A clinician perspective: It's never too late to benefit from telomerase activation therapy

Dr. Joseph M. Raffaele, M.D.
Tom Berenguer, M.D.

Dr. Joseph M. Raffaele, M.D.
Well it's great to have you on the show, Tom, we've known each other for quite a while. I've been sort of in the telomere trenches early on, sort of trying to get the word out there and treating patients with it. I'm excited to talk to you about, a little bit more about the start, about your journey and how you got to where you are in age management or longevity medicine. However you want to call it these days. What interested you in the field, and then how you sort of got involved in telomerase activation and learning about the role of telomeres in aging, and how you use telomere biology in your practice.

Tom Berenguer, M.D.
Right, it's a pleasure being with you, Joe. Thanks for inviting me, I would say that my involvement started by attending the age management meetings, just seeing the TA-65 booth, which was very small in the beginning around 2011, 2012. Eventually leading to my undergoing testing and starting the use of TA-65, and then expanding it to my patients, as I learned more and more about it, my enthusiasm for it increased and my knowledge base also, and to this day, now eight years after I started, I remain highly enthusiastic. And although my patient base is small, based on the length of time I've been in practice at my age, my patients remain very positive about it and about its benefits.

Dr. Joseph M. Raffaele, M.D.
So you obviously weren't initially trained as an age management physician, what sort of made you get into the field? And what kinds of treatments do you use along with TA-65?

Tom Berenguer, M.D.
I actually was trained in age management medicine with cenogenics. I started with them in 2005 and then went independent in 2009. So my interest in age management began early after

I stopped my OBGYN practice in '04. It expanded considerably with introduction to TA-65 and telomere science. But as I said just a few minutes ago, that enthusiasm has not waned one bit during this eight year interval. And I remain very, very positive about not only its benefits, but about the sophistication of the testing and monitoring of patients who are considering it and using it.

Dr. Joseph M. Raffaele, M.D.
So you, since you trained in age management, I meant originally you were an OBGYN, because back when you and I first started in medicine, there wasn't any field like this. So in terms of other types of therapies you use, you do hormone optimization in your practice, supplements, diet, and curious how you fit that into discussions with your patients about telomere, testing it out, you do telomere testing, in your practice, so you can tell us about that as well.

Tom Berenguer, M.D.
Right, the practice that I have is focused very sharply on lifestyle improvement and the areas of nutrition and exercise supplementation where it is beneficial, and any other approaches which will add to the goal of extending longevity and making patients healthier while they are alive. TA-65 in my view has been a significant contributor to those goals.

Dr. Joseph M. Raffaele, M.D.
So you start out with baseline testing on your patients with telomere length?

Tom Berenguer, M.D.
Yes, yes all patients who have started use of TA-65 in my practice, undergo baseline testing and regular testing, which I originally and largely continue yearly. The pandemic has interrupted testing significantly, as well as patient visits and the entire medical picture. But I will surely return to a regular program of annual testing for the patients. In that regard, I have communicated with you regarding various sources of the testing. And I started out with life length, had some use of repeat diagnostics in Canada, and have returned to life length because of the fact that they have ironed out, solved the problems with their testing templates. And I have confidence in the results that I'm receiving now.

Dr. Joseph M. Raffaele, M.D.
Yeah, no I think that's absolutely true. They had a little glitch there with ranges there for awhile, but their assay certainly is good. So you said you use it for people who are going to go on TA-65. Do you screen all your patients when they come in to see whether or not they need to worry about it? Or, I know it's a money issue to a certain extent, obviously the testing is not inexpensive, but when you're talking about a supplement like TA-65, I think it might've told you

I've lectured about a patient who came in of mine, who wanted to be on TA-65. The reason she came to see me, a 52 year old, and she ended up having telomeres that were about as long as the average 20 year old. So didn't need them at that time. And she still doesn't actually,

Tom Berenguer, M.D.
Right.

Dr. Joseph M. Raffaele, M.D.
She's still up there in that 20 to 21 year old range. Of course she needed a bunch of other things, hormone replacement therapy, she needed to have her homocysteine level worked on, et cetera. So do you try to do screening on your patients? Or how do you approach that?

