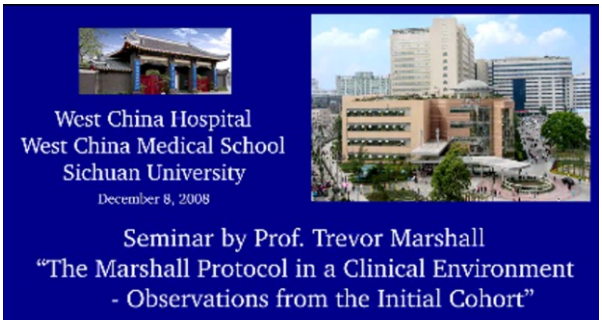
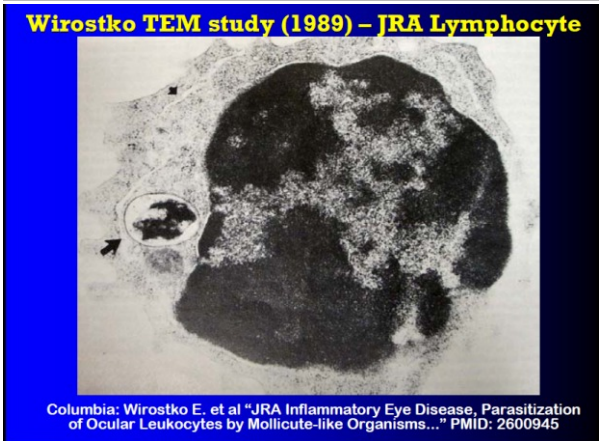
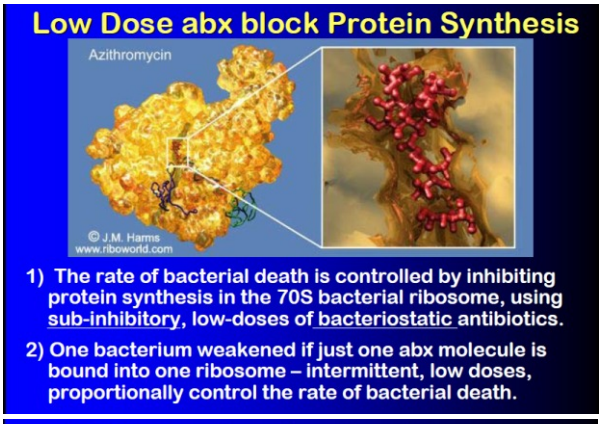
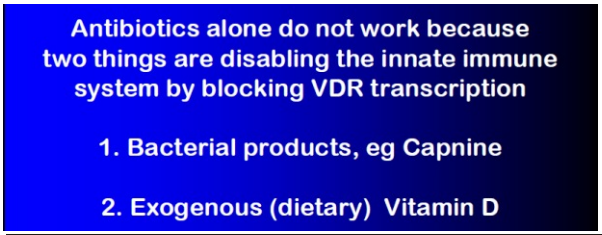








The Marshall Protocol in a Clinical Environment: Observations from the Initial Cohort

PRESENTED BY PROF TREVOR MARSHALL
Director, Autoimmunity Research Foundation

West China Hospital, West China Medical School, Sichuan University.
December 5-7, 2008. Transcript of www.vimeo.com/2599416 video.

Need to understand disease process

This is a quotation from the commissioner of the U.S. FDA when he was speaking to congress back in 2006. He said, "New scientific discoveries are generating an emerging science of safety … This new science combines an understanding of disease and its origins at the molecular level (including adverse events) with new methods of signal detection, data mining, and analysis…."

The FDA Commissioner recognizes that we can do so much more in medicine if we understand the underlying disease processes, because then we can predict adverse effects; we can figure out what signals we should be detecting. That's really what we have done. We started from an understanding of the disease process to try and produce a therapy that works.

Review

Just reviewing quickly, this is what we are dealing with. We are dealing with the inclusions in the cytoplasm of nucleated phagocytic cells.

This is a lymphocyte. This is a big inclusion but there are also different shapes, bacterial colonies as well.

Low Dose abx block Protein Synthesis

Now we can use low-dose antibiotics to block the protein synthesis by blocking the 70S bacterial ribosome.

One bacterium is weakened if just one antibiotic molecule is bound into just one ribosome, because then the ribosome can't function. You only need one antibiotic molecule to bind into one ribosome and you have blocked that bacterium from producing — out of that ribosome, at least.

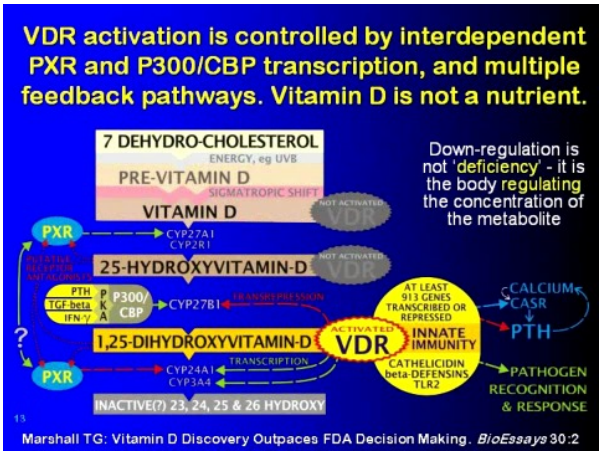
Intermittent, low doses can proportionally control the rate of bacterial death.

