

## Immunosuppressives – A Patient's Findings

Bad things happen to us all. For a myriad of reasons, we can end up being in a bad place. Life's adventure, as wonderful as it is, has its pitfalls too. No matter who you are, whatever your background or circumstances, stuff happens. Sometimes it's bad stuff.

I know because it happened to me, and if you're reading this, chances are you're in the same place.

So, I thought I'd write about it. Not why I ended up needing an organ transplant, but why I'm very much alive still and more specifically, what it is that will keep me (and you) that way.

I want to know what the doctors did to me exactly, and *why it continues to work*. This document concerns the latter. I'll cover the operation itself in another "patient's findings".

If all of this doesn't interest you, that's fine. Just follow the advice of your doctors – they really do know best – and you won't go wrong. But I firmly believe that if you take the time to read at least some of this, it will motivate you to take your pills – because they matter.

### 1) Introduction

- i. Statement of intent
- ii. Comments on level of details discussed
- iii. Writing style

### 2) Our Immune System and How It Works

- i. Why we have an immune system
- ii. Defences
- iii. Immune mechanisms
- iv. T-Cells, B-Cells and memory

### 3) Immunosuppressive Agents

- i. Introduction
- ii. Tacrolimus
- iii. The Mechanism (How it works)
- iv. Advagraf vs Prograf

### 4) Conclusions and a Message

### 5) Questions, Further Research

### 6) Bibliography

## 1) Introduction

### i.) Statement of intent

**To understand why I have to take the anti-reject drug tacrolimus in the form of Advagraf, what it does and why it is essential to my staying alive.**

### ii.) Comments on level of details discussed

This is a tricky one. Most people I have encountered just accept what they are told. After all, the doctors know best, right? Well yes, they do. Man, they really *do* know their stuff. And it's complex shit we're talking about here. So, say thank you next time you see your doctors – and really mean it.

But medical people tend to keep it simple for us mere mortals. No need to go into the details. Just accept that it works and do what I say...

And that seems to be about the right level for most people. It's a sad fact that a little information can be dangerous, leading to all sorts of wrong conclusions drawn by the patient. Classically, people latch on to one or two details and ignore the rest. Ask a post-operative patient what he/she knows about their medication, and you'll probably hear something along the lines of:

"Gotta take 'em on time and don't eat for an hour before or after – or is that *two* hours after? No hang on, if you eat, wait at least two hours before taking the pills – I think...Umm...anyway. Avoid grapefruit at all costs! The stuff will kill ya!"

**(Staying away from grapefruit at all costs is very good advice, by the way. Loosely put, it competes with the tacrolimus and stops it getting to and "binding" in the proper places – a bit like those annoying people who sit on the outside seats of buses...)**

Now, that's probably being unfair to many patients but you get my point. We are certainly neither uninformed nor ill-informed, but we find ourselves equipped with only enough information to avoid serious danger ("Don't touch the electrical wires, son! They'll fry you alive!").

Personally, I want to know *why* I'll get "fried alive". And just *how* will it kill me? Will it light me up like a Christmas tree? Or will it turn my insides into guacamole? Maybe my eyes will cross, and I'll just have time to say "That's good stuff!" before assuming a permanent horizontal position.

I don't intend to be morbid in the least. I just want to know. Maybe you do too. Or maybe you don't.

**In all events, what follows is a very incomplete and amateur account of what your immune system does and how immunosuppressive medications work. If you start panicking or feel your eyes glazing over, just read the bits in bold type. I'll also include an "In a Nutshell" summary after each section for the really busy folk amongst you.**

**Alternatively, think of it as layers of an onion:**

|                               |  |
|-------------------------------|--|
| <b>First layer of detail:</b> | <b>Read the opening paragraphs and the "In a Nutshell" parts</b>     |
| <b>Second layer:</b>          | <b>Read all the bits in bold type too</b>                            |
| <b>Third layer:</b>           | <b>Read all of my ramblings</b>                                      |
| <b>Fourth:</b>                | <b>Refer to the bibliography in the appendix for further reading</b> |
| <b>Fifth:</b>                 | <b>Go back to school and become a doctor</b>                         |

### **iii.) Writing style**

You have probably noticed by now that this document is not written in a formal manner. This is on purpose, and here's why:

To discover what I wanted to know, I had to read a lot of medical reviews and reports. These are not fun to read, believe me. By their very nature, they contain many abbreviations and a lot of terminology used only by doctors, researchers and scientists. Here's an example: "*statistically non-inferior*". And another: "*existing treatment armamentarium*" (both from H T Silva et al, comparing one year post-op results in kidney transplant patients in the American Journal of Transplantation, 2007). *Armamentarium* means "big room where you keep the weapons", by the way. Honestly, I ask you. Severe case of verbal diarrhea there, if you ask me. I suppose they have to carry a certain "*gravitas*" to be accepted by the medical community. And that's me being polite about it.