Tom Berenguer, M.D.
The answer is partial, I do screen some patients, particularly the older patients who I anticipate are going to have a worse profile than younger patients. And my patient age range is from 40 to 80, but skewed heavily toward the over 65 age group. Well, I should say over 60 would be more accurate, that age, that median age for my patients has shifted as time has passed, but I have screened for a good number of patients who like your example, really would not benefit with TA-65, at least for the present time. And for some patients I screened who would benefit and they've declined, but largely the screening that I've done, which has not been uniform across the board, has turned up results that indicate patients would benefit from the use of TA-65.

Dr. Joseph M. Raffaele, M.D.
And any of those cases stand out to you in terms of the length of their telomeres at when they started, and any other sort of clinical attributes that they might have, that go along with that? Or in response to the therapies? I know you do repeat testing.

Tom Berenguer, M.D.
Right, the profile of my patients is unusual in that they are, we are four to one male, and they are almost all entrepreneurs, business people. They are highly motivated, highly successful, and highly stressed. And so that latter factor contributes significantly, I believe, to the profiles that I see on the baselines for these patients, it has been very encouraging and positive that despite the high stress nature of the work of most of my patients, they've responded well to the lifestyle improvements and to TA-65 use.

Dr. Joseph M. Raffaele, M.D.
What are some of those lifestyle improvements you do?

Tom Berenguer, M.D.
Say that again?

Dr. Joseph M. Raffaele, M.D.
What are some of those lifestyle improvements that you prescribe specifically? Because there's some controversy about them, you know, some people think, and I have some ultra runners in my practice, and then people that do a lot of high intensity stuff, then there are people who want to just do walking. What kinds of prescriptions do you give?

Tom Berenguer, M.D.
Yeah, good question. The lifestyle recommendations I've made and monitoring my patients, have evolved. In the beginning, it was narrower in terms of what I recommended, that was based on my early exposure to the age management world and the lack of experience in dealing with this, back in '05 and '06 and '07. But as time has passed, I realized that just as in so many aspects of life, one size does not fit all. And so nutrition programs, which in the beginning were very similar to say, the zone diet, have evolved into a list of potential dietary avenues that patients can travel, based upon their particular, not desires, but what fits them best and what they will follow. Right now, it's in general, simply low-glycemic. It's low sugar, and the goal is to have patients consume in general, less than a hundred grams of carbohydrate a day. That is a goal. It's not a practical marker for a certain number of them, because I have a couple of patients who are outliers.

They are very large framed, and therefore simply based upon muscle mass and body weight, require more of everything. So tailoring programs, including nutrition programs to patients, has been one of the goals that I've achieved over time. The exercise programs are geared to a wide range of activity. I emphasize weight training, I emphasize high intensity interval cardio, as compared with say, running, I don't like running because not just my own experience, which was very bad in terms of affects on knees and hips. But because of the known detrimental effects of the constant pounding on the turf to the skeletal system, particularly the knees and hips and back. So I discourage patients from running on treadmills or even running outside, but if they like to do it, then I try to get them to follow the regimens that are gonna be least potentially destructive to their skeletal systems.

Dr. Joseph M. Raffaele, M.D.
Yeah, I mean running is very efficient in terms of calorie burning and cardiovascular, but that the toll for most people that don't have really good genetics for it is pretty rough. I've done triathlons and trained for them, and the running part can be the most, sort of causes the most wear and tear. So have you noticed anything in terms of telomere length with people in terms

of their body composition and shorter telomeres, in particularly overweight people or anything like that? Or maybe you don't have a large enough database to sort of to see that.