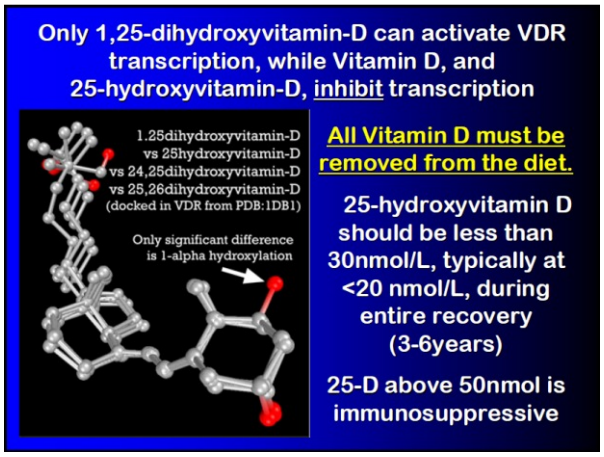
Antibiotics not enough

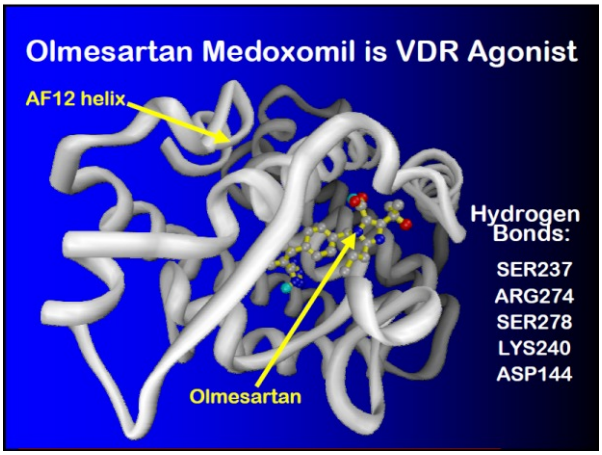
But antibiotics on their own do not [always] work, because two things are disabling the innate immune system by blocking VDR transcription.

The first is bacterial products such as capnine.

Capnine is just a bacterial product which comes out of gliding bacteria, such as the lysobacter type of gliding bacteria, and it is very common in a biofilm. It is sort of like a slug moving along the







ground or a snail and leaving a trail behind it. It is a similar sort of thing. When these bacteria move through biofilm, they leave a trail of capnine behind them. And capnine happens to block the VDR. We have shown that in silico. I am sure there are lots of other substances that different species produce; that is just one of them.

Secondly, exogenous (dietary) vitamin D will block the human innate immune system from doing its job properly. And as the patients become more sick, they become more sensitive to dietary vitamin D.

Dietary Vitamin D

Now, dietary vitamin D is not a problem in China. You don't have your milk supplemented, as far as I can read (I can not read the box very well). But in America, everything is supplemented with vitamin D, because in America, people think that vitamin D is good for them, and the more they get, the better it is. So they have vitamin D in their milk, it is put into the cheese, it is put into some butters, it is put into orange juice. Orange juice is fortified with vitamin D now. So in America it is very hard to avoid vitamin D at this point.

Vitamin D makes people feel good, because it is an immune suppressant. It suppresses the immune system's response to these microbiota. It makes people feel good because it suppresses the symptoms in much the same way as you give people a corticosteroid to suppress the immune system, and they feel good. Well, generally they feel good, except for the neurological side sequellea [effects].

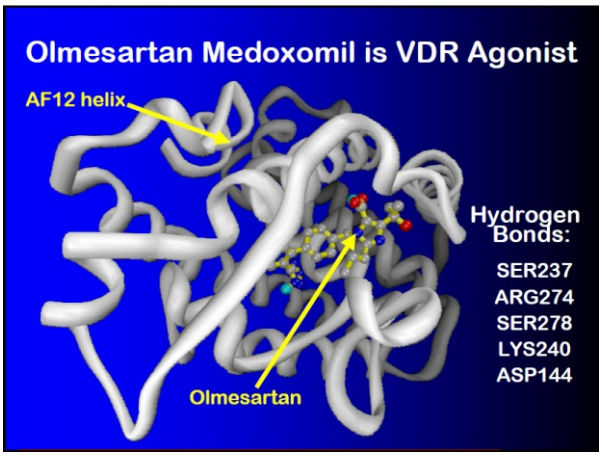
And, as we said in the previous presentation, the VDR activation is controlled by a number of nuclear receptors: the PXR, the P300/CBP which is actually a transcription factor, and the VDR. Vitamin D is not a nutrient.

Olmesartan medoxomil

Now, what we have found is that olmesartan medoxomil is a VDR agonist.

Olmesartan was produced as an angiotensin 2 receptor antagonist, a receptor blocker, which it does a very good job of, and it does it at quite low concentrations. It has been extensively safety-tested by the FDA, and it is one of the safest drugs in the formulary. As far as the FDA is concerned, they have seen no data indicating any unsafe level for ingestion of olmesartan. It is a very new drug; it was passed through the U.S. FDA in 2002. And I know there is a manufacturer here in China that is capable of manufacturing olmesartan — presumably for your local market.

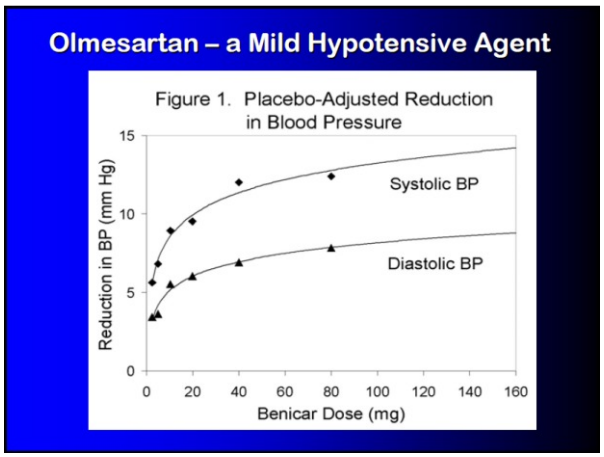
This is the VDR, and this is a different type of in silico image. What we have here is a static image. It is still three-dimensional, we have got some depth — the darker helices are supposed to be farther in the background than these lighter ones — but it is not moving. It is very quick to do these [static] analyses [but] it is very slow to do the analysis of a moving molecule, because you



have got to do so many simulations. You have got to simulate each one of those little movements of the molecule.

But what I have shown here is olmesartan. This is the drug, with the two oxygens up here, the oxygen in the other position. But it exactly mimics the position of the active oxygens in the 1,25D molecule. And then you have the nitrogens involved, in the imidazole and the tetrazole loops down here, these do the rest of the agonistic functions that allow this molecule to "turn on" the VDR.