Consider then, my choice of style to be an attempt to render the information into a plebian-friendly format. Not that we're plebs of course, we just want to know a bit more detail – delivered in a digestible form.

It's not a fun subject, and there's no way around that. But I hope you find the following explanations informative and at the same time, amusing.

## **2) Our Immune System and How It Works**

### **i.) Why we have an immune system**

This section is long, I know, but I think it's important to start here if we are to understand how anti-reject drugs such as tacrolimus have been designed. **Read only as much as you want to. Remember, I'll mark in bold type what I think is most important and I'll add an "In a Nutshell" summary at the end, as promised.**

Biology is all about sex and not dying. This deals with the "not dying" part. Not the sex bit. Sorry about that. I'll try to include some if possible...

**Personally, I like not dying. I like to do it every day in all sorts of ways.** I don't jump out of planes, go into war zones or take drugs. I do however, enjoy playing sports with my son, taking

apart old computers that I find on the scrap heap and I really enjoy the company of the opposite sex – the more intimate the better (see? told you I'd spice this up a bit).

**To do all of these things, we are equipped with an immune system. It stops you dying from all that dirt on the ground and nasty stuff inside dusty computers and...all that. You get the point.**

**Our bodies come with a commando SWAT-like elite team of microscopic assassins who deal with all those little devils in the air, on your hands, hair, lungs, eyeballs and every orifice you have. These "little devils" are called *pathogens*.**

**You will probably be aware of your body's assassins, not least by the trail of death they leave behind – pus.**

**Not only do they identify and kill incoming enemies, *they keep files on them in case their kind ever returns*.** You are at this very moment covered in pathogens who want a part of you. They can't be blamed really. After all, you are a warm, high energy, nutrient-rich, salty, wet, sexy beast...

**Now, most of these organisms living inside you actually make life better, but some little devils, or pathogens, aren't so helpful. In fact, they want to turn you into a factory for their children.**

The next part goes into a lot more detail, so again, just read the parts in bold or equally, feel free to skip all of it and go to the "In a Nutshell" below.

## ii.) Defences

**Basically, we have two types of immunity: Your *innate (non-specific)* immunity which responds quickly and in the same way to a variety of pathogens, whether your body has seen them before or not, and your *acquired (adapted)* immunity which develops as you grow up.**

Only vertebrates have this second, acquired form of immunity and you started "learning" it from the moment you left the sterile protection of your mother's womb – that's why babies are always getting sick - they have little protection. It's also the reason vaccines work, but that's another story.

Your innate immunity is a much more basic thing. It doesn't care whether the invaders are bacteria, a virus or a fungus – it attacks them all. Even if the enemies get inside, it finds and assassinates them - ninja-style.

**The first lines of defence are your skin and mucous membranes.** The skin is oily and slightly acidic and not that easy to penetrate. Oh, and I'm sorry about this, but your digestive tract is technically the outside of you as far as your immune system is concerned – both the inside and out are considered to be part of the skin.

The mucous membranes line the inside parts of you that are exposed to the outside. They include your lungs, your nose, eyes, mouth and sex organs. Mucous is a viscous fluid substance which traps the microbes and "sweeps" them outside. That's why your nose, eyes, ears, lungs etc., ooze in such beautiful and attractive ways when you're sick. By the way, feeling shitty when you're ill may or may not be part of Nature's design. Either way, it makes you want to stay at home and in bed, thus isolating you and lessening the chances of your infecting other people.

**The second line of defence is your inflammatory response.** The specialists here are things called *Mast Cells*, present in the connective tissues, which constantly search for suspicious objects - usually unknown proteins - and then release signalling molecules, such as *histamines* for example, which make your blood vessels more permeable and allow fluids to flow to the infected area, thus producing inflammation.

But they also bring in your ***white blood cells (infection fighters)*** which beat the crap out of the

**enemy invaders** – cool if you have a cut or a splinter. Not so cool if your body triggers a response against something not really harmful, like pollen or dust or, say, peanuts. They call this an **allergic reaction**, and it's treated with *antihistamines* which suppress the histamine triggers and basically force your body to stop panicking about nothing. That concept is important, as we will see later.