Tom Berenguer, M.D.
Just one note before we leave the exercise arena, and that is about the cardio training. I emphasize that there's a difference between the endurance that you acquire through running in general, and the conditioning that you acquire through a high intensity interval cardio, conditioning is what will help us to stay alive and healthier longer, particularly heart and lungs, because those are the two organ systems that principally are gonna fail us as we get older. So I pound on that with patients to try to convince them that testing, challenging the heart and lungs with a high intensity cardio is more productive than steady running outside. In addition to the reduction and the stress on the skeleton. Regarding the telomeres, very definitely notice a difference in patients who enter, who have bad genetics in terms of their physical shape, their physical makeup, which is of course, genetically determined. The individual with the particular body shape that I have have alluded to, the Indian, the South American Indian physiology is particularly susceptible to metabolic deterioration, whether it's a development of metabolic syndrome or other undesirable metabolic changes over time. So those patients, and I have a few, have started at baseline and worst condition in terms of telomere length and percentage of short telomeres than the majority of the others.

Dr. Joseph M. Raffaele, M.D.
Have you come across anybody would qualify as a telomaropathy, meaning in the bottom one percentile for their age?

Tom Berenguer, M.D.
No, I have not done that. I've looked for them, but I have not seen anyone who is that much of an outlier to qualify for that category. I hope I never do.

Dr. Joseph M. Raffaele, M.D.
Yeah, well I mean, for your patient's sake, I do as well, but I certainly have, and you know, giving as the bottom 1%, you probably will, as your numbers go up and, you know, oftentimes particularly in the younger patients, you don't see anything particularly different about them phenotypically, other than perhaps premature graying, and so that's why, you know, I like to do the case finding, you could call it screening, but it's really more case finding, for these people that have a, you could call it a ticking time bomb. It's really a, it's a clock that's there that's been set way forward. So that, I had a 40 year old that came in with seven year old telomere lengths. And that person is somebody who really is in need of being quite sure that they do the things from a lifestyle exercise and diet standpoint to keep their telomeres from getting shorter, but

also, you know, excellent candidates potentially for TA-65. But yeah, I do. What's the shortest telomere length you've seen, just out of curiosity? I always like to talk to, you know, active practitioners about their -

Tom Berenguer, M.D.
I would have to look to see the answer to that, but they have fallen into the area, to the zone of short telomeres and 25, about 25% of cases. I can certainly get that data for you, but off the top of my head, I can't tell you the shortest one, but there've been about one in four who have fallen into the category of short telomeres.

Dr. Joseph M. Raffaele, M.D.
Right okay, yeah. So that's definitely a good candidate to get on TA-65. And how about, well, what's the longest, perhaps besides yourself, the longest you've been treating a particular patient, and what's been your experience with both the trajectory of the tests, if they've done repeat testing over the years, and also fluctuation in the test?

Tom Berenguer, M.D.
Eight years is the duration of the longest patient, longest use for any patient. The trajectory has been uniformly good. There has been a fairly consistent initial burst for use of a better word, a burst of improvement, and then a leveling off or plateauing of the improvement. But even with smaller increments of improvement, continued improvement with, as I mentioned earlier, the problems with the testing templates at life length, that returned erroneous results for about two years. With that aside, the improvement has been incremental, initially greater, and then less as time passed, but continued improvement. What I've not been able to do is correlate the incremental improvement with dosing. Well, I've struggled with the question of what is the best dose for a given patient and should dosing be based on something more than the amount of improvement, ie, body weight, or other factors?

Dr. Joseph M. Raffaele, M.D.
You know, I don't think there's any evidence for any kinds of markers like body weight, body fatness, or age or gender as I mean, there may be, but the data isn't there for it. I think part of the reason for that is the initial studies that the company did on bioavailability, is that it's very, very wide, up to five fold I think, differences with the same dose in peak levels and individuals that couldn't really necessarily be explained by weight or gender or anything like that. So I mean, I struggle with that as well. Do you use the lymphocyte subset panel that's available from UCLA at all? 'Cause you can sometimes use that. I've used that to titrate dose if I don't see a response in senescent T cells in the first three to six months, then I'll raise the dose. I start everybody out on 250. And then because of, you know, you wanna give them the dose that

works at the lowest dose, but again, there's some people that need higher doses. Unfortunately, you know, the study that we published on the varying doses, even breaking up the doses into twice a day, didn't show any major difference. I mean, the good news is that all doses improve telomere length, and all dosing regimens did, but it didn't tell us which one was better. And so, you know, I don't know that the take home from that is that, you know, the lowest dose once a day works for everybody. 'Cause I pretty clearly see that that's not the case. I think perhaps the study just needed to be larger to get information about differences between dosing and dosing regimens, and perhaps longer, which of course gets expensive because it was a full year. In any case yeah, I think if you started with those, I mean, I definitely do and other doctors I've talked to and practitioners that use TA-65 have struggled with that.

