im excited to introduce todays lecture

professor in multiple departments at

virginia commonwealth university school

of pharmacy he is also the vice chair of

the department of pharmaceutics and the

director of the pharmacokinetic and

pharmacodynamic laboratory at the school

of pharmacy in addition he is a fellow

in the center for study of complex

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in 9 jurgen received his md and phd

from sarland university in germany

from 9 to 9 he was the director of

clinical research and development at the

institute for clinical pharmacology in

gunstro germany then completed

postdoctoral fellowship training at the

university of florida

in 9 jurgen joined the faculty of vcu

school of pharmacy he has published

extensively and presented extensively in

the area of quantitative pharmacology

im confident you will enjoy todays

lecture

welcome this is jurgen bennett

im your entertainer for today as part

of the

principles in clinical pharmacology

course

at nih im a clinical pharmacologist and

a professor at the virginia commonwealth

university school of pharmacy

my topic for today is pkpd of protein

drugs so were going to

get into the world of biotech

so if you look at the outlines and the

objectives that i put together we talk

about how different those proteins are

in terms of their

absorption distribution metabolism and

excretion how different they are from

small molecule drugs that most of us are

quite familiar with

we specifically focus then in on pkpd

relationships of growth for

costimulating factors and monoclonal

antibodies

that are commonly used

and then ill wrap

up todays presentation by getting into

something that is very current and

thats the

approval of biosimilar drugs in the

united states which are

the equivalent of generic small molecule

drugs

as you can see i have a bunch of

resources

that are available when you download the

class material

my outline is such that we talk about

admin first

then we get into pkpd

well discuss something that is fairly

unique to protein drugs and that is

their ability to elicit immune response

im going to spend a significant amount

of time talking about monoclonal

antibodies

then go into two examples uh one example

uh that im going to lecture on the

second example

uh that i put in as an exercise that

ill let you do on your own and i review

the key with you

and then we get into the biosimilar

drugs

all right so let me

just start off by saying that protein

drugs or large molecule

drugs are very different from small

molecular weight drugs that are defined

as less than a thousand dots

for those small molecule drugs there are

a couple of things that we know about in

general

that they are subject to a passive

diffusion across membranes for

lipophilic drugs

and

or they may require if they are polar

drugs they may require active drug

transports

okay and we pretty much

know a lot about their various drug

transporters

again depending on their lipophilicity

they can be highly plasma protein bound

or tissue bound or not

depending on their lipophilicity or

polarity they can also be subject to

primary excretion by the kidney or

hepatic metabolism or biliary excretion

and their drug targets the receptors

that we are or enzymes that we are

trying to inhibit or somehow affect

are

extravascular

for quite a few drugs

their tissue distribution is organ flow

limited so we can draw some fairly

general conclusions for example about

liver

clearance and

renal cancer

and you can see none of this is true for

protein drugs

so for small molecular weight drugs the

main physical chemical property

in general is their lipophilicity

polarity

for protein drugs as youre going to see

in a minute

its

much more

molecular weight in their particular

structure especially for glycoproteins

so here you have a general pkpd review

or overview

that the drug has to get absorbed into

the blood uh for

protein drugs thats usually by

intravenous

infusion or subcutaneous injection

the drug can

interact with plasma proteins and youre

going to see for protein drugs thats

usually not something we worry about

they can distribute

into peripheral tissues

including the tissue

that contains the receptors or the

targets that we call the effect

compartment and can interact and cause a

pharmacological response

and

the drugs are

eliminated

by hepatic metabolism and or reading

excretion okay

the top part here anything that relates

to how the dose

turns into a concentration be referred

to as kinetics

anything down here how the drug

bound to the receptor turns into a

pharmacological response we refer to

pharmacodynamics

now if we look at the absorption

thats where the first

major difference starts to emerge

the protein drugs have large molecular

weights much larger than the thousands

that are used as a cut off

which makes them basically unable to

permeate

membranes gi membranes so they would not

have any gi permeability to speak of and

sometimes even more importantly

they are subject to all kinds of

chemical and enzymatic degradation in

the gut so there

would be a lot of first pass effect that

would prevent them from ever reaching

systemic levels

therefore they are not suitable for all

administration and as i mentioned before

they usually given intravenously

subcutaneously and sometimes

intramuscularly depending on

the dose and the volume

now even

that you have to keep in mind that if

you give them by any route other than

the iv route where theyre being

injected or infused directly into the

bloodstream

you give them subcutaneously into a

subcutaneous depot or im into a muscular