### iii.) Immune mechanisms

**Most of the assassinations are performed by your white blood cells, also known as *leukocytes*. Now, these guys are the big hitters. They have a VIP pass to go anywhere in the body except for the central nervous system, the brain and the spinal cord which are all super-duper high security zones for obvious reasons.** Simply put, they can move through the circulatory system and when they get to a place they're needed, they signal the capillary to open a gap between its cells so that they can perform *diapedesis*. That's a Greek word doctors like to use. I call it "oozing through". You have lots of different types of leukocytes – even some of your very own personal ones, just for you. Some leukocytes, called *phagocytes* ("eating monsters" in Greek) chase down invading cells and engulf them. Pretty cool, huh? Some phagocytes called *neutrophils* move around really quickly to where the action is. Once they've made a kill, they just roll over and die, collecting into what we lovingly call "pus".

Also, you have some big, bad-ass eating monsters called *macrophages*. Being the equivalent of Sumo wrestlers, they don't move around a lot, but rather hang out in your various organs. They can also detect when one of your cells has gone crazy, like a *cancer cell*, and kill those too. In addition, they can eat a lot of cells before they die – big, big "macro" eaters.

**However, the really nasty invader-killing is done by some cells known technically as "*The Natural Killer Cells*".**

(Yes, that is what the docs named them in a very brief moment of lucidity. Or maybe not. This was in 1973 you understand. Check out some of the names for sub-atomic particles from the same hallucinogenic-rich era. Pity it didn't last, I say).

Natural Killer Cells are unique in that they are the only eating monsters (ok, ok, phagocytes) in the *innate* immune system which can destroy other human cells if they are unhealthy (deemed to be lacking a certain protein called MHC1 – Major Histocompatibility Complex). They bind with it and secrete enzymes which dissolve the unhealthy cell's membrane. A bit like death by acid bath. Think about that – your body can actually kill bits of itself!

I think it's worth mentioning *dendritic cells* while we're on the subject. They hang around on your skin, in your nose, stomach and intestines and kill the pathogens. And then, **they carry information back to the spleen and the lymph nodes where this intelligence about the war front is passed to the *acquired* immune system.**

**That's important. The acquired system (I'm sure you'll remember) has to learn as much as it can about all pathogens, store this information and use it to "invent" new defences against them.** Once learned, or acquired, the immune system can now go about looking for signs of all sorts of invaders and foreign bodies. These signs are called *Antigens* (Antibody Generators). Now, antibodies aren't very powerful on their own (they're just proteins produced by B-Cells – pfffft), but they can swarm around a pathogen, slowing it up, and send chemical signals back to the monster eaters saying "Hey guys – dinnertime!".

### iv.) T-Cells, B-Cells and memory

**The acquired immune system has its own type of white blood cells, called *lymphocytes*. They target specific things they already know about. They come in two main types: T-Cells and B-**

**Cells.** Very approximately speaking, T-Cells deal with pathogens already infecting your cells, while B-Cells deal with the pathogens in your *humoral system*. That just means they are floating around in your fluids having a good laugh (not really), but haven't infected you yet.

This is all getting a bit too detailed, so let's just say that **Helper T-Cells gather info from other immune system cells in a *Cell-Mediated Response***, typically the monster eaters, who present the T-Cells with the proteins left over from its recent victims. **By means of chemical thingys called *Interleukins (1 & 2)***, the T-Cells receive and scream out the message "Problem over here! Yes here, in sector 15!". Then the shit really hits the fan: The T-Cells start duplicating like crazy, becoming ***Effector*** and ***Memory*** T-Cells.

B-cells perform similar functions but in addition produce antibodies at enormous rates to kill the pathogens in a *humoral response*.

**The important thing to remember is the *memory* element to all of this. Oh, and the *screaming out the message* part too...**

All of that just goes to show how marvellous Nature is. Truly wonderful. But, hey, give me about 3,8 billion years to work on the problem and I could solve it – well, maybe not, then...

Now, how the heck are we going to trick this super-sophisticated killing machine into accepting up to 2kg of a transplanted foreign body? Tricky one. Let's press on...

## **Our Immune System and How It Works**

### **In a Nutshell**

- **Our immune system comes equipped with extremely efficient assassins**
- **Their sole function is to keep out the bad guys, called pathogens**
- **There are various lines of defence in this permanent war**
- **The assassins move around looking for invaders on the cellular level**
- **They kill the bad guys, "talk" to each other about it and the immune system *remembers the enemies for future reference.***

## **3) Immunosuppressive Agents**

### **i.) Introduction**

**So, how are we going to stop the assassins doing their work and save our new organs?**

Before we start explaining what immunosuppressants actually do, let's just recap the immune system's *modus operandi* (that's Latin for "methods/means of operating". Uh oh, I'm catching "doctor-speak" disease...)