Tom Berenguer, M.D.
Right, in regard to the dosing, it's of significance to me as a clinician treating patients day to day, that the data are not conclusive about advantage of say daily versus twice daily dosing. We know the half-life of TA-65 isn't long, it's less than 12 hours. And so on paper it should be a twice a day dosing. It should be superior to a daily dosing, but the data from the studies that I've seen don't clearly indicate that, it would be wonderful if we had definitive data on a daily versus twice daily. Because if daily dosing is equal to a twice daily dosing, then the compliance among patients is enormously greater. You and I well know of the difficulty in getting patients to comply with anything more than daily dosing.

Dr. Joseph M. Raffaele, M.D.
Yeah, no question about it. I mean, and, and even if it was, I mean, women taking progesterone, I usually get them to take out at night in addition to their morning medications. But you know, there's a fairly compelling reason for that. If they don't they'll start having bleeding. And they won't sleep as well for the vast majority of them, but with men, we don't have that. And then, you know, twice a day is just, well maybe if you took it at bedtime, you would probably, you know, that's not as good as splitting up with the doses if you did it truly BID. So yeah, there are those challenges, but you see an increase in telomere length and then you see plateauing. Have you had anybody that hasn't responded in terms of stopping attrition or maintaining telomere length?

Tom Berenguer, M.D.
No, I've had some dips, by that I mean I've had some patients who have been ill from one source or another, some who have undergone surgery and the stress of the surgery has caused a decrease in telomere length, another kind of stress, but it simply emphasizes and I've conveyed that to patients, that stress in any form is bad, and prolonged stress is much worse.

And so one of the lifestyle issues that I pursue with patients in addition to nutrition and exercise, hormone support and supplementation, is stress control.

Dr. Joseph M. Raffaele, M.D.
Oh, do you use meditation and other relaxation techniques?

Tom Berenguer, M.D.
Yeah, so whatever works, I'm not wedded to any one, but I simply tell patients to pace themselves and in a basic sense to recognize the stress is there and to admit that they need to take steps to deal with it and to neutralize it. So it may be as simple as ordering vacation time, time away from the job on a daily basis, taking weekends off and not turning the computer on. The list is endless, but there are so many ways to deal with stress, in addition to the standard meditative approaches that patients are not aware of. And they really don't seem to understand, even sophisticated patients, how impactful stress is in a negative way on health in general, including telomere length.

Dr. Joseph M. Raffaele, M.D.
Yeah, it sounds like I might have to start incorporating some of those suggestions into my life. Right now, my telomeres are holding steady, perhaps because of TA-65, I mean, I do exercise a lot. So when you first sit down with patients to have a conversation with them, and let's say you have telomere length results in hand. What kind of a sort of informed consent discussion do you have with them around potential benefits, what to look for, but also, you know, there is that, and you can answer this last, that sort of, sort of more this question that most patients come up with, is there any risk of cancer with TA-65?

Tom Berenguer, M.D.
Right, the informed consent session that I have with patients before it's starting TA-65 and sometimes along the way, if any new evidence emerges, has to do with the data that we have. And we have significant data on the cancer risk, which once again, as with say growth hormone, the theory versus the practice are quite divergent, quite different, with growth hormone as with TA-65, the theory would support an increasing and cancer risk in general, because of the nature of the medication, how it works. But practically speaking, it's been quite the opposite. So I tell them, here are the data we have that do not support any increased cancer risk. And in fact, with preservation of telomere length, the strengthening of the immune system will help to reduce cancer mutations. And to, as it were nip them in the bud, before they reach a point that they are self-sufficient.