depot

you dont necessarily expect them to be

00 bioavailable because what can happen

locally is degradation in those tissues

for example proteolysis in the lymphatic

system

furthermore so we have reduction in

bioavailability uh even if we give them

by parental routes

uh in addition to that uh the

uh uptake or the absorption from those

uh tissue uh

compartments

for large protein drugs in particular

involves the lymphatic system rather

than the blood capillaries so if you

give a small molecular weight drug

uh substitute well i am the absorption

from

the side that youre setting is by

capillaries

which are relatively rapidly perfused

on the other hand if you give the same

or if you give a different drug a

protein drug by the same route

you now have to depend on the lymphatic

system to absorb the drug into the

bloodstream

which is convective by nature rather

than diffusion and blood flow limited so

therefore its much much more

slowly

distribution

again due to their large size

which limits their mobility across

biological membranes

most protein drugs are pretty much

restricted to the vascular

space for the most part that means you

would expect their volume distribution

to be if its purely intravascular three

to five liters for kilogram person or

if they can at least get to the

interstitial space

it would be around liters per

kilogram so those are relatively

speaking

small volumes of distribution that you

would expect for protein drugs in

general

in addition to that as i alluded to

before

they are not expected to be plasma

protein bound

like a lot of small molecular weight

especially lipophilic drugs do

however they can be uh

taken up or bind to

extravascular

tissues

and thats particularly true for

monoclonal antibodies that target

targets in the blood or in plasma and

that would increase their volume

distribution beyond the three liters

of intravascular space

just like for the absorption from the

subcutaneous or intramuscular depot

any extravascular distribution of

protein drugs

occurs by

convection

and possibly trans cellular endocytosis

which are slow processes

so you can see here

the extra

im sorry the vascular space

where along with the flow of fluid water

and electrolytes

by convection

you have a flow of

protein drugs

okay and you can see that the

clearance by the lymphatic

system

is uh much much faster than the uh

clearance by exterization

which again means that their

distribution just like the absorption in

general and im talking about

extravascular uh

distribution is very slow

now how do

protein drugs get eliminated again

different from small molecules which are

typically eliminated by the liver and

the kidney

they are basically

protein drugs that is are basically

subject to the same pathways

that dietary or endogenous proteins are

subject to

so they can

form a myriad of metabolites ultimately

the terminal metabolites are the amino

acids and

whatever carbohydrates were part of the

original protein

and those

especially the amino acids are

ultimately recycled into their

endogenous pools

so theyre not necessarily excreted in

the bile or in the urine

the bitter excretion or renal excretion

of the parent protein the intact protein

itself is insignificant

now the breakdown of those protein drugs

the proteolysis typically occurs

enzymatically but it can occur

almost everywhere in the body

including the blood so for some proteins

they have a very short halflife in

blood because theyre broken down in

blood

which is typically not the case

with very few exceptions for small

molecular weight drugs

what that means is that for some of

those especially

their total clearance might be so rapid

that it actually exceeds cardiac output

and ive already due to the fact that

they can be degraded in the gut

which may be relevant in terms of

elimination if they are secreted in the

gi tract as well

now here we have the first

role that the

molecular weight plays so proteins

that are smaller than thirty thousand

dollars

can be filtered in the renal glomeruli

however

so they are showing up in the primary

urine however uh after that subsequently

to that they are

theyre theyre subject to

renal metabolism so what usually shows

up in urine is not the parent drug but

some of the metabolites unless theyre

reabsorbed

on the other hand if you look at the

liver

the role that the liver might play uh

the only way that those proteins can get

in the liver is by a receptormediated

endocytosis or rme

okay so they have to be taken up by

particular transporters were going to

look at some in some in a minute

before they can metabolize

in the lysosomes by the endopeptidases

as i said before that are

responsible for breaking down endogenous

or dietary proteins as well

so right here theres a table that i

took from

the book chapters that i make reference

to

that points out

the differences we can see the typical

small molecule drugs

five hundred to a thousand dollars

elimination side liver

okay

you talk about passive diffusion as i

mentioned before for some of the bigger

ones there may be

drug transport is involved

but the main determinant physical

chemical is their lipophilicity and

their molecular structure their

molecular structure would tell you

what transporters and what enzymes

lipophilicity is more responsible for

crossing biological membranes

the moment you go above a thousand so

lets look at small proteins and

peptides

the main

eliminating organ here would be the

kidney as i mentioned before

by chlamela filtration however theres

subsequent renal degradation on

metabolism

