australia, Canada and the USA. There were various issues with the clinical trials with palovarotene, and I'll discuss these in a bit more details in the follow-up slides. But to guide you on this therapy, there are two papers that I'd like to draw your attention to. One is a review that we did for a

journal review on palovarotene and its role in fibrodysplasia ossificans. The other is a statement by the ICC in general on the use palovarotene in FOP.

Some of the issues related to palovarotene, while it is absolutely novel to have a registered drug for this very rare disease, there were some concerns about side effects, the cost of treatment, and specifically the side effect of growth delay. So premature epiphyseal closure was identified as a risk in children receiving palovarotene through the clinical trial. And this was a major stumbling block in the continuation of the trial and caused an FDA black box warning. There are other less severe side effects such as myocutaneous adverse reactions, which one sees with all of the retinoids, which this drug is. And then some other issues that you can see that were identified in the trial.

But in total, palovarotene resulted in the end of the major clinical trials where there were 54% reduction in heterotopic ossification. That's like taking 20 cubic centimeters of bone measured by CT and reducing it over the course of a year to 10 centimeters, i.e., 10 centimeters of bone developed rather than 20 centimeters of bone. It doesn't actually cause the reversal of bone and shrinking of bone down or turning it back into muscle. The trial was relatively short and the people that enrolled had relatively advanced disease. And so no change in function could be shown. This was an issue for the regulators to approve the drug.

And the flare-up rate was also not better between the palovarotene group and the historical control that was used, the so-called natural history study. There was a high rate of withdrawal from the trial because of adverse events and because of the issues with premature epiphyseal closure and some of the side effects. The ICC guidelines go through the other medicines that have been used historically in FOP. The first is class 1 medications that are generally accepted as safe and have a role in FOP.

These are the non-steroidals and prednisone as I've outlined in the previous slides, but increasingly in order to address the inflammatory component to the immune system, which we know is important in FOP, various other class 2 medications not registered for FOP management, but registered for the management of other autoimmune conditions or auto-inflammatory conditions such as montelukast inhibitors. Mast cells have been shown to play a role in tissue that is about to become ossified. Obviously trying to inhibit the function of osteoblasts through Pamidronate and Zoledronate has been an approach.

And this is the use of bisphosphonates in treating flare-ups is well established in FOP, especially prolonged painful flare-ups. And then increasingly the use of medicines such as canakinumab, anakinra, tofacitinib, and imatinib, the JAK inhibitors and the IL-1 inhibitors. There are several case series where these are being explored as therapies for FOP, but again, none of them are registered for FOP and none of them have been the subject of rigorous randomized controlled clinical trial. Yet there is recognition that on a needs basis and a case-by-case basis, these therapies can be employed. The ICC has a statement on the use of these kinds of therapies in FOP as well.

And lastly, I just very briefly want to point out that there are several clinical trials underway. They're all listed there and just recently there results of the monoclonal antibody against Activin A, the fifth one on the list there garetosmab have been released and these results have been very promising. Raphaella do want to summarize?

Raphaella Stander:

Yes. So before we close, let's step back and take a look at the key clinical reminders. So first, always check the toes. Secondly, prevention is key. Avoid biopsies and invasive trauma. And third, keep with the trials and new treatments. This is a rapidly evolving field and we want to create hope for these patients. And that depends on us staying current. So never forget that we have referral pathways. We

spoke about ICC, IFOPA, Chris already briefly mention Tin Soldiers and just remember that none of us actually manage this alone. We need a whole team.

Chris Scott:

The genetics of FOP, as I mentioned very briefly, is that it's autosomally dominantly inherited, meaning that if someone with FOP has a child, their child has a 50% risk of carrying the FOP gene and developing FOP. Virtually all people with a mutation will develop FOP. So that's the first important point. The second point to consider is that there are many multi-generational families with FOP, but the choice to have children is obviously a very sensitive one and pregnancies are not that common in FOP. It was multi-generational families though that led to the identification of the first gene. And so the decision on whether to have children or not is obviously up to each individual with FOP.

But once that decision is made and a pregnancy is underway, it is possible to diagnose FOP either in utero using ultrasound, looking at the toes, or identifying it with other methods such as amniocentesis or then identifying whether the child has FOP just clinically at birth. But that's obviously a very complicated area of medicine and it's a rich area for discussion in FOP. Absolutely, 100% depends on the context in which you find yourself. IL-1 inhibitors, for instance, are totally unavailable in most of the world. It's only really Europe, the USA and some regions in the East, Russia, for instance, and Japan and South America, where IL-1 inhibitors are available. They're not available in India or Africa or much of Southeast Asia.

And so one of the drugs I mentioned is called canakinumab is extremely expensive. It's in the order $20,000 U.S. per month, so totally inaccessible for most people. Having said that, in some healthcare systems, including some centers in the U.S., people have managed to motivate with funders to be able to give these therapies. And so that's where this body of experience with it comes from. And the initial paper was written by colleagues in Israel. We were able to access it for people with FOP. But the cost of these therapies combined with a relatively low evidence base makes it very, very difficult to convince funders to pay for it.