When this molecule is docked in the VDR, there is an average of seven hydrogen bonds that are active at any one point in time. It is very, very strongly bound into the molecule, and it binds in such a way that the receptor is activated. And for those of you who are technically inclined I have listed the hydrogen bonds, the residues that they are formed with, and you will find that they are exactly the same residues that 1,25 dioxyvitamin D binds to.

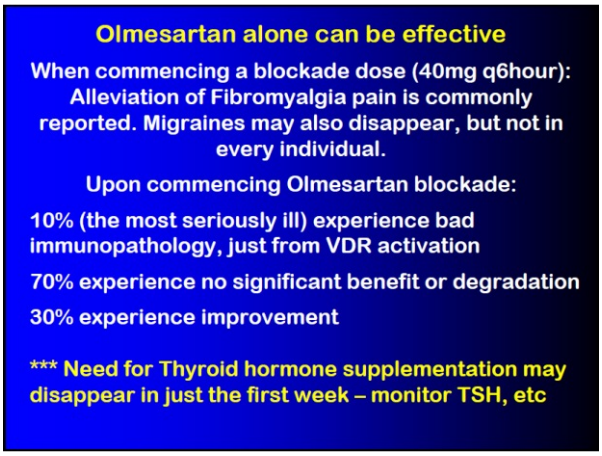


So what is olmesartan?

Well, it is a mild hypertensive agent. It is given for high blood pressure. And as the head of the FDA Cardiovascular Disease Division told me, "It is not a very good one, either. It does not depress the blood pressure very much at all." As you can see there is a maximum effect of somewhere around 12 millimeters of mercury here, maximum — in systolic and diastolic — and less on diastolic, of course.

The interesting thing is you have got down here the dose of medication — 0, 20, 40, 60, through 160 mg, and up here you have got the reduction in blood pressure. Nearly all of the reduction in blood pressure occurs at quite low doses, down here. By the time you get to 20 mg a day, nearly all of the reduction in blood pressure has occurred. That is because this drug is a very good angiotensin 2 receptor antagonist. It is very good at blocking the angiotensin 2 receptors.

But the other task it does, the VDR agonism, it does at slightly higher concentrations — up in the region of this part of the curve, between 120 and 160 mg a day of olmesartan. And up there, it not only blocks the angiotensin 2 receptor, but it also activates the VDR.



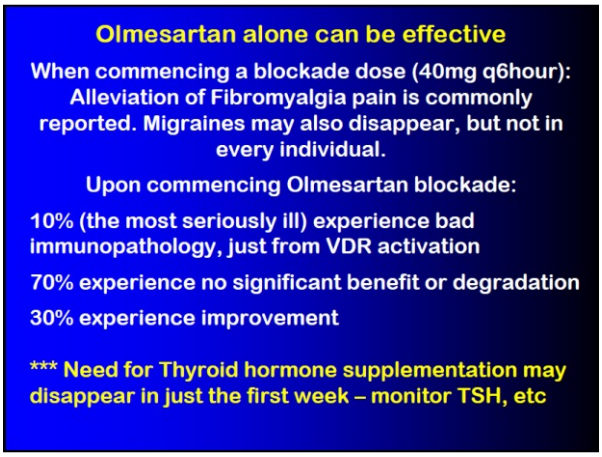
Olmesartan alone

Olmesartan on its own can be effective. So just giving the patient olmesartan, at the correct dose — not the anti-hypertensive dose of 20 mg a day — usually just makes them feel worse rather than better, because their system is pulsing on and off, every day, which is not much fun. So you have to give Olmesartan continuously, every six hours. We typically say 40 mg every 6 hours is a base dose.

When you give that dose, quite often, right at the commencement of the blockade — within the first couple of weeks — you will find that fibromyalgia pain, typically, is reduced. Migraines also can

disappear, but not in every individual. There was a study of ARBs in migraines, and I think they found about 60% efficacy with a different ARB (candesartan). But that is about what we have seen.

Of course, for those people whose migraines disappear, this is a godsend, because it is such a difficult thing to treat.

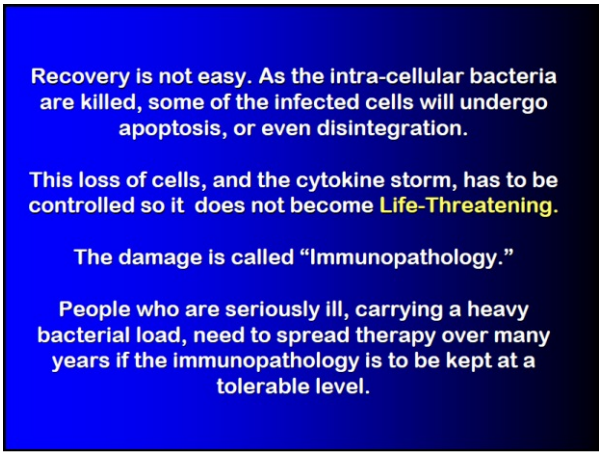


Olmesartan alone can do that. Also, when you start olmesartan, we have found that about ten per cent — the most seriously ill patients — experience bad immunopathology, just from the VDR activation. When you turn on the immune system, the most seriously ill patients — the ones that have had the most therapy — typically, about ten per cent can experience quite a lot of immunopathology and be very uncomfortable.

But most of the patients, about seventy per cent, experience no real benefit or degradation. Sometimes they feel a little better. They usually feel a little better.

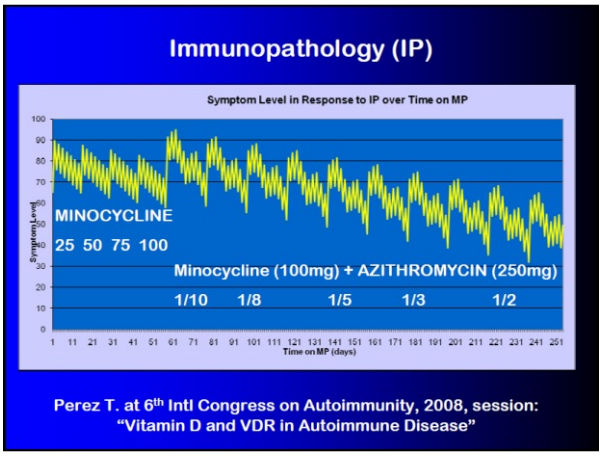
And about thirty per cent experience significant improvement, particularly in pain, in migraine, or just in general — “Hey, I feel better,” type of thing.

