



MIGRAINE WORLD SUMMIT

INTERVIEWS WITH WORLD LEADING EXPERTS

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TRANSCRIPT

UNDERSTANDING TREATMENT FAILURE AND OPTIONS

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Introduction (00:02): In acute migraine treatment, we say that there's a drug failure when the drug cannot lead to substantial pain improvement. But also in this case, there are some factors which matter, and the main factors are the dose of the drug and the timing of the absorption of the drug.

Carl Cincinnato (00:36): Despite advances in the management of migraine, some of us do not experience adequate pain relief with acute or preventive treatments. This leads to a higher burden and disability, not to mention the toll it takes on work, relationships, and family. To help us navigate difficult-to-treat migraine is Dr. Simona Sacco. Dr. Sacco, welcome to the Migraine World Summit.

Dr. Sacco (00:56): Thank you. It's my pleasure to be here.

Carl Cincinnato (01:00): What is your definition of difficult-to-treat migraine?

Dr. Sacco (01:03): Thank you for your question. As you already said, there are many patients with migraine who have a low burden of the disease, and they are reasonably well managed with current therapies. But there's a proportion of patients who do not have adequate pain relief with the use of the available remedies. And so we consider migraine to be difficult to treat when the patient has tried several preventives which were not able to significantly reduce the frequency of the attacks; or the patient can also be considered difficult to treat if the attacks couldn't be cured by acute therapies.

Dr. Sacco (02:10): Well, this is a general concept which is not difficult to be accepted. However, it's much more difficult to find a precise definition regarding thresholds for the number of drugs or the number of headache days per month which should be present to consider the patient as having difficult-to-treat migraine. In the past, there were some attempts to provide definitions of difficult-to-treat migraine, but none of them so far has reached wide acceptance. And one of the reasons for the lack of wide acceptance is that the threshold you decide to select depends on the aim of your definition.

Dr. Sacco (03:17): I will try to explain. If your aim is to escalate treatment — for example, if your aim is to give botulinum toxin or a monoclonal antibody acting on CGRP to one patient — the threshold should be necessarily low. But if your aim is to really understand the biological basis of lack of response to treatment, or to develop some new interventional and possibly risky treatment, the threshold should be necessarily higher. And for this reason the European Headache Federation developed a new definition of difficult-to-treat migraine, which includes two categories which may respond to the different needs. So on the one side we have resistant migraine, and the patients with resistant migraine are those who continue to have at least eight debilitating headache days per month, despite treatment with at least three preventive treatment classes. And on the other side we have refractory migraine, who are patients who have the same number of migraine days — so eight debilitating headache days per month — but who could not obtain adequate pain relief with the use of all the available treatment classes and by the use of analgesics.

Carl Cincinnato (05:17): OK. So if you have resistant migraine, it means you've failed several therapies; if you've got refractory migraine, you've failed all of them.

Dr. Sacco (05:27): Yes, exactly.



Carl Cincinnato (05:27): So how common is refractory migraine?

Dr. Sacco (05:31): This is a good question, but we don't know exactly the epidemiology. In the general population, difficult-to-treat patients represent only a minority; most migraines in the general population are low-burden migraine. However, the situation is different if you look to patients [who] refer to a tertiary headache center. Here the epidemiology changes, and the proportion of difficult-to-treat patients may become relevant. So far as there was no widely accepted definition, we do not know the exact epidemiology. There's one study which indicated that about 5% of patients referring to headache centers have refractory migraine, according to the definition which was used in that study.

Carl Cincinnato (06:41): So if you have refractory migraine, does that mean that you've failed all the treatments that you've been given, or does it mean that you're going to fail all treatments, and so there are no treatments for you?

Dr. Sacco (06:56): It means that you have failed all pharmacological treatments. Of course, at the tertiary headache centers there are some strategies which can be put in place by physicians with a lot of expertise in this field, which can try to provide some benefits in pain control to patients. For example, a physician can try to associate one drug with another; to combine pharmacological with nonpharmacological treatment; they can try to suggest some strategies aimed to control behaviors, to control trigger factors which can be associated with lack of pharmacological responses.

Carl Cincinnato (07:56): So what are the major preventive drug classes that are considered when evaluating if someone has refractory migraine?

Dr. Sacco (08:05): Well, the drug classes which should be considered are those which have proved to be effective in randomized controlled trials, and which are suggested by evidence-based guidelines for migraine prevention. So they include mostly antidepressants, beta blockers, calcium channel blockers, especially in Europe; they include angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, botulinum toxin, and, of course, the monoclonal antibodies acting on CGRP.

Carl Cincinnato (08:56): OK, so that's a good point. To be classified as refractory migraine, you have to have failed at least one drug within all those classes. What constitutes a drug failure?