so you wouldnt see any pair and drug in

urine as is the case for the small

molecular drugs so the molecular weight

now becomes a major determinant

for the larger protein so here looking

at 0 000 to 00 000 which would include

monoclonal antibodies

you have this receptormediated

endocytosis not only in the liver but in

other organs as were going to see in a

minute as well

and theyre depending very much on the

charge and the

sugar entity of those glycoproteins

because some of those transporters

target

mannose or fucos

the even larger uh proteins they

actually have to be optimized in order

to be

absorbed

and if theyre really big this is larger

than 0 000

they need to be taken up into the cell

by

phagocytosis and particle aggregation

would be the major

determinant on how much of this happens

so lets look at the renal metabolism

so you can see this is a glomerulus

blood coming in and then blood flowing

along the tubulin so this would be the

renal proximal tubulin

so

small proteins up to about 0 to 0 000

get filtered

but then they can

be broken down in the primary urine

itself

they can be broken down

in the brush border or they can be taken

up in the

tubular cells and then

metabolized or broken down in the

lysosomes either way there wouldnt be

any parent

protein that comes out in urine

theres also a possibility for some of

them at least that the proteins actually

get

taken up from the peritubular

vasculature

into the tubal cells and being broken

down as well

either way the only thing that would

show up in the terminal and the

ultimate secondary urine would be

metabolites not pendrive

and down here we have hepatic uptick and

you can see its not just hepatic uptake

before we alluded to that its also

uptake into other tissues

whether we have endothelial cells

copper

and you can see without going into a

great uh detail

you can see they all involved rme

receptormediated endocytosis and you

can see those receptors they basically

target

carbohydrates okay

mannose fucos and what have you and

there are various examples of drugs

that are known to be subject to those

uptake systems so this is very different

from a small molecular weight drug

now in addition to that

for

some proteins they actually get broken

and im going to show you two examples

for that they actually get metabolized

by virtue of interacting with their

target so they interact with high

affinity and low capacity to surface

receptors

and then by virtue of doing that theyre

exerting their effect but theyre also

being taken up in the cells and then

becomes subject to endocytosis

and lysosomal degradation

this is called targetmediated drug

disposition and were going to use

a

monoclonal antibody

as an example that follows a similar

pathway

now speaking about immunoglobulins as i

point out here albumin conjugates and

immunoglobulin and gs which are

basically

monoclonal antibodies uh or monoclonal

antibodies are made from

derivatives of igg

they interact with a very particular

receptor called fcrn or the neonatal fc

receptor

and its named neoc neonatal because the

first time it was discovered

it was found to be responsible for

transferring igg across the placenta

from the maternal to the fetal blood

its also

present for example outside the placenta

which obviously is the reason why it

plays a role in proximal small intestine

and its it involves transcytosis

the

fcrn as it relates to igg drugs

is present throughout the entire body so

any endothelial cells monocytes

macrophages dendritic cells all kinds of

immune cells and its role is to protect

the igg the endogenous as well as the

exogenous drugs

from lysosomal degradation

and it

provides a salvage pathway and it

recycles so this is the main reason why

the halflife of iggs is as long as it

is and were going to discuss that in

more detail

for right now let just see what the role

plays of the fcrn mediated recycling

plays for

igg and albumin

so this scheme here compares igg and

arbumine relative to their

daily

formation so percent of the

circulating amount

gets formed every day and at steady

state gets removed

for albumin gets formed eleven

percent gets removed

at steady state but how do we get to

this removal or

uh

catabolic route

well you can see that uh if you look at

igg

90 or im sorry

would be removed every day if it were

not for

about

being recycled so the net result is that

only percent get removed

on the other hand if you look at albumin

albumin the difference between the

net

removal and the actual

catabolic efficiency is much less

because

the recycling the fcrn mediated

recycling contribution is less

so you can see that a significant

portion

of catabolism for iggs

is protected by recycling

the igg

which as i said before leads to a

relatively long halflife

now lets look at a couple of just

schematically a couple of elimination

pathways

for protein drugs

uh three different kinds that i want to

show here the first one is related to

the presence of adas or antidrug

antibodies

so this is a phenomenon that is

particular to a large molecules protein

drugs

where the body develops its own

antibodies

towards the protein

so this would be the body creating

the antibody and the antibody is then

uh catalyzed so you have

what we call a turnover model now this

antibody however has the ability to

react with a protein drug

and facilitate its degradation

okay so one elimination would be the

unintended formation typically

unintended formation of adas

that facilitate elimination of protein

drugs

the second scheme here looks at the

protein drug

that is again different from a small