I have got a very important proviso down at the bottom. If the patient is on thyroid hormone supplementation, you must measure it regularly. When you start the Benicar (olmesartan), within just the first week, the requirement of the dose of T3 or T4 that you are giving them may drop very rapidly as the hormones adjust in the body. So when you start olmesartan, you have got to be very careful to measure the thyroid hormones and adjust their supplementation those first few weeks. And certainly, within the first six months, you would find that most of the thyroid supplementation is no longer needed.



Dealing with immunopathology

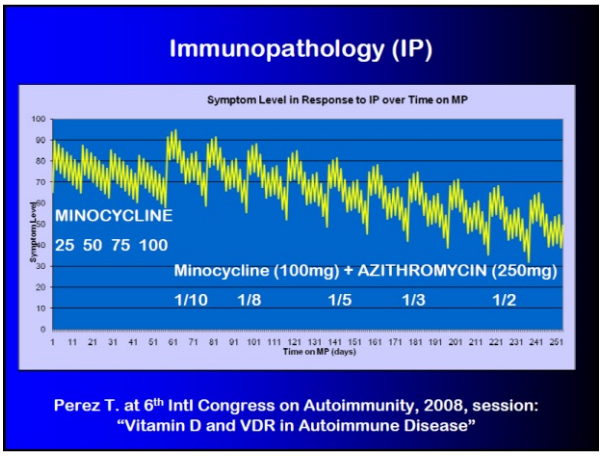
This is a repeat of the slide from the previous presentation. Recovery is not easy, because as the bacteria within the cells are killed, some of the cells will die as well. It is a very important concept. There is no way of killing these bacteria within the cells without killing some cells as well. The secret to being able to do it is to understand that, and also to do it slowly. Slowly and surely.



Immunopathology

This was the graph that was presented at the Portugal Autoimmunity Conference by Captain Tom Perez. This is a graph of immunopathology. It was drawn by one of the patients who have recovered, and it was her idea of what she felt immunopathology was like. It is like the symptom level in response over time.

She has 100% up here. That was the symptom level before she started the therapy. Once she started the minocycline at 25 mg every two day dose — very low dose — 25 mg every 48 hours is what they start at. Then over a period of time they can build up the amount of minocycline they are taking as they work down their bacterial load. And you can see the jumps here in the



immunopathology. When the IP drops down to a level that the patient is very comfortable with, then they say, "Okay, let's increase the dose up again" and then they start with this 90% level. A little bit less suffering than when they started the therapy is what the 90% means.

Then by the time they get to 100 mg of minocycline every 48 hours [and their symptoms become tolerable], at that point they are put onto the addition of a second antibiotic — either azithromycin or clyndamycin. This graph shows azithromycin.

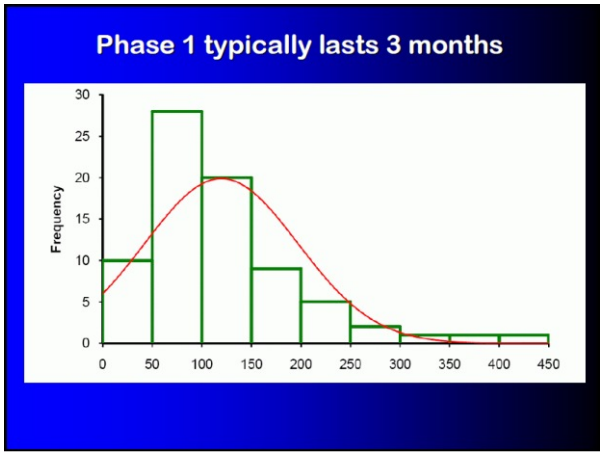
Now, this is one-tenth of a tablet. When they add one-tenth of a tablet of azithromycin every ten days, many patients cannot handle the extra amount of immunopathology. It is just amazing to see how much the sensitivity to the antibiotics is increased by the activation of the VDR with the olmesartan. So they start at a tenth, they go to an eighth of a tablet, a fifth of a tablet, a third of a tablet, and finally end up with a half of a tablet (250 mg). And you'll notice that you have got this ten day pulsation here in the symptom levels over time.

Rate of recovery

But you notice that she has drawn that the symptom levels are gradually decreasing over time. If we have got days (she has 251 days here) by the time she had got up to about nine months (251 days), she thought her symptoms were around forty to fifty per cent.

By the time they have got up to about two years, the blood work is essentially cleaned up. By the time they get to three years, their lipids, their cholesterol, their LDL and HDL level will be back in range; their triglycerides will be back in range. You will see the blood work confirming the recovery of the body at about that point, between the two and three year mark. You will also see it earlier, but it is less marked. When they get to about two years, that is really the beginning of the recovery period. Up until that stage, it is pretty tough going for the average patient through this region.

Phase One

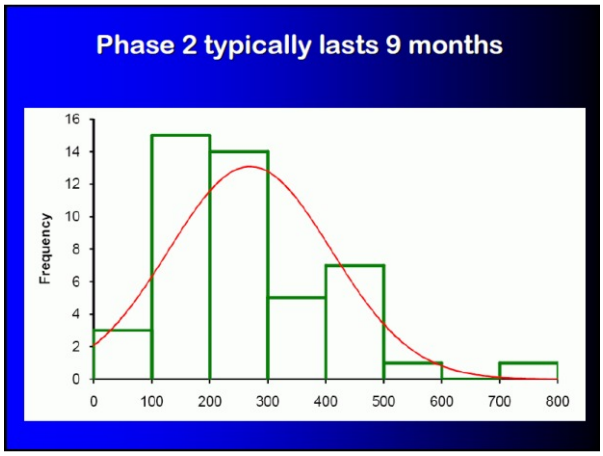


How long do they stay on phase 1?