Dr. Joseph M. Raffaele, M.D.
Yeah, so any other things you talk to them about in terms of side effects or things that you've seen anecdotally, potentially beneficial, and have you heard anything back from them on that?

Tom Berenguer, M.D.
Yes, I give them anecdotes because we don't have enough information at this stage to be able to stay definitively that that TA-65 does this or that, the goals are to protect the telomeres, the length of telomeres, to strengthen the immune system, to reduce senescent T cells and therefore also strengthen the immune system. It all is linked together, that's how I present it to them. But anecdotally I have, for example, two patients who swear that they've, each has TA-65 for six or seven years, and both swear that they go to the dentist less frequently because they don't accumulate plaque nearly as rapidly as they did before they began TA-65 use. Now that floored me at the beginning. And when the second patient made that announcement, I scratched my head and I started looking for it, but I didn't find much.

Dr. Joseph M. Raffaele, M.D.
Yeah, no I mean, that's kind of interesting that, you know, we hear things like that. You don't know whether that's from the TA-65 or not, but I mean, we've certainly had documented cases of improvements in presbyopia and even myopia in patients.

Tom Berenguer, M.D.
Yes.

Dr. Joseph M. Raffaele, M.D.
And there's obviously good reasons why that might occur, particularly for the myopia, if it has anything to do with macular, early macular degeneration in the retinal epithelial cells, pigmented epithelial cells being able to regenerate themselves better on it. Tom Dowd actually published a study on some improvements with that, MAIA instrument to show improvements in macular health. But other things, you know, you hear about recovery from workouts. If you have any, you know, high intensity athletes or long endurance athletes, which I think, you know, the training for these endurance athletes is really pretty, probably pretty bad for your telomere lengths, when it gets past a certain level, which it does oftentimes, seeing them able to improve their personal bests in areas is kind of an interesting thing. And hopefully it will be looked at more and more closely, just getting back to the whole, you know, I think, the conversation that I have in terms of the theory versus practice, which I guess is a good way to put it. I mean, with growth hormone, you and I both been in this field long enough that there was all this talk about, well, growth hormone causes cells to divide and therefore increases your risk of cancer. And there's some observational studies that came out and then was of course the animal

models with our transgenic animal models, you know, it's that same fallacious reasoning that takes place with testosterone. You know, men have more cardiovascular disease, men have more testosterone, therefore testosterone increases your risk of cardiovascular disease. You know, just easy

Tom Berenguer, M.D.
Right.

Dr. Joseph M. Raffaele, M.D.
To think about, but not borne out, when you look at the data, particularly the Rhoda data, where we see an increase in cancer over every decile from the lowest decile, from the highest decile to the shortest decile in cancer risk and mortality. There are other mitigating factors, perhaps ones like you mentioned, the immune system improvement and reduction in oxidative stress because of the health that TA-65 can bring to your mitochondria, the health benefits it can bring to your mitochondria. So, you know, I would just as you do, and as I do with my patients, counsel patients to look at the data that we have and not the theory that people put forth, because oftentimes that's not the case, unless you have hard data to show otherwise.

Tom Berenguer, M.D.
There is another anecdotal case I have, a patient from Memphis who is in his late fifties, has been taking TA-65 for six years, when he began iron man competition, initially he was able to continue his hormone support program, but he stopped that because of his concern that, even in an amateur status, he could be tested. And if he were shown to be on any hormone support, he would be disqualified. After stopping the hormone support program, and continuing the TA-65, he must have sent me a dozen emails and text messages about his continued improvement in his area of physical performance, and he was convinced, and I'm pretty certain also that the TA-65 continued to contribute to his performance and all of those areas. And that TA-65 was largely responsible for his ability to continue at that high level of physical performance in the face of loss of all the hormone support.

Dr. Joseph M. Raffaele, M.D.
So he was an iron man triathlete, which of course the iron man itself is not what really beats you up, it's the training for it which is incredible. Did he, how old would did you say he was, was he in his fifties?

Tom Berenguer, M.D.
He's 59.

Dr. Joseph M. Raffaele, M.D.
Yeah, that's a -

Tom Berenguer, M.D.
He Wound up in the top 10 in the country in is his age group.