molecular drug that is eliminated not

only from what we call the central

compartment so this would be the plasma

compartment where the drug is being

given to and its being removed from

but it can also this is the protein drug

now can also go to tissues

and being removed from those peripheral

tissue compartments okay so there is a

twostep

elimination that is different most of

the time from small molecular weight

drug

drugs and then i already use the term

target mediated drug disposition which

is

very relevant for monoclonal antibodies

so this is a little more complicated so

r would be the target or the receptor

that the monoclonal antibodies intended

to interact with

its being formed continuously and its

being eliminated continuously so we are

at steady state

now this receptor that interacts you can

see with an equilibrium reaction with a

protein drug

and you now have a second elimination

pathway for the receptor so the receptor

is indulgently

removed but its also removed after

interaction with the monoclonal antibody

and obviously it is that effect

that is

intended by giving

the protein the drug we need the

monoclonal antibody to hit the receptor

now the reason why thats important

those processes

can be saturable meaning

those dependent and they can be time

dependent we can have nonlinear pk which

is for small molecular weight drugs the

exception

the example

that im showing here were looking at

the plasma concentration

on a logarithmic scale versus time

and a

macrophage colonize colony stimulating

factors mcsf

is given by iv

at

three different concentrations so you

can see this is the low concentration

the intermediate concentration and the

high concentration

and what you see here is what we like to

call in pk lingua the hockey stick

okay which is typical for a nonlinear

or saturable drug so initially there is

a distribution theres a plateau phase

and this is when the concentrations

drop below

the saturation levels and we have a

relatively

rapid elimination

so you can see for all those three doses

the most rapid elimination occurs at low

concentrations

that are below

the saturation level and any

higher concentrations

lead to this plateau

now in addition to

this uh propensity to uh be associated

with noninner pk at least for some of

the protein drugs

their pkpd relationship their

relationship between

the

concentrations in blood and the

target effects

can be

very shall we say indirect

meaning there are multiple steps

between

achieving drug levels and actually

observing the effects so for example as

i point out here for growth stimulating

factors which would include

erythropoietin ipo

filgrastim the example that i used later

on and the one that we just talked about

the

mgcsf

their pkpd typically follows what i call

the indirect effect model meaning there

is a pronounced lag time between plasma

concentrations and pharmacological

effects

based on their mechanism of action

so let me just illustrate that by using

arithmetic

which as you know stimulates

the formation of red blood cells

so what you have here in blue would be

the pharmacokinetic part of this model

so erythropoietin is given into a

central compartment and its being

eliminated

and this would be a saturable

elimination pathway characterized by v

max

the maximum

elimination rate and km which would be

the saturation level or the affinity

constant that i alluded to early on so

this is the kinetic model

now how does

erythropoietin

lead to increased red blood cell levels

in blood

but it does that in the bone marrow by

stimulating precursor cells

so p and p are precursor cells

are are the reticulocytes which are the

immediate precursors to red blood cells

so each of those precursor cells

leads to

by maturation leads to the next level

they all have a finite

uh lifespan which is what the taw

relates to

okay so you can see there is a an effect

that slowly occurs because each of those

stimulations

has to translate into increased

concentrations of the subsequent

red blood cell or precursor

in addition to that

as i alluded as alluded to here in the

uh scheme there is a negative feedback

system that if the reticulocytes go up

meaning you

a lot of red blood cells are going to be

formed down the road that actually down

regulates some of their precursors

okay so what that means is that to get

from the drug level to the effect

theres a whole chain of events that

have to occur that take time

and we have

nonlinearities built in and you can see

in this particular example the

stimulation relationships thats what

the st stands for

both follow

what we call emax relationships so they

can be saturable depending on how the

drug concentration compares to the

effective concentration the ec 0 value

to illustrate that

to get away from the scheme and actually

look at data

on the top graph so youre looking at

multiple doses of erythropoietin

in humans

and youre going to look at

reticulocytes on the top

red blood cells at the bottom and

hemoglobin

at the very bottom

okay and you can see that with each

administration of erythropoietin

the reticulocytes go up

and they peak after about 00 hours and

then theyre being basically maintained

until the last dose is given and they

drop off

on the other hand if you look at

the red blood cells

nothing really changes until maybe 00

hours so while those reticulocytes go up

we dont see the red blood cells yet

because they havent matured or the

reticulocytes havent matured yet

then they mature and the red blood cells

continue to go up

even as the reticulocytes

decline

so it is

the

lifespan of those red blood cells and