So there's two ways to view that question. If you're in a position to be able to do the genetics, absolutely there is value in that. There are also variant forms of FOP, different mutations to the R206H mutation, that's the classical one. About 10% of people will have a variant mutation, and so they might have different disease expression, different phenotype, sometimes milder, sometimes more severe. And so it's useful from that perspective. In the context of these expensive therapies, I think many of the funders would expect the genetic confirmation of the diagnosis. As a clinician who practiced for many years in Africa, and I'm sure Raphaella agrees practicing in South Africa, that the clinical diagnosis, the phenotype is so clear and so obvious in most cases, that to do the basics in management and preventive care shouldn't require a genetic test.

If there were an affordable therapy that worked for everyone and was accessible in places where genetic testing wasn't accessible, I don't think there would be huge, personally, I don't think there'd be huge risk in employing this therapy based on a clear-cut clinical diagnosis of FOP. It's usually clear-cut if you've got some experience with FOP. So yeah, a genetic test is ideal but is inaccessible for a lot of people. And I wouldn't let that hold back basic management of FOP in an area where genetic testing isn't available.

Raphaella Stander:

So we're all listed on ICC websites and IFOPA is in contact with all the clinicians, Tin Soldiers and IFOPA. So we often get sent pictures or emails and then we all sort of communicate as a team. In South Africa,

our resources are so limited that a lot of GPs will manage these patients outside in the periphery, but the management will be a lot of, it'll be online via email and WhatsApp and communicating online, but it's hard to actually get them to a specialist center. So a lot of our patients are actually living in rural areas, and because, I mean I've just got one of our families refuses to go to the specialist hospital, so they'll phone us or WhatsApp us or email us just because the doctors there don't understand FOP.

So even a lot of our work is just trying to advocate for patients out there to understand. Even our medical aides in South Africa don't actually... A lot of them don't even know what FOP is. So we'll send them motivational letters explaining what the disease is. So actually to find a doctor that knows anything about FOP is very difficult. So these patients a lot of the time, they don't see the doctors in the area. And for them, the clinical trials have been super useful because then you actually are attending a specialist center once a month.

Chris Scott:

And I want to build on something Raphaella said, the fact is, the reality is that there are a few FOP experts in the world, but there are always opportunities for those experts to guide the management of patients remotely. And Tin Soldiers plays a big role not only in identifying caregivers in a specific locality that can support the diagnosis and management of FOP. For instance, we had a patient referred to Tin Soldiers from Uganda, a very rural village. But because we knew a pediatric rheumatologist in the area, we could refer the patient to the pediatric rheumatologist, get the diagnosis confirmed, and then empower that physician with all the knowledge they need through various educational programs, et cetera, to be able to manage FOP.

In other countries like the USA or Canada, there are experts available and referral networks are available for you to be able to at least have a consultation with an FOP expert. But the care almost always will depend on local caregivers with the guiding hand of experts when needed. And in that way, you slowly grow the expertise in FOP. Everyone who's managed the patient with FOP can consider themselves an expert eventually. So it's important to just make that connection and get in touch with the people who are available to help guide that transformation of you from being someone who's just seen one patient of FOP to someone who perhaps becomes a regional leader in the management of FOP.

That's in fact what happened to both Raphaella and I. We both started caring for patients with FOP and we weren't born FOP experts or had any particular knowledge about FOP until we encountered our first patients. And that was the case with me in 2010. And I reached out to the international FOP community and learned about it through that mechanism. And I think that I encourage people if they make a diagnosis of FOP to stay involved and to develop that expertise. It's not rocket science, it's just a matter of working at it and accumulating experience over time.

It takes the whole team sometimes to make the diagnosis, and it's very important in the diagnostic journey, if you're having doubts, Tin Soldiers is there to help you understand whether this might be a case of FOP. Tin Soldiers as a network of clinicians all over the world who will be able to integrate a patient into a diagnostic pathway and eventually a care pathway as well. And then once Tin Soldiers has helped to make the diagnosis and also to educate caregivers and educate people who potentially could make the diagnosis of FOP, the International FOP Association or regional FOP associations are absolutely valuable resources to support patients through this very, very difficult diagnosis.

And these organizations, such as the IFOPA do amazing work. But if you have a new patient with FOP or you suspect you might have someone and you're not sure, then by all means, reach out to the Tin Soldiers as listed over there. Or send Raphaella or I email and we'll connect you up to them and help confirm the diagnosis. I think that's the end of it. We'd like to thank you for your time. I'd like to thank

Raphaella for her contributions. I'd also like to thank the organizers and the sponsors for sponsoring this educational webinar. We hope you found it useful. Thank you very much and have a good day.