**Step 1: Foreign bodies enter our system**

**Step 2: Patrolling assassins (mostly T-Cells) detect the early kills by other assassins, and start**

talking loudly about it.

**Step 3: All hell breaks loose, and every type of killer gets triggered by the T-Cells and roll into action, doing what they do best.**

**Step 4: They keep doing this until there are no more of those particular "bad guys" left (or they lose the battle and sometimes you die as a somewhat unfortunate consequence).**

Now, where can we intervene to interrupt this process? Not at the first step – we have to introduce the new organ, don't forget.

Maybe at step 2 then. Could we stop the assassins killing in the first place? Might not be a good idea to stop them completely. After all, we still need them to kill other bad guys, like flu viruses, etc.

Hmm...Remember those antihistamines? They stopped the immune system from "panicking" and going into full "kill-everything-that-has-this-particular-id tag-attached-to it" mode.

Step 3? Looks like it's a bit late in the process to intervene here, and at step 4, you might as well sit back, buy some popcorn and enjoy the fight in all its glory for all the good you can do at this stage.

No, back to step 2 it is. **If we could stop those T-Cells from talking about the early kills, then multiplying and telling everyone about it. Or if we could just *slow down* those pesky, overly-efficient Helper T-Cells.**

**They "read" the enzymes secreted and posted as *antigens* by the *natural killers, macrophages* and others by detecting their *interleukin 1* messages and shout about it using *interleukin 2*.**

**And that, very simply put admittedly, is what tacrolimus does – it mutes all the shouting. Let's investigate.**

But before we do, has it struck you, as it did me, that if only you could make the foreign body (organ) seem... well, *not foreign* in the first place, all would be simple? Man, life would be so much easier if we could give the soon-to-be-implanted organ some sort of diplomatic passport.

I mean, then the security guards inside all of us would just wave it through all check points.

Like, how do you get French citizenship? Marry one of them!

And that is what scientists and biologists are trying to do, as they understand the genetic coding better. Take a bit of you, say, stick it into the donor organ, let it "grow" and "become" part of your DNA, sorta, kinda thing... Then pop the organ into you, and hey presto! It'd be:

"Hey there, Uncle Vanya!", your immune system would say; "We remember you, old boy! Long time no see. Come in, come in. Sit down, make yourself comfortable. After all, anything for the family, eh? *Mi casa es ta casa*", and all that...

It'll be a reality in our lifetimes, I assure you. But for now, we'd better get back to understanding what we have available to us today – tacrolimus.

## **ii.) Tacrolimus**

(If you're wondering about the origins of the name, it's derived from *Tsukuba macrolide*, an immunosuppressant which is produced by a Japanese soil bacterium, *Streptomyces tsukubaensis* and was discovered in 1987).

## Here's a core tip from the World Journal of Transplantation (WJT), published in March 2016:

"Tacrolimus is an immunosuppressive agent to prevent and treat allograft rejection in solid organ transplant recipients. An extended release tacrolimus formulation known as Astagraf XL is now available which allows for once-daily dosing, with the potential to improve adherence. Both tacrolimus formulations have demonstrated comparable steady-state systemic tacrolimus exposure in de novo kidney and liver transplant recipients. The following review will address the pharmacokinetics of extended release tacrolimus, the data in solid-organ transplantation and the pharmacoeconomic considerations of extended release tacrolimus compared to twice daily tacrolimus."

**"Y'all *what*, now?" I hear you cry. Don't panic! Ok, do, and just read the bits in bold, or even better, jump to the "In a Nutshell" - as you wish.**

It must be said that this is where even the best of us decide to turn off the intellectual highway of knowledge, preferring instead to stop the car, break out the sandwiches and coffee while we watch and wave to the super-brains (doctors and the like) as they whizz past us. But fear not, intrepid reader, because I have ventured a little further along the path at great personal risk of overheating my brain - just for you.