the maturation of reticulocytes

into red blood cells

that makes the ultimate response which

is the increased red blood cells or

increase in hemoglobin

much much

slower than the primary response which

would be the increased reticulocytes

similar to that another growth

stimulating factor so now were looking

at phil graston again thats going to be

my example a drug in a few minutes

uh gcsf

in blue we have the pk model so here we

have the drug being given into a one

compartment body model

the main difference to epo we now have

two routes of elimination

whats called a linear route and a

neutrophil route

so this drug is

metabolized via binding to this

neutrophil receptors that im going to

discuss later on this is a sessional

process

the linear clearance is

elimination by the kidney because its a

relatively small molecule

now how does that relate into uh

pharmacological effects again were

looking in the bone marrow at precursor

cells to the white blood cells or the

absolute neutrophil count that we can

measure in the peripheral blood

and the stimulation

to the precursor cells

takes time depending on and you can see

some of their spans 0 hours 0 hours in

9 hours so thats how long it takes

after you stimulate those precursor

cells before they uh

show up in plasma as or peripheral blood

as neutrophical

and heres the corresponding plots so on

the left hand side youre looking at the

serum or plasma concentration versus

time single doses after a subcutaneous

injection

you can see

the concentrations increase with higher

doses

their terminal slope seems to be very

similar

okay on the other hand if you look at

the pharmacological effect so this is

the absolute neutrophil count versus

time

you can see with increasing doses

the peak effect gets later

and later so at the highest dose it

takes

six days

for the

neutrophil count to achieve its maximum

even though the peak plasma

concentrations are cheap within two days

whats the reason well the reason is

that the effect has to work its way

through the various progenitor cells

okay so this is an indirect effect model

and its the

cytokinetic model meaning

the time the life span and the various

transfer constants between those

precursor cells

drive

the time profile in the pharmacological

response

okay something unique

with unrelated to the pkpd of protein

drugs is their ability as i mentioned

before to cause immunogenicity

so they can cause

immune responses

anything from anaphylactic shock to

neutralizing

antibodies and ive listed here excuse

me ive listed here a few potential

consequences so you can have loss of

efficacy

for example if you have

patients with hemophilia

and they develop antibodies to factor 0

a factor

theyre basically unable even with high

doses

to use factor as a way to

replace

the

missing clotting factor

okay and you can see some of the

monoclonal antibodies and you talk about

that in the exercise

on the other hand sometimes those

immune responses meaning those antidrug

antibodies can actually mimic

the drug itself so growth hormone the

antibodies themselves also have

uh as a pharmacological response

similar to what growth hormones does

they can neutralize endogenous proteins

uh this is the story about epo

a while ago when they changed the

formulation of ipo i think they changed

the

rubber of the

the top of the uh glass wire that had

epo

it changed the structure of ipo and ipo

became now immunogenic and patients that

received that

erythropoietin actually developed

antibody to erythropoietin that targeted

not only the exogenous but also their

own erythropoietin so they were

completely unable to produce red blood

cells

because their endogenous uh protein was

neutralized by those adas and then i

already mentioned allergy anaphylaxis

and serum sickness if you have lots of

circulating ada

complexes with the protein drugs

this is just from a kinetic point of

view

the formation of adas can actually

typically increase clearance because

youre now removing protein drug

from the circulation

so they can actually reduce the activity

in rare cases they can also

increase im sorry decrease the

clearance and increase the activity but

thats the exception the main concern is

that you have adas

that the incl the clearance of those

protein drugs is enhanced and the

activity is reduced

where does the immunity come from

where weve already talked about

potential differences in sequence

especially when we use nonhuman

amino acid sequences as we do for

some of the monoclonal antibodies

their glycosylation pattern i think this

is some something that is currently

investigated very

intensely to find out what carbohydrate

change in what position

might induce imogenicity because if we

understand that we can actually avoid it

and then the other thing to keep in mind

is that the

proteins themselves

can interact

and form trimers tetramers what have you

okay and their impurities and

contaminants as a result of the

biological synthesis

formulation technology all this goes

into the potential risk to cause

immunogenicity

for the purpose of this lecture were

going to talk about the glycosylation

pattern and the sequence variation a

little bit later on

okay now let me switch to then a

particular kind of protein drugs

that really have a major have had a

major impact on therapeutics and those

are monoclonal antibodies

the reason being is theyre so highly

selective and have such a high affinity

for their intended target that theyre

about as close to the magic bullet that

paul airlie stipulated in the early part

of the 0th century

so theyre about as close to

[Music]