Dr. Sacco (09:06): Criteria for drug failure include two major issues: one is the lack of efficacy, and the other is the lack of tolerability. Lack of efficacy is when the patient continues to have frequent debilitating headache while he or she is on treatment with a given preventive drug. It's very important [when] say[ing] that there's a treatment failure to check that the dose of the drug is adequate, because taking a drug below the minimum effective dose may be responsible for poor efficacy. It is also important to check that the patient has been taking the drug for a sufficiently long period, because we know that some of the available preventives need titration and do not work very early. For oral drugs, the minimum required duration of treatment is around two months after reaching the therapeutic dose. For botulinum toxin, the minimal required treatment period is about two cycles, which is equal to six months. And for the monoclonal antibodies acting on CGRP, it is three months.



Dr. Sacco (10:50): Another reason for failure is the lack of tolerability, because many patients do not tolerate the available preventives because of side effects, which can lead to discontinuation. And this problem is mostly associated with migraine oral preventive drugs. Headache specialists need to work on this in order to try to do the best to avoid patients discontinuing treatment unless it is strictly necessary. Some side effects can be tolerated by patients if they are alerted about their possible occurrence. For example, with the use of topiramate, it's very common to have paresthesia in the fingers. This may alarm the patient unless you have explained in advance that this is a benign situation.

Carl Cincinnato (12:05): Can you explain? Is that "pins and needles" or numbness?

Dr. Sacco (12:08): Yes, it's sort of needles at the point of your fingers. And it's also important to advise patients that some side effects will disappear while going on with treatment and some of them can be managed by making small changes in the treatment, such as a small decrease in the dose or changes in the timing at which the drug is administered.

Dr. Sacco (12:43): And we have also to consider that in some cases the drugs may not work also simply because the diagnosis is not correct. Patients may have a condition different from migraine, or they may also have a coexisting condition on top of migraine which cannot be treated with migraine preventive drugs.

Carl Cincinnato (13:11): So for migraine preventive treatments, the reason or the criteria for drug failure, or the drivers of that, may be based on having the right dose; trying the preventive for enough time for it to work; and as you said, sometimes the drugs need to be titrated up; and then tolerability, as well. And so given that there were between six and nine different classes of preventive treatments, if we're giving each a fair duration to build up to the maximum dose, it could take several years to go through all of those different treatment classes. Is that true?

Dr. Sacco (13:51): It depends also on the tolerabilities, because some patients take the drug for a very short period. So it is really necessarily, in some cases, one or two weeks, because the side effects are too bothersome to be tolerated. However, usually patients with refractory migraine come to our centers with a long migraine history, and so they date back the use of the first migraine preventives to many years before. In this case, we do not run again through drugs which were failed in the past; we just trust in what the patients report to us.

Carl Cincinnato (14:45): So that covers prevention and refractory headache or migraine [response] to preventives. What about on the acute treatment side? What constitutes a failure of an acute migraine treatment?

Dr. Sacco (14:59): In acute migraine treatment, we say that there's a drug failure when the drug cannot lead to substantial pain improvement. But also in this case there are some factors which matter, and the main factors are the dose of the drug and the timing of the absorption of the drug. There are some patients who tend to take a lower than recommended dose, and this is not good, because it's better to take a full dose in order to have complete pain relief than taking a half-dose first, and then [later] another half-dose because the first half-dose was not effective.



Dr. Sacco (16:01): Additionally, in migraine patients, attacks can be completely stopped only when the drug is taken very early, at the beginning of the symptoms. If the drug is taken later, the pain cascade is too widespread to be completely blocked by any drug. And a further point which is important is the way of administration, because some patients have early nausea. And when nausea is present, this usually indicates that there's some impairment in the motility of the gastrointestinal system, and these may lead to a delay or to incomplete absorption of an oral drug. If this is suspected, it's better to use non-oral drugs, such as suppositories, sublingual pills, or intramuscular injections.

Dr. Sacco (17:22): It's also important to note that if a patient does not have a positive response to one drug class — for example, if a patient does not respond to one NSAID — it's worth trying another drug in the same class, so another NSAID or another treatment. So it's important to say that an acute drug is not effective only if the patient's taken the full dose at the right time, in the right formulation, and has tried at least two drugs of the class.

Carl Cincinnato (18:07): That is some excellent advice that you just provided there, which is, I think, worth recapping. So acute treatments are different [from] preventives in the sense that if you try one treatment within a class, it doesn't exclude the other treatments in the same class, because unlike preventives, there is a chance that others could help. And as you mentioned — NSAIDs (nonsteroidal anti-inflammatories), triptans — it's worth trying another type if the first wasn't successful. And then you also mentioned about the timing of the dose and how important it is to treat the attack earlier, before the pain has had time to disseminate through the body. And then also, finally, was the dose. So three things to be thinking about from an acute treatment perspective, which are quite different from preventives. So thank you for sharing that.

Carl Cincinnato (19:01): If someone's taken an acute treatment [and] is experiencing what they might describe as a refractory migraine, or a migraine that hasn't responded to the first-line or second-line treatment, when should they go to the hospital?