Phase 1 is the period where they are just getting minocycline. They are building up the minocycline dose they can tolerate, from 25 mg every 48 hours to 100 mg every 48 hours. Phase 1 typically lasts three months. This is the diagram, the histogram that was produced from that same data that we saw on the other graph of all the ordinary conditions that have resolved — rheumatoid arthritis, Hashimoto's, etc. — and you can see that the most common period is typically around 70 days. If you draw the curve through it, it comes somewhere around 120 days or 4 months. But we say typically 3 months.

After 3 months, we try to transition people to two antibiotics, because we are very concerned about getting an even killing —

killing the bacteria in an even manner, not just getting rid of one species or another species. And that is best done with multiple attacks on the protein synthesis.

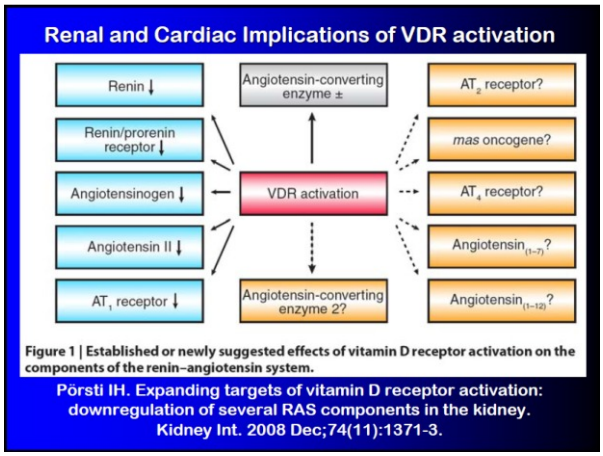


Phase Two

So typically they stay about 90 days in Phase 1, and then the two-antibiotic stage, they typically stay about nine months. You can see down here the number of days, and somewhere around 270 days is the average amount of time.

The most common is around 150 days, or about 5 months. But they are in the two-antibiotics phase for that long, and by the time they get out here, their immunopathology has dropped to a level where we can increment the antibiotic, increment the killing a little bit further.

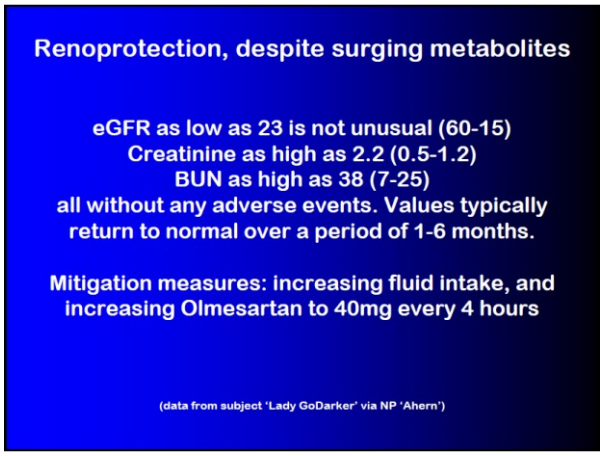
We do that by adding a third antibiotic, either clyndamycin or azithromycin — depending on what we started phase 2 with.



Problems

Now, here are some of the problems that we get. The VDR transcribes 913 genes. It affects just about every function of the body — which is one of the reasons that the body goes haywire when the bacteria block the VDR. This slide is from Porsti et al, in *Kidney International*, December 2008. This came out just a few days before I left the U.S. This paper shows that when the VDR is activated, it downregulates renin production; it downregulates the renin/prorenin receptor; it downregulates angiotensinogen, angiotensin II, and the angiotensin1 receptor. It also affects the angiotensin-converting enzyme — that ACE that we saw back there on the disease map — and also a new angiotensin-converting enzyme that is still being identified. It affects the angiotensin2 receptor, oncogenes, and a number of other genes as well. These are subsets of the 913 genes affected by the VDR.

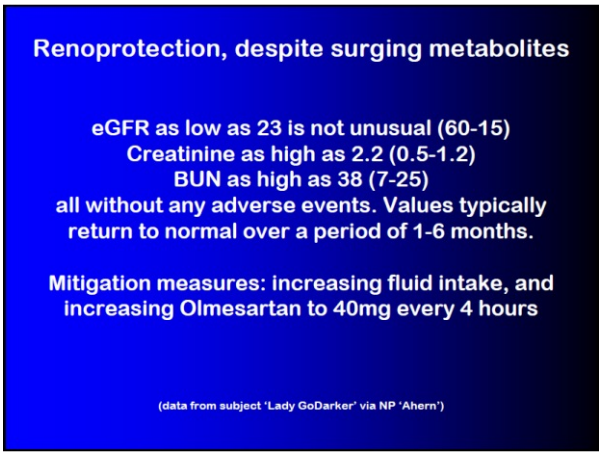
The Vitamin D receptor activation profoundly affects the renin/angiotensin system. As the kidneys heal, all of these metabolites will be changing around. But notice that renin, a nasty one, is being downregulated.



Renoprotection, despite surging metabolites

However, that is not what you see when you measure the kidney function. This is one patient whose nurse practitioner reported the data to me. This particular patient was very sick. She presented with a Glomerular filtration rate, a GFR, as low as 23. The typical range is 60, and 15 is typically where you initiate dialysis. She was at 23; and she was fine, until the blood work results came back, and Doc said, “Wait a minute!” Creatinine went to 2.2 on a normal range of 0.5 to 1.2. I don’t know how that compares with the units you use here in China. These are U.S. units. That is why I put the range on, as well as the value that she went to. She went to almost twice the maximum creatinine range.

This is really big, “hit the panic button” type of data coming back.



And yet the patient felt fine, because the VDR activation was protecting the kidneys. And as the kidneys were rebalancing their function, as they were healing, this is what you see in the blood work.

The blood urea nitrogen (BUN) went as high as 38 (normal 7-25). All of this occurred without any adverse events. The values typically return back to normal over a period of between one and six months, depending on the patient. That's the time taken for the kidneys to heal.