just hitting the target rather than

having offtarget effects even though as

youre going to see in a minute

they all have

potential for

nontarget related risks

so whats the basic structure of a

monoclonal antibody as i mentioned

before theyre basically

most of at least the ones that are

currently approved are igg

drugs

so if you look at the molecule here it

looks like

the only multimedia show for today

they look like a vcu cheerleader

or like a y

so you have the

fc

part of the molecule down here

and you have the fab part of the

molecule of the two ends of the y

the top part here thats where the

antigen binding region is

composed of a light and a heavy chain so

this is what makes the specificity of

each of those monoclonals

you can see they are connected the two

chains and the various

sections of the protein are

connected by uh diazofite bonds

and as i mentioned before the fc segment

the the stem if you like

thats responsible for the effector

function whereas the

fab

section is responsible for the antigen

i also point out

and its highlighted here in those green

circles

that there are lots of carbohydrates

in those monoclonal antibodies so there

are large molecules and theyre

glycoproteins

this is to give you some idea how they

compare across the various classes so

im only going to focus in on igg

because as far as im aware those are

the only ones that are therapeutically

available but i want you to realize that

endogenously we have iga those are

typically on epithelial surfaces

igm

those are the macro clobulins igd and

ige

those are

related to

histamine release on mast cells

but the monoclonal antibodies are

typically from the igg class so lets

see what they have in common

you can see their molecular weight as i

said before relatively high 0 to 0

000

you can see their halflife is to the

tune of three to four weeks

with the exception of ig

and

three

okay

now

what do they do in terms of their

effector function

they all activate to some extent the

complement pathway im going to talk in

a minute about they do not activate the

alternate alternative complement pathway

they are

not present on

mature b cells

probably most important thing to keep in

mind is their ability to bind or not to

bind to the fc receptors remember those

are the receptors

that contribute to the recycling and the

prolonged halflife

okay so

igg

is

the most commonly used backbone

for drugs

that you want to target and knock out

because they allow you to bind to the

target and induce

a factor to remove it

now in terms of the convention that we

use to name them again this is different

from small molecular weight drugs that

all have their

pretty generic name

uh we have murine antibodies they would

be mom

im going to talk about them because

they all have

an un

acceptable risk of chronic causing

immune responses however we do have

chimeric antibodies so you can see those

are antibodies where the

fab the

antigen binding part of the molecule

is murine meaning based on mouse

sequence the rest of the molecule is

human

we have humanized antibodies the zoo

maps

that have basically uh small

sequences of murine but they are

otherwise they are fully humanized and

then we have the gold standards nowadays

which would be a fully human antibodies

where both the fab

and the fc sequence are all

human so you can see adelumi map which

is one of the tnf antagonists

is a human antibody

and you can see that infliximab which is

another tnf thats a chemeric antibody

now what are the effector

processes in other words once those

monoclonal antibodies hit their target

how do they remove it

either by complement complement

dependent cytotoxicity or by antibody

dependent cellular toxicity cdcc or adcc

lets look at cdc first

so here you can see thats the

monoclonal antibody

the little

y

that binds to a target in this case it

would be a surface target

this would be a cd0 which is a target

for retoxy map

by binding

the fc receptors so the bottom part if

you like the stem of the molecule

activates complement

complement proteins gather and they form

whats called a membrane attack complex

a membrane im sorry protein complex

that basically

opens up a pore

and through that pore basically you have

the extracellular and the intracellular

flu fluid being in contact and the cell

is going to be lysed

okay so the binding of the

monoclonal antibody to the target leads

to fc mediated

complement activation which kills the

cell

that would be cdc complement

on the other hand if you look at the

adcc

you now have again a target

that the monoclonal antibody has bound

to and now the fc

the bottom part of that molecule

interacts with

fc gamma receptors that are present on

other immune cells in this case would be

macrophage a monocyte

or a natural killer cell

okay so here the monochrome antibody

hits the target and then it activates

other immune cells

to destroy the target and the cell

associated with it so this requires

revised

requires complement

this requires

other

immune cells

the last thing that i want to review

with you in more detail is this fcrn

mediated recycling

so regardless of what target igg or

monoclonal antibodies have

they are subject to fcrn or the neonatal

fcr receptor

recycling so how does that work well

this would be the igg could be the

endogenous igg or it could be the

monochrome antibody