Dr. Sacco (19:16): Usually I have to say that it's not a good thing to go to the hospital for a long-lasting migraine attack, but of course, in some cases, after the patient has tried several treatments, the pain is so unbearable that they refer to the hospital. There's no exact moment which can be generalized to every patient because each patient has their own personal history, and so they know which are the drugs which usually work and which usually do not work. So the suggestion is to go to the hospital when they've tried all the possible remedies they have at home. But I think what is important to say, and an important message to give, is that when this happens, it indicates that there is something which is not working in the correct way. And so if a patient has the need to refer to the hospital for the management of an acute migraine attack, the patient should also consider to refer to a headache center for evaluation, because probably those patients need some adjustments in their preventive strategies or in their acute attack strategies.

Carl Cincinnato (21:03): So it sounds like there may be an opportunity to speak to the headache specialist about what to do if your first-line treatment doesn't work, and what options you might have with a second- or potentially a third-line treatment, rather than going to a hospital where you may be waiting under bright lights, surrounded by sick people, and not necessarily prioritized amongst the group.



Dr. Sacco (21:26): Yes, and often when acute treatments do not work, it is the case to consider starting preventive treatment, or to improve the prevention if the patient already has a preventive treatment going on.

Carl Cincinnato (21:46): Are there any similarities between a refractory migraine attack — and maybe that's not a good use given the definitions that we've just described for refractory migraine, but an attack that will not disappear — and a status migraine?

Dr. Sacco (22:01): Well, it's not exactly the same, because status migrainosus is a long-lasting pain situation, which is really, really hard to control with any of the available acute attack treatments. But patients who have refractory headache are at higher risk to develop status migrainosus.

Carl Cincinnato (22:33): What are some reasons why someone might be having migraine every single day?

Dr. Sacco (22:37): When a patient is starting to have migraine every single day, there is a mechanism of chronification which is going on. The mechanism of migraine chronification is very intriguing, and it's [as of] now not entirely understood. What we know so far is that chronification for many patients is a gradual process. It develops slowly over time, and it is associated with a mixture of factors. Many migraine patients who have migraine every single day have a long history of migraine, and what happens is that at a certain point migraines start to worsen, and the worsening usually is associated with the presence of a triggering factor. And the triggering factor may be — is usually different from subject to subject. For some, the worsening may happen in the setting of a stressful event. For others, it may happen in the setting of a trauma. For others it may happen in the setting of hormonal changes, for example, transition to menopause or in the postpartum period. But in others we simply cannot identify any precipitating factors.

Dr. Sacco (24:28): There's now ongoing, really a lot of research in the process of chronification, and the hypothesis is that the patient who has severe headaches for many years has started to process sensory inputs in a different way from the patient who has few or mild headaches, and over time those recurrent headaches can model certain brain areas and certain brain circuits. And we also know that at some point those brain areas and brain circuits become different in a stable way, and that this probably indicates the point where it starts also refractoriness to treatment, and the process is harder to be reverted.

Carl Cincinnato (25:41): Is that the most difficult type of migraine to treat, or is there another type of migraine that's more difficult?

Dr. Sacco (25:47): I think the most difficult-to-treat migraine is the long-lasting chronic migraine, and the factors which usually alert us that there may be a poor response to treatment are associated with psychiatric comorbidities or some particular personality profiles. Also, medication overuse is an unfavorable prognostic marker, especially if the patient reports that they have tried and failed the strategies to stop the medication overuse. And also other comorbidities may be markers of difficult-to-treat migraine; for example, obesity, coexistence of inflammatory disorders — for example, arthritis is very common in difficult-to-treat migraine — or also coexistence with other chronic pain conditions, such as fibromyalgia or low back pain.



Carl Cincinnato (27:09): So it sounds like there are a number of different classes that people can try, and if they haven't tried all of them that there are opportunities for getting access to those, particularly if they've failed several classes of treatments already from a preventive perspective; and there are also options within classes for acute treatments. What about some treatments that we haven't discussed, like nonpharmacological treatments, such as nerve blocks or stimulation devices? Can they be used in combination? And can some preventive classes be combined — for example, Botox with an anti-CGRP — to try to provide some relief for people with chronic or refractory migraine?

Dr. Sacco (27:51): We have also a number of nonpharmacological treatments in the migraine field. They include the nerve blocks, but they include, also, neurostimulation, such as vagal-nerve stimulation, suboccipital, or supraorbital stimulation. We have transcranial electrical stimulation; we have acupuncture; we have biofeedback; and we have relaxation techniques, cognitive behavior therapies. The point is that for those nonpharmacological treatments, there's a general lack of high-quality studies. They are less used than pharmacological treatments because they are less accessible; they depend more on the professional person who's giving the treatment, and they are also less standardized.

Carl Cincinnato (29:10): So it sounds like there is hope for someone who has refractory migraine. There are combinations of classes; there are different alternative treatments and complementary therapies that they can do alongside that — which we've hinted at — through lifestyle and behavioral changes or trigger management; as well as nonpharmacological options.

Carl Cincinnato (29:29): Dr. Simona Sacco, thank you very much for your time and joining us on the Migraine World Summit.

Dr. Sacco (29:35): Thank you. It was really a pleasure to be here and to have the opportunity to discuss and share my point of view about difficult-to-treat migraine.