**First, let's de-jargon the above "core tip". *Allograft* means the organ is not from your immediate blood family, but at least it's from the same species – human (good news, eh?). *Solid organ* means they don't put a pretend, picture/photo of one in there (just joking). *Astagraf XL* is a brand name – we'll be talking about another one, namely *Advagraf*. Maybe the "XL" is for the American market... (It denotes extended-release, really, but that's no fun).**

**Now, *adherence* is an important word. It means the number (usually expressed as a percentage) of people who continue to take their medication correctly, and is one of the main reasons for my writing all of this. A shocking – truly shocking - number of you get very lax about remembering or bothering to take your meds as time goes by. You are technically known as *non-adherents*, but believe me, doctors have other choice names for you. How many of you "non-adhere", you may ask? Oh, *about 66%*.**

**For the record, I find that just plain stupid, bordering on suicidal, you naughty, naughty children, you...**

The rest of the extract just talks about the long term differences (or lack thereof) between twice daily and once daily dosing, and how much extra money it costs to treat you disobedient, non-adherent people.

**Oh, and the *increase in death rates as a result* is thrown in there too - just saying...**

### iii.) The Mechanism (How it works)

**Here's the WJT again:**

**Tacrolimus** (Prograf®, Astellas Pharma Europe Ltd, Staines, United Kingdom; referred to as tacrolimus-BID) **is an immunosuppressive agent to prevent and treat allograft rejection** in solid organ transplant recipients in combination with mycophenolate mofetil (MMF), corticosteroids, with or without basiliximab induction.

**And some more:**

**Tacrolimus-BID** is a calcineurin inhibitor which **exerts its immunosuppressive effect through inhibition of interleukin-2 expression and subsequent T-lymphocyte activation**<sup>[4,5]</sup>. It has variable oral absorption and is a substrate of P-glycoprotein with **metabolism through cytochrome**

**P4503A enzymes in the liver and small intestine.** Studies have demonstrated differences in tacrolimus pharmacokinetics across various ethnic groups with **higher doses needed in African American and Latin American recipients**<sup>[6,7]</sup>. Therapeutic drug monitoring is essential to optimizing outcomes due to its variable bioavailability and narrow therapeutic index<sup>[8]</sup>. Trough concentrations ( $C_{min}$ ) are the standard monitoring parameter due to its correlation with overall drug exposure (area under the curve from 0-24 h;  $AUC_{0-24}$ ) and clinical efficacy.

Ok, now even I'm panicking. Deep breaths everyone. De-jargoning about to begin:

(By the way, did you notice those little numbers in square brackets? They refer to other studies and reviews, all of which are many pages long. And yes, I have read most of the ones that are open source – just for the wild, giddy joy of it. What a laugh I had...)

The first part is easy enough, really. **Tacrolimus-BID (or TAC) simply means it's in the form of Prograf<sup>®</sup>**, the brand name most of us encounter as the twice daily variety. **It puts the gag on the helper T-Cells we talked about earlier, remember? These T-Cells like to shout about the detected invaders using a "chemical language" called *interleukin-2* and that activates other T-Cells who call in the immune system's multiple assassins, mostly white blood cells, or *lymphocytes*.**

"**Mycophenolate mofetil (MMF)**, corticosteroids, with or without basiliximab induction" means you take **CellCept<sup>®</sup>**, throw in some body-building extra hot spices, with the option of a pinch of basil for seasoning – personally, I prefer parsley, sage, rosemary and thyme...

**Variable oral absorption loosely means that each one of us has a different "sponge effect" for mopping up the stuff, depending on many factors**, and we're not even going to go into substrates, different types of proteins and cytochromes – *especially* not ones with unfriendly names like P4503A. Now, if it were "Bob" or "Anne", then maybe...

It is interesting to note that African and Latin Americans seem to need higher doses, though. I wonder if that means that their immune systems are more evolved and therefore more efficient than "whiteys" like me. Possibly, and if so, good on them, I say. Who's the superior folk now, eh?

The rest of the extract deals with how tricky it is to dose correctly, needing close monitoring by means of blood samples primarily, to measure how much tacrolimus is still coursing around inside you after a specific amount of time. Therapeutic monitoring is very important to understand. This is where the specialist doctors work very hard to follow your progress, adjusting, tweaking and fixing in order to give you and your new organs every chance of success.

A bit like a parent with a toddler learning to ride a bike:

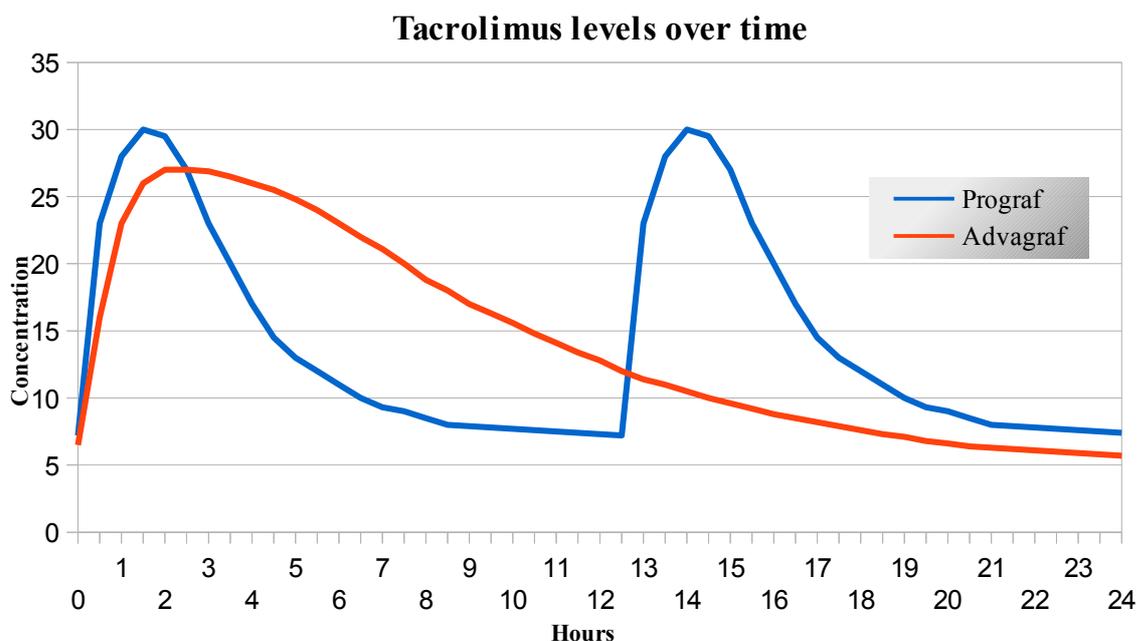
First two stabilisers, then just one – a quick adjustment, a helping hand and a long push before said toddler keels off through forty five degrees and beyond, perhaps achieving the horizontal *mouth-full-of-dirt-and-grazed-knees* position with accompanying tears and required parental hugs and kisses.

Now, I'm not saying you should expect your doctor's hugs and kisses (more's the pity, in my case), but I like to believe that these wonderful specialists actually bite their fingernails and hold their breath as you and I wobble off into the distance unaided and towards freedom. They care that much about what they do – and about us.

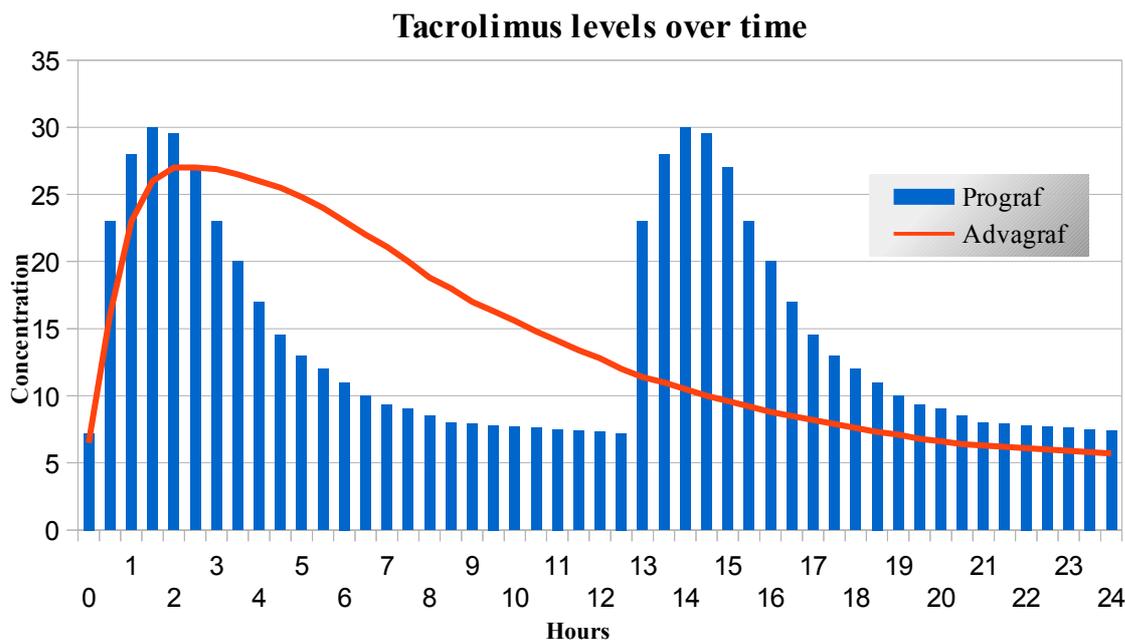
#### iv.) Advagraf vs Prograf

To understand the difference between these two forms of tacrolimus we first need to discuss how they work through the body, or if you like, how they get "absorbed" and "distributed".