Dr. Joseph M. Raffaele, M.D.
Yeah, I have some masters athletes that get to that level and see improvements on T 65, but also worried about their hormone replacement therapy as well, once you get too good and you start to win, then you have to step back a little bit on that, even though it's, you know, we're just replacing the physiologic levels, you know?

Tom Berenguer, M.D.
Yeah.

Dr. Joseph M. Raffaele, M.D.
It's something they shouldn't necessarily be doing in these competitions, because it does give an advantage cause it does work. Have you had any adverse effects that you've seen in patients at all?

Tom Berenguer, M.D.
No, none that I could link even even casually to TA-65 use. Occasionally a patient will note some mild gastrointestinal symptoms, but it's really insignificant. So the answer is no, no side effect profile of any note, compare with just about any RX medication I've ever written.

Dr. Joseph M. Raffaele, M.D.
Right well you know, the molecule is fairly inert other than its effect on the promoter for the telomerase gene. I mean, there may be some off target activity in the bombesin system, but that hasn't really been worked out that well, but say, I mean, I have hundreds of patients and then probably thousands of patient years of patients on it, and I haven't seen anything that's had anybody have to stop TA-65. So that's a good bit of, and I talked to many physicians, and with your patient base and things, how many over the years have you been treating?

Tom Berenguer, M.D.
Oh, I've treated about 50 altogether. I currently have 22 patients. And I think I can, I'm going to put on a, I'm going to make a greater effort to enroll some of my non-users into the program by approaching them with the senescent T cell logic, as opposed to the previous approach, which had to do with biological age decreasing. Most of my patients are sophisticated enough that

they understand if it's put into a format which makes sense. My previous view of the senescent T cell testing was that it would be hard for them to understand and to translate that to their personal situation. But I see that it is possible to do that. And it makes just as much sense as doing a median telomere length test, or percentage of short telomeres, and reporting that in terms of biological age.

Dr. Joseph M. Raffaele, M.D.
Yeah, and it's a shorter term marker. We, I use both typically, but in terms of short-term dosing, that's the one I rely on more, because even with a pretty small coefficient variation of two to 3%, which is sort of what a repeat diagnostics is, I'm not aware of right off the top of my head, what it is with life length, but it's in that ballpark, and expected telomere length loss for the year, which is 0.05 kilobases, you're talking about 0.2 to 0.3 kilobases in test to test variation. So it takes a while to get an idea about whether or not you're going in the right direction with telomere testing. And so the senescent T cells do work out nicely. I also sort of just, if patients are cost averse, it's about 350 to 400 bucks for the UCLA lymphocyte subset panel which gives you those markers, let's just refresh our audience's memory or introduce them to the fact that it's the CD28 negative suppressor cells, and the CD8 positive, CD28 negative suppressor cells that we looked at in the study that showed a significant reduction in a large, 500 patient randomized controlled trial of TA-65, about 20% in CMV positive patients and around 10% in CMV negative patients. So that is I think, a good marker to look at, but if you can't afford it, just don't want to do that, then you can look at the immune risk profile, which is just the CD4/CD8 ratio that you can get at lab Corp request and a regular lymphocyte panel from them. And if they're below one, you really want to get them on something. And if they move out of that from below one to above one, and 1.5 to 2.5 is optimal, then you've really made a big improvement in their potential longevity I think, and immune health. So, but I think going forward, that is a good approach. We have software, you know, that can help you track that, we should actually talk to you about getting your practice set up for that, because that's makes it real easy. We give them a grade, what we call an immuno age and it could be helpful. I find it easier for patients to think of it in terms of grades and years. So I'll talk to you about that afterwards. Let me, well it's been great talking to you. Do you have any closing thoughts about where you're gonna go with your practice and your use of telomere biology and your other approaches?