Mitigation measures

The only thing that a physician needs to do is increase fluid intake, and increase the olmesartan to 40 mg every four hours, to make sure the VDR is doing its job perfectly.

To treat a patient in this way is totally counter-intuitive. The thing that the average physician in the west does — he sees the creatinine high and says, "It has got to be the angiotensin receptor blocker. I'll stop the olmesartan." The moment they do that, the patient loses the protection of the ARB, and the kidneys can degrade.

We had one patient that happened to, who went into hospital. The physician panicked, and the patient was on dialysis within two weeks. That is the only patient out of our cohort of eleven hundred who had kidney problems, and that was after the drug was withdrawn instead of being left on to do its job.

Problem for structuring a clinical trial

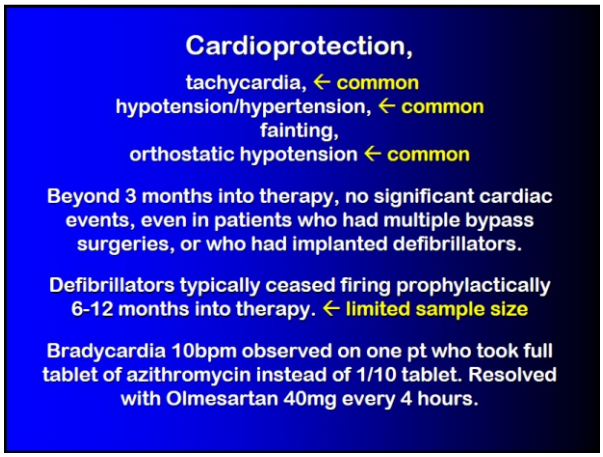
But this is totally the opposite response to what a physician would have. This presents a real problem when you are trying to structure a clinical trial. How do you persuade a review board that this is the way you want to treat the patient? Anybody on the review board would say in advance, "Well, that is ridiculous."

Now, when you are faced with a patient, and the patient is fine, and everything else is fine, it is easier to make a clinical decision — "Well, let's just stick with it and see what happens." Which is, essentially, what we do. But when you try to plan a study, ahead, with a review board, this type of thing is a real problem.

Emergency situations

There are emergency room situations, as well, when you are preparing the emergency room instructions, which have to be very carefully monitored. For example, the average antibiotic used in the emergency room could create very high levels of immunopathology. Intravenous clyndamycin, for example, may well be fatal, because the immunopathology would just soar sky high. So you have to be careful what antibiotics you use.

Luckily the fluoroquinolines are very effective against acute infections and have virtually no effect on this microbiota. A couple of the cephalosporins can be used. So there are antibiotics available for acute infection events, but it has to be written into



the therapy plan.

We have some emergency room instructions written in English that I can let you look at, and I think we have got most of the main issues covered in those.

Cardioprotection

Now what about the heart? How does the heart change as we are getting rid of this systemic disease from the body? How does cardiac function change?

Well, this is what we typically see in patients when they start the protocol. We typically see tachycardia. We have seen tachycardia as high as 250 sometimes. Not very often, but sometimes. And of course it does not do the patient any harm. The panic causes harm more than the tachycardia.

We see either hypertension or hypotension. That is fairly common. But the thing to notice is that people can do a working job, a normal working job, with blood pressures of 65 over 35. We have had a number of subjects at that level. Because when they are on the angiotensin receptor blocker what you are measuring as their blood pressure does not relate 100% to what a healthy person with that blood pressure would be feeling like.

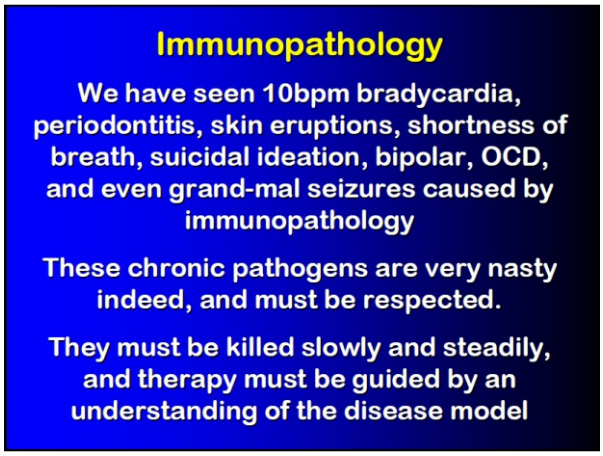
There is fainting. Fainting, however, is due to a disease process. It is not due to the blood pressure. The fainting and the feeling faint, dizziness, is not a side effect of the drug. It is a side effect of the disease process. And very, very common is orthostatic hypotension. That means if somebody crouches down on their haunches and then stands up again, there will be a rush of blood away from their head, and they will feel momentarily dizzy. Virtually everybody experiences that — anybody who is ill. People who are not so ill — okay. They won't get it. But anybody who is seriously ill, like the people I was looking at in the wards today, will experience orthostatic hypotension.

Now, beyond three months into therapy, we have not seen any significant cardiac events, even in patients who had multiple by-pass surgeries, or who had implanted defibrillators.

We had several subjects in the cohort who had implanted defibrillators. What typically happens is that the defibrillators no longer have to work after about 6 to 12 months into the therapy. There are no longer any abnormal beats, and the defibrillator just sits there, and whenever it is interrogated to see whether it is fired, it usually has not fired. However, I will point out, we have a limited sample size. We have just got two or three subjects with implanted defibrillators.

Careful antibiotic dosing necessary

This is an example of what happens when you don't follow the antibiotic dosing carefully. We had one case of bradycardia — 10 beats per minute (bpm) — observed on somebody who took a full tablet of azithromycin instead of 1/10 of a tablet at the start of



phase 2. That resolved with just olmesartan 40 mg every 4 hours (and an extremely nervous cardiologist).

But the immunopathology is a real problem. Trying to figure out how to manage that in a clinical environment is key to being successful in treating these diseases.