Before we begin, I should point out that the AUC means Area Under Curve ( $AUC_{0-24}$  is the area from time of dosing (zero hour) to 24 hours later, for example), and it gives doctors an idea how much tacrolimus is being used up and how quickly. It's the area under the curvy lines which plot the levels of tacrolimus concentrations over time. A graph would (very approximately) look like this:



Or maybe this graph shows the AUC for the Prograf more clearly:



Now, if you can imagine the blue bit (Prograf) above the red line (Advagraf) on the right being removed and squeezed into the white empty space below the red line on the left, it's fair to say that the two have similar AUC's – i.e., similar amounts of tacrolimus inside your body over a 24-hour

period.

**You can see the Prograf has to be taken every 12 hours, reaching maximum concentration levels after about an hour, then tailing off fairly rapidly as it "breaks down" in the body. The Advagraf, on the other hand, takes at least two hours to reach its max. concentration (or  $C_{max}$ ) and is also broken down or "liberated" into the body by means of enzymes in the liver and small intestine, but *more slowly*.**

**We will see why soon – and the answer might surprise you.**

That all looks easy enough, doesn't it? Boring, I admit, but not too hard to understand. So, now we're all experts!

Well, not really.

Not at all, in fact.

In the real world, it's a bit more complicated. Here's why:

**Absorption, distribution, metabolism and excretion.**

(Oh, and a whole host of other factors too, but these are the main ones).

**Absorption, as we've already seen, varies with each one of us** and can be really messed up by things such as grapefruit juice, bizarrely, which stops the tacrolimus from binding, thus reducing maximum concentrations, leading to not enough protection and waste amounts sloshing around as unused residuals (not good).

**Distribution can vary depending on organ function efficiency, blood thickness** and whether your underwear is too tight, cutting off circulation (just kidding). Anyway, it varies a lot.

**Metabolism is an enormous element influencing primarily the speed of absorption.** Something called "the diurnal effect" means that your body breaks stuff down about 35% more slowly in the evening and at night. **That's why we take Advagraf in the morning, on an empty stomach and why we wait until it's absorbed to its maximum levels to set us up nicely for the day ahead.**

I'm personally very interested in this part of the process. Doctors, you understand, are doing the equivalent of juggling a dozen balls at the same time as they try to get your dosage just right, despite your unhelpful lack of compliance. It's like trying to change a kicking baby's diaper.

"If only you'd hold still, kid, we'd be able to get to the park/shops/party on time! Yes, yes, it's very amusing to kick your pudgy little legs like that and smile at me, almost melting my heart with the love I feel for you, but *just keep still for a moment...* Ahhh, now look at what you've done. Right, a change of clothes for *both of us* then...".

Well, whatever. At this stage, at least, I can control the situation to some degree. If I just stop kicking, take my pills on time, don't eat for a while, then eat the right things, that'll be one less ball to juggle.

And who knows, we might even get to the party on time...

**Finally, there's excretion. By testing and measuring blood, urine and stool samples, doctors can learn a lot about residual levels of tacrolimus, thereby enabling them to control dosages.**

**So, how do those clever boffins in the science labs get Advagraf to work over a 24-hour period? The answer is – wait for it – drum roll, please...Ethylcellulose.**

Once more from the WJT:

**Extended release tacrolimus is a modified release formulation, which utilizes ethylcellulose to prolong the drug release profile in the gastrointestinal tract via water permeation<sup>[9]</sup>. Extended release tacrolimus has similar absorption, distribution, metabolism and excretion to tacrolimus-BID.**

Not impressed? Nor was I, but I laughed a lot. Let me explain...

**Ethylcellulose is a polymer. A whole family of polymers, more accurately. Plastics or emulsions, if you like. They are used *everywhere* and are present in your food, your plastic packaging, electronics and, most importantly for us, in (and on) medicines. They coat things and protect them. Don't want water or other elements like acids attacking and rotting your wood/metal/food/skin/etc? Think paint, varnish, food preservatives and you've got it.**

The Dow chemical company has this to say about them in their technical manual:

**These multifunctional, water-insoluble, organosoluble polymers are used in many pharmaceutical specialty applications. They function as binders; tough flexible film formers; masking and time-release agents; water barriers; and rheology modifiers, to name a few.**

**Ignoring the terrible punctuation, what Dow means is that they're polymer varnishes, plastics and emulsions. Nothing more, nothing less.**

Of course, it's a bit more involved than just spraying it on the outside of the tablets (although they do this too – and in the inks used to write "5mg" or whatever), but I can't get the image out of my head of a little man in a white lab coat, one eye closed, tongue sticking out as he laboriously paints every single molecule of tacrolimus with a *really* small paint brush...