it gets it binds to the fcrn on the cell

surface

it forms an endosome and the endosome

gets

internalized

okay so you now have inside the endosome

you have

the

igg

both free and the igg that is bound to

the fcrn

the igg that is free is then metabolized

broken down in the lysosome so thats

gone

on the other hand the fcrn

bound

uh monoclonal antibody is protected from

this degradation

and it gets recycled to the cell surface

where the antigen i mean the antibody is

then released again

so you have recycling of portion

and you have breakdown of some of it

and remember this is not related to the

fab this is not related to the

antibody

targeting part of the molecule this is

all related to the fc portion of it

so if you put this together monoclonal

antibodies are subject to two parallel

elimination pathways

the first one that ive already alluded

to is

tmdd or target mediated drug disposition

so here the

monoclonal antibody by virtue of its fab

forms an equilibrium with a drug target

it tags it and then you have subsequent

elimination

via fc mediated processes so this could

be cdc or adcc

this is a pathway that is highly

selective it only occurs if the drug

binds to the target

and it depends on how much target and

how much drug there is in other words it

is saturable and depends on the

concentration of both of the

uh contributors to this complex but in

addition to that

any uh andy uh any monoclonal antibody

is also subject to this relatively

nonselective fcrn mediated

okay so here

with the fc part of the molecule you

have endocytosis

and subsequent

degradation

however any of the monoclonal that is

bound to the fcrn is protected and gets

recycled

so this is a pathway that does not

depend on target concentration because

the target is not involved

and it is usually not saturable

however something that i didnt point

out here that i want to point out

verbally is

that this process happens not only for

monochromes but also for endogenous igg

so you have endogenous igg the patients

igg

compete with mono potential at least

compete with monoclonal antibodies for

those binding site which then could

prevent them from being recycled

the reason why this is important from a

kinetic point of view the combination of

those pathways

along with the fact that the target

itself changes over time means that

there is a potential for those and

timedependent pharmacokinetics

so lets look at an example where we

work out those

various relationships

so this is a

antibody that targets a surface receptor

cda

on t cells

okay so you have the free

antibody

that interacts with its target

it forms a complex

and this is a reversible interaction

however this complex itself

is now subject to this as i mentioned

before tmdt

so specific sessionable receptor

mediated clearance and you can see there

are various fc receptors

that lead to the removal

of the

target that is bound to the monoclonal

in addition to that the monoclonal by

itself can also be removed by this

nonsaturable

fcrn pathways

okay so this is nonsaturable

this is saturable and depends on how

much target there is

so if you look at again the

concentration in plasma versus time

use for the different doses from to

0 milligrams so this is 00 fold range

in doses you see again what i like to

call the hockey stick

that with higher doses you get a

plateau

but the terminal

rapid elimination is the same across

doses because now the concentrations are

below

the saturation level

what is and i didnt put the numbers

here but if you look at the clearance

values across those doses you can see

that

from the lowest to the highest dose the

clearance is reduced 0fold so this is

strongly nonlinear

you also see an increase in

im sorry a decrease in volume of

distribution

only about twofold that means with

increasing doses you have saturated now

the binding sites not only the removal

sides

okay so this is typical for tmdd that

both clearance and volume go down

now if we look at the

pkpd relationship so this is now not

after iv but after subcutaneous

administration of one of those doses

and were looking at the left hand side

at the plasma concentration

and here we are looking at the

concentration of the target

on the right hand side versus time

so you can see after subcutaneous

administration

uh the monoclonal antibody

concentrations and plasma go up they

peak and they decline

consistent with that you can see that

the target concentrations

go down as well

okay so the drug hits the target that

binding is

almost instantaneously and the target

gets removed and then as the monoclonal

antibody

concentrations decline meaning as that

monoclonal antibody complex is being

removed

you have a re

recovery of the

target so the target comes

back

because the removal now gets less and

less and the target gets regenerated

okay

and you can see that is true whether you

look at the expression or youre looking

at the binding sites

okay so here you can see that the target

concentrations

have a direct or the target levels i

should say i have a direct correlation

with the concentration of drug

but they also depend on the turnover of

the target

underneath you have now repeat those

studies in patients with psoriasis the

idea being is that by hitting the target

by knocking out those t cells

that the psoriasis

and other immune disease

should be

[Music]