Tom Berenguer, M.D.
Yes, yes I do have a couple of comments. The discussion you just made about the benefits of measurement of a senescent T cells with the UCLA test or otherwise, makes sense. That is a item for discussion that will resonate with patients and will impress them, getting patients like, I should say my group of patients are impatient to get results. They're impatient about just about everything, which is a major part of their success. They move forward quickly and they

move forward aggressively in general, which is not so good for stress, but it's very good for their personal achievement and for their level of satisfaction. So getting those results back to them quickly or frequently will reinforce their use of TA-65 and perhaps convince some non-users to become users. And in the same vein, the geriatrics journal, a study that I just read from you and the coauthors, was good. It would be great to have a study that had two years or three year duration, and it involved even more subjects as always. But the data from that study impressed me in a couple of ways. One is the dose, that it may be that that daily dosing is just as good as twice daily dosing, despite the half-life. I would love that to be the case, because I can get my existing patients, some of them are just very difficult about taking anything, but once a day anything, several of them take all their supplements at one time the entire day.

Dr. Joseph M. Raffaele, M.D.
Right.

Tom Berenguer, M.D.
I don't know how they do that, but they do it, but that's just the nature of my patient base. So if that were to appear over time, I would love that, the other point in the study was the CMV negative patients. 32% of them, there was no comparison in terms of their response, compare with CMV positive patients. I would love to see that because if I can tell one of my patients who is CMV positive, that he is that, and that his chance of experiencing short telomere development over time is greater than a CMV negative patient, then he's more likely to adhere to not only the lifestyle program, but to switch to a program involving use of TA-65.

Dr. Joseph M. Raffaele, M.D.
Yeah, so interestingly, there was, I mean, I'm not sure what you're pointing out, but there was a comparison, I mean CMV negative patients. This is why I test CMV serostatus in all my patients, do typically have 25 to 30% the number of senescent T cells that CMV positive ones do. And so they have less of a burden of senescent cells. And I was surprised to see that they in fact actually had an improvement in them, even though they in fact, did not have a whole lot of them. And I thought that was great, because that meant that even patients who aren't CMV positive will benefit in an immune rejuvenating effect. Of course the magnitude of the effect was less, but that's because they didn't have as big a burden on them. I mean, the average person that's CMV positive has about 250 to 300 senescent T cells per microliter, versus the CMV negative being around 60 or so. So we did see reduction. I'd even see patients that come in at 20, 30 and go down to 10 or 15, which is a good thing, and at percentage wise, a pretty reasonable drop. But I agree with you certainly on continuation, because I see patients continue to see improvement in senescent T cells, you know, at one year, two years, et cetera, you know, perhaps we'll get the company to do that at some point.

Tom Berenguer, M.D.
Well looking for that longer duration study, which will yield so much more information. And to my mind be a real blockbuster over the population who should be taking TA-65, but are not.

Dr. Joseph M. Raffaele, M.D.
Yeah, no so hopefully look, the company will invest in another study. We're waiting right now for the results of the tactic trial, which is the TA-65 after a first MI, to prevent second MI, based, not so much on endothelial cells, but more based on the known idea, the relatively well worked out idea that is the T regulatory cells, and the immunosenescence that puts people at increased risk for inflammation and cardiovascular events. And so, Dr. Spiradopolis in the UK has enrolled patients to look at that as a primary endpoint reduction in senescent T cells. So you'll see another study showing hopefully a beneficial effect to corroborate this effect. And then as secondary end points, they do have a secondary MI's or a secondary need for revascularization, but it probably won't be powered enough for that. It's a pilot study to look at, you know, to see whether or not you can get the reduction in senescent T cells in this group. So that'll be more in the senescent T cell side of the story for TA-65.

Tom Berenguer, M.D.
Joe, the future of telomere science is extremely exciting. I wish I were as young as you, sp I could be around longer to enjoy the developments that I know are coming.

Dr. Joseph M. Raffaele, M.D.
Well you know, if they come as soon as I expect them they will, that we may be having this conversation in 20, 30 years from now.

Tom Berenguer, M.D.
I hope we do.

Dr. Joseph M. Raffaele, M.D.
Alright, well it's been great talking to you, Tom. Thanks for taking the time out.

Tom Berenguer, M.D.
I've enjoyed it, Joe. Have a good day and remaining week.

Dr. Joseph M. Raffaele, M.D.
All right, take care.