**So why use Advagraf at all? Why not just stick with the tried and tested Prograf?**

Why indeed. (Not that Advagraf hasn't been tried and tested too, believe me – I've seen papers dating from the 1990's). Only once or twice during my research did I catch hints at **the benefits of avoiding concentration peaks and troughs**. There appears to be general consent, but no conclusive research to date, that this may indeed be desirable for the obvious reason that excess unused tacrolimus coursing around in the body is definitely unwanted, so having to "saturate" the body twice a day creates more periods of high tacrolimus levels in the body. **This can potentially lead to *supratherapeutic concentration***. Hence the careful therapeutic monitoring that follows the early post operation days and weeks, as doctors try to determine initial doses for each individual during this tricky period, with the **ultimate goal of settling on the *steady state concentrations* needed to ensure organ protection with minimum suppression of the immune system.**

**But make no mistake, by the way. The very presence of immunosuppressants comes with a price. Our bodies are, and will always be, susceptible to infection as a result.**

Now, that doesn't mean that you have to go and do a "Howard Hughes job" on it, locking yourself into a penthouse suite of a hotel, refusing to go out, avoiding all human contact and therefore a normal life. Far from it. **Just avoid obvious potential germ-infected environments** (so, if you're a cess-pool maintenance worker, for example, I'd seriously suggest a change of career), **wash your hands and body often, and above all, *eat properly!*** I cannot stress this enough, but more about all that later...

**It seems to boil down to the very basic and overwhelming fact that once daily dosing helps patients make fewer mistakes when they are entrusted with, say, a month's supply of pills to take all on their own. With no doctor or nurse present to proffer a spoonful of sugar as the medicine goes down.**

I feel I must add that all the reviews and studies seem to carry a hint of desperation to convince the authorities (the FDA in particular) that Advagraf does the same thing as Prograf after some minor differences in the first few days/weeks.

**All that work, all that study, all that *time and money* – just to make it easier for you and me not to forget to take tacrolimus, which *saves our lives*.**

(Of course, maybe everybody who contributed to every article or "sponsor requested review" has a stake in the company producing Advagraf, and stands to make a fortune from it if, or more likely when, it is approved worldwide and for all organ transplantations – stranger things have happened and serious amounts of money are involved here, but I think not – I could be wrong though...)

**So, Advagraf vs Prograf – the difference? A new, beefed up form of tacrolimus armed to the teeth to resist as long as possible while it suppresses the *interleukin-2 chemical messages*? Not at all. Essentially, Advagraf/Astragraf XL has a layer of emulsion that slows down the progress of your body's enzymes as they reach the tacrolimus and liberate it. No great sorcery or ground breaking science at all.**

**I think it's important to stress that the tacrolimus molecule remains exactly the same, no matter which form it comes in.** Any side effects one may develop with either Prograf or Advagraf/Astragraf XL are NOT attributable to changes in the drug itself, but rather to a whole host of other factors, some of which may be linked to the different rate of liberation that might not suit you personally. It works just fine for me, but you are you, and I am me – nobody special in any way (despite what me mammy told me...)

**At the risk of repetition, I must emphasize again that *I am no doctor* and I have no intention of giving advice concerning medications – that is what your medical specialists are there for. All I'm saying is that if they suggest a move to the once daily formats, don't think you are being used as a guinea pig, or are suffering from some sort of budget cuts/lack of financial medical cover. Quite the opposite, in all likelihood.**

## **Immunosuppressive Agents**

### **In a Nutshell**

- **The easiest way to stop our body rejecting transplants is to prevent it triggering the assassins who do the killing.**
- **Tacrolimus is an immunosuppressant designed to inhibit interleukin-2 expression and thus T-lymphocyte activation, meaning the assassins don't go all "balrog" about things.**
- **Other methods to fool the immune system may be viable in the future**
- **Tacrolimus comes in twice-daily and once-daily forms, namely, Prograf and Advagraf**

- **Advagraf has a protective coating to slow the decaying process, therefore prolonging its liberation.**
- **Once-daily dosing increases patients' adherence to essential medication regimes, and the reduced frequency of peaks and troughs is considered to be an added benefit.**