Types of immunopathology

So we have seen brachycardia, we have seen periodontitis, skin eruptions, shortness of breath, suicidal ideation, bipolar exacerbations, OCD exacerbations, and even one or two grand mal seizures caused by immunopathology.

Once again, the grand mal was caused by a Canadian who took a full tablet of azithromycin at the start of phase 2, instead of 1/10 of a tablet.

All these diseases are related. They are all related to the microbiota, they are all related to immunopathology.

The chronic pathogens are very nasty indeed. We have to respect these bacteria. This microbiota has done a wonderful job of integrating itself with Homo sapiens. They are very nasty pathogens, but at the same time, we must respect them. We must kill them slowly and steadily, and the therapy must be guided by an understanding of the disease model, just as the FDA commissioner was saying. When we understand the disease model, it is so much safer to move forward.

Okay. That is my last formal slide. So — are there any questions?

Question 1

Question: [paraphrased] Thank you, that was an excellent lecture. I got a new idea from you, that when we use an antibiotic to kill bacteria in the cell, we also kill the cell, and that leads to a cytokine storm, and that can produce severe symptoms in the body. So you do want to slow down the killing. I think that is a good idea. The symptoms are not caused by the bacteria themselves, but by what happens when the bacteria are killed. I think you are right.

So you use olmesartan to get the VDR working. But sometimes antibiotics will work alone. So what makes the VDR stop working? And also, how do these bacteria cause cardiovascular disease? And also, how many diseases does this microbiota cause?

Answer: Let me answer the first question. Firstly, the VDR does not suddenly stop working. People get incrementally ill as they age. Mostly they get to middle age before the VDR is totally not working. So in the earlier stages of the disease process, you do not need the olmesartan as much as you need the right antibiotics and a lowered intake of vitamin D. So you need to control the vitamin D, you need to control the antibiotics, and antibiotics alone will work with early stage disease. But as the disease gets worse and worse, more and more of the VDR function is blocked off. More and more of the genes cease to function properly.

Now, in terms of cardiovascular disease, coming from this microbiota, all I can tell you is what we have observed. If you think about it, cardiovascular disease — and I am not talking about arrhythmia, I am talking about straight out plaque and stroke and that sort of thing — is caused by an accumulation of dead cells in the mechanically quiet region of veins and arteries. There is an accumulation of dead cells. You can find streptococcus in those cells. There is a study within the last six months that found strep in plaque.

We do not really know what forms the plaque, and we do not have enough experience yet with using the MP — we have only been using it five or six years — we do not have enough experience yet to know whether or not the plaque forms when the immune system is working properly. But everything we see points to the plaque being formed by the immune system not working properly. In other words, cardiovascular disease is related to this microbiota, because the microbiota turn off the innate immune system, and cause all these other things to go wrong, all the way from the neurological conditions to the cardiac conditions.

Now, as time goes by we will get more and more data, and also people like yourselves will get the data as well; and we will have to compare notes and get a better feeling for this. But we have had over 1100 patients through our cohort at this point, we have got 550 still fully reporting, and many of them are at three plus years on the protocol, and some of them are at five, six years now.

We have had no strokes. We have had no fatal cardiac events. And we have had no [active] cancers in that cohort, and these are very, very sick patients. You can read their stories on the Internet. The study is open. Everybody can look at the data. Well, not quite. We hide off the day to day reporting from the general public. But any physician can write to me and get a password, and you see the entire site.

By physician I mean health professional. That includes nurses and other health professionals. Any health professional can get a password to see the private Health Professionals' Discussion Area, where we discuss the science and specific patient cases, where this ladygodarker's data was discussed, for example. And also access to the entire message base. There are something like 150,000 messages at the moment that have been left by all the patients during this study. That can all be searched. So you can go and look at the data for yourself if you have got a question.

It is a very different way of doing a study, but it was really the only way we could figure out to do it, given that when we started, we did not have this knowledge. We had a little bit of knowledge about immunopathology. We had very little knowledge about the kidney changes; we had very little knowledge about the cardiac changes. This bradycardia event was very early — that was 2003. And then we started to be very, very insistent on the dosing of azythromycin. So that was just the way we did it.

Now, as time goes by we will be able to get better data. We do have the data from the patients who were on defibrillators, which shows that demand for the defibrillator drops as they recover. So whatever was causing the arrhythmia that was firing the defibrillator goes away as the microbiota goes away. There is another data point. At this point, it is anecdotal, not a hundred per cent proven, but then, I don't think anything much with regard to cardiovascular disease is a hundred per cent proven at this point. So it is another possibility there that we can look at as we move forward.

Yes, there are a lot of genes transcribed by the VDR, and when these get knocked out, these are specific diseases, not just the autoimmune diseases. Obviously when the metastasis suppressor gets knocked out, you would expect it to be easier for the cells to metastasize. The protein it generates is MIM -Missing In metastasis. What effect does this have on cancers? We can not tell you. All we can tell you is that the cohort has no active metastasis. The entire group, of fairly high risk individuals. So I think as time goes forward, the full impact of what this microbiota does to the body will be opened up by the NIH study defining what the organisms are, and what their genes are, and what the similarities are between those genes and the human genes, and what the interferences are between the bacterial genes and the human genes and it will also be opened up as we collect more and more data on more and more individuals, which have slightly different microbiota accumulated over time.

Different individuals are exposed to different foods. Many of the bacteria come down in the foods, from the animals, from the meat for example, different water supplies — you name it. And as we get more experience with the whole spectrum of diseases that the microbiota can cause, I think that the number of diseases is going to expand, rather than contract.

Does that answer your question? Do you want to ask the next question now?

Question 2

Question: Yes. I am just looking for confirmation. I am not sure I understand you clearly. You mentioned VDR activation was caused by PTH, by and downstream P300/CBP, and then you use the drug olmesartan to regulate this?

Answer: What olmesartan does, it comes in directly here and turns on the transcription, regardless of what is happening out here. So this can stay out of bounds, with the exception that, if the patient takes in a lot of vitamin D from their diet, some of it is converted to 1,25 dioxyvitamin-D, and that high level affects other receptors, not just the VDR. It affects the glucocorticoid and the thyroid, particularly. Therefore, the dietary vitamin D has to be kept below 15 nanomolars, or there won't be any immunopathology, there won't be any bug-killing. So that is the issue in relation to vitamin D.

Question: [paraphrased] So it activates the vitamin D receptor, and that affects the genes for some of the peptides that are essential for antibacterial function?

Answer: Yes. In particular the cathelicidin, the beta defensin, and toll-like receptor 2, and to a lesser extent, toll-like receptor 4 are very dependent on VDR activation.

Question 3

By activating the Vitamin D receptor, just like your drugs, it will affect many genes. Some it activates and some it represses. So some can treat patients with some disease, but some will have side-effects.

Answer: That is an interesting thing. You're saying there are negative effects of activating the VDR, as well as positive effects.

What we are dealing with is a hormonal control system in man, where, if the VDR is working and the glucocorticoid receptor is working and the progesterone receptor is working and the estrogen receptor is working and the thyroid receptors are working, then the whole system works. What we are doing is restoring the ability of that whole system to work by switching the VDR on again.

Now, what we are not doing is allowing the estrogen beta to downregulate the VDR, because VDR is transcribed by estrogen beta. So therefore, we are not allowing the downregulation because that drug is forcing it hard-on. At some point, though, the patients stop taking the olmesartan, because they no longer need it. For example, we were talking about 4-hour dosing — 40 mg every four hours when the patients are ill. They desperately need it when they are ill, because the effect of the drug has died off in four hours. But as they get better, they will go to six, eight, and even twelve hour spacing between the doses, because the symptoms disappear. At that point the body has the ability to start going in and down-regulating the VDR if that is what is necessary.

So by allowing the patient to adjust the olmesartan dosage within the range that we have specified, and with the guidelines that we print, and by allowing them to adjust their own antibiotic dosing, depending on what they can tolerate, we have really taken away a lot of the potential damage to be done by forcing the VDR on, or by creating too many cytokines.

But it is a very different paradigm. What we have done is totally alien to normal, conventional medicine. And as we go forward from here we have got to sit down and collaborate and think about ways that we can move from what we have done — the proof of concept, if you like — into conventional medicine.

Last night I spoke about Dr. Greg Blaney in Canada. He has done that with his patient base. He is operating independently of us. He has about 200 seriously ill patients. At the Autoimmunity Congress he reported on a few of them, and also gave overall data on most of them.

Here is another resource that we can use as we try and plan. What can we do with this knowledge? That is really what we need to know from here on. We have this knowledge. The knowledge has been confirmed by Dr. Blaney and literally hundreds of doctors all around the world whose patients have managed to replicate our success, and who are part of our success, in fact. So the question now is, based on this knowledge, how can we move that to the benefit of the entire population? Certainly, the entire population who are ill and need help at this point.

Ultimately it will be the entire population, because once we understand the human microbiome, we will want to make sure we can control that human microbiome. I know, because that is what human beings do. They try to control their environment.

Question 4

Question: Thank you for your wonderful presentation. [paraphrased] I want to ask about vaccinations. Some vaccinations, as far as I know, vaccinations can

aggravate disease. I wonder if you have any experience, What exactly is your position on vaccinations?

Answer: Well, there are a number of members of our cohort who have had vaccinations for everything from tetanus through to the normal influenza vaccination (routine every year, at least in America people are advised to have influenza vaccinations) without any obvious adverse events. However, we do discourage them from having the yearly influenza vaccination, because we feel it is just adding a level of risk that they do not need. Once they are on the protocol, we do not have any acute inflammatory events. We have periodontitis; we have lots of skin eruptions and things, but nothing that can be tracked back to an acute infection. That is the first thing I would say.

Now, in terms of vaccines themselves, vaccines do a very important job. Vaccines have wiped out smallpox, and they have wiped out polio, essentially. Those are very good, positive things.

We still have to fully investigate exactly what vaccines do, because we have used the postulates of Koch to decide that if we inject a live organism like BCG Mycobacteria bovum, for example, in order to beat tuberculosis, that it beats tuberculosis. But we also know that BCG is associated with a very high incidence of sarcoidosis, many years after the vaccination. So the question is — what happens when we add to this microbiota with vaccination? That is not very well defined. It is something we just have to study as we move forward.

My feeling at this point would be to say, if you need the vaccination, you have to have the vaccination. The acute disease is worse than any increase in your microbiota, and we know how to work down that microbiota anyway, with the VDR agonist and antibiotic over time. So always, it is better to have the vaccination.

But there is no doubt — especially with vaccines that are produced in other animals — there is no doubt that we are introducing bacteria along with the known organism in those vaccines, because we can't filter out these L-forms. (The NIH said that we are dealing with approximately 10% human cells, and 90% bacterial cells.)

The reason is because these bacteria can form cells, in a biofilm environment, that are absolutely tiny; and those cells cannot be filtered through the manufacturing process. So, depending on the vaccine — whether it's a live vaccine or a killed vaccine — will determine whether there's a chance that other bacteria, incidental to the manufacturing process (due perhaps to contamination or perhaps to something wrong with the animal) will be transferred through to the human being.

There is no doubt some of that occurs, but we know the vaccine also does good. And now that we understand this microbiota and how it accumulates, and how to deal with it, I am even more convinced that we need to use vaccinations for those diseases where the vaccinations are effective and needed. But we do not typically advise the American subjects in our cohort to have their yearly vaccination against the 'flu.' And we have not had any problems from avoiding that.

So you know what I'm talking about: routine [as opposed to] important vaccinations.

What I would say, however, is that I am very concerned about the practice in the west of giving vaccinations for hepatitis to children that are newborns, before they even leave the hospital after birth, because their immune systems are not working properly at this point. Their adaptive immune system has not kicked in for a month or two, and when their innate immune systems are compromised by the large amount of vitamin D that children are given these days, that mothers are given in the West and that children are given when they are born, their innate immune system is not capable of reacting correctly to that hepatitis vaccine that they are given just after birth (in the West). I do not know if you do that in China yet. That I am concerned about. But other vaccines are fine.