should be bene should be benefiting from

that so what youre looking at here is

again over time now look at the

different time scale because youre now

looking at repeat doses once a week

on the

uh left hand side were looking at the

drug concentrations so you can see

weekly doses the drug concentrations

they go up and then be at steady state

and at the last dose the drug

concentrations decline

in yellow were looking now at the

target and the target is on the right

hand scale and you can see that with the

first dose

the target is knocked out and it remains

knocked out basically until the last

dose is given

and then the target gets

regenerated it comes back

okay and you can see that the target and

the free binding sites just like in this

brought here they basically power

if we now relate that to the clinical

effect thats what the clinicians care

about

uh they have whats called a paisey

score uh

uh psoriasis area and severity index and

thats in purple and you can see that

thats core

even though the

uh

target gets knocked out right away

thats cause changes very slowly

and even after the last dose that score

only slowly returns back so there is a

further delay

from translating the

knock down of the target the cd

a cda

to uh uh relating that to the uh

clinical symptom which tells us

downstream of this target there is

pathophysiology that basically explains

for this lag as well

okay let me go through one example and

the second one as i said its your

exercise

so the first example is a growth

stimulating

factor for phil grasstem gcsf

and i want to start off by showing you

how different this protein

is from a monoclonal

okay you can see its much smaller

okay its about twenty thousand dalton

monoclonal is about a hundred fifty

thousand

it is

nonglycosylated so we dont have to

worry about various carbohydrates

it is a single

chain

uh uh

protein as opposed to the four

the the two light and the two heavy

chains in the monoclonal

okay so field grassland should be uh

much easier to deal with in terms of uh

the manufacturing than

a monoclone

what does it do well as i mentioned

before it binds to a

specific receptor on the surface of

white blood cells and their precursors

and by binding to the cell surface

receptor gcsf receptor

that gets translated in cell

proliferation

so it leads to

increased maturation of white blood

cells

however

and the reason why i use it as an

example

it has a very complex kinetic properties

because it is subject to nonrenal im

sorry nonsaturable renal elimination

because its a relatively small protein

and then it has a second pathway and

thats the one that causes trouble

because that pathway depends on how much

receptor there is

so this binding to the receptor not only

leads to the

intended pharmacological response

increased white blood cells but it also

leads to the breakdown of the drug in

the first place

so its limited this elimination is

limited by how many white blood cells

there are

and

therefore it becomes saturable and

time dependent

so lets look at a couple of plots to

illustrate that and they are part of one

of the handouts that ive included with

the class material

so lets look at after iv administration

so here

phil grassland is given intravenously as

an infusion i think over 0 minutes

and you can see after a single dose it

looks

doesnt look like a hockey stick so it

looks like it might fall a linear pk

if you look underneath

the pharmacological response the

uh

absolute neutrophil count versus dose

im sorry versus time

you can see that the absolute neutrophil

count goes up peaks and then it goes

down

main thing as i alluded to before

the plasma concentrations peak right at

the end of the infusion after 0 minutes

however the white blood cells dont peak

until after about 0 hours

so again we have this disconnect is lag

time that is caused by the

maturation the cytokinetic model

on the right hand side

we are now changing the administration

route

and were giving a few grasping

subcutaneously so you now can see

concentrations in plasma go up they peak

and then they go down maybe with a

longer halflife so maybe theres a

little flipflop

underneath we can see again the uh

absolutely count goes up and it peaks

and you can see the change here

is less than it is after iv because we

dont have complete bioavailability you

can see after subcutaneous

administration the peak levels are about

0 after iv they are more than 00

more importantly

when we look at repeat those

administrations so now were giving the

drug subcutaneously

uh repeatedly at different doses

so at the very top we are looking at the

plasma concentration of the filigrasium

versus time so this is the first dose

second dose and so on and lets just

compare for the low dose thats

micrograms per kilogram the first dose

and the last dose

and you can see that at the first dose

the drug levels are higher than after

the last dose

lets look at a higher dose

five micrograms per kilogram the first

dose has higher doses than the last dose

and the same is true for the highest

dose

so over time

the drug concentrations

behave

very different from what you would

expect there is no accumulation theres

the opposite theres a loss of

concentrations over time

all right lets look underneath what

happens to the pharmacological response

so here youre looking at the absolute

neutrophil count versus time

and you can see the absolute neutrophil

count goes up goes up

and the highest level are

are achieved as you would have expected

after the last dose

okay so you can note that at the first

dose when we have the highest drug level

we also have the lowest white blood cell

count

at the last dose when we have a reduced

drug levels we also have the highest

white blood cell count

and obviously this is the explanation

as i mentioned

before the elimination at least part of

it the major part of it is of a field

grad stem depends on how many

neutrophils we have

so as we have more neutrophils

the clearance is increased and we have

lowered or reduced levels

okay so

when you look over time so this is based

on a model that they used in this

particular paper

if you look at the

amount of

receptor that is available for the drug

to bind

to exert its effect but also to be

eliminated

that receptor goes up

or if you look at the

better way to look at it if you look at

the clearance the instantaneous

clearance over time

you can see within each dose

the clearance because its a saturable

clearance goes down and then it recovers

prior to the next dose okay but in

addition to that over time because you

now have more white blood cells you also

have an increase in residual clearance

so at the last dose

the clearance is much higher than after

the first house

now

so thats

complex time and concentration depending

now one of the advantages or one of

these advantages of grassland is it has

to be given fairly frequently so

attempts are made to improve that and

one way to do that is by percolating it

so this is a covalent

binding of filgrastim to

propylene ethylene glycol im sorry

polyethylene glycol

that increases the molecular weight

to above 0 000 which basically shuts

down the renal excretion

and if you go back we are shutting down

this pathway

and the pedulated

filgrastim now has only one way to leave

the body and that its via this

receptormediated degradation

so again lets look at a study so this

is a study on top were looking at the

concentration of the pegulated field

grass stem and underneath were looking

at the

neutrophil count

and im going to explain to you in a

minute what happens to those neutral

faults

so you can see first that the

concentrations increase

those dependently

and stay around longer than after the

nonpegulated so the nonpegulated are

the triangles and you can see all those

half lines or terminal decline

is

more slowly so we can give it less

frequently thats obviously the intent

now if you look at the anc we now have

to appreciate that those studies were

done in patients that underwent

chemotherapy so they got a testose if

you like or a prechemotherapy dose

and they saw a timedependent increase

in

nutrition

on day they received

their chemotherapy which was highly

mildly suppressive so you would expect

the

white blood cells to go down a day later

they got their second dose of of field

grasted

and you can see that even though there

was a

drop in white blood cell because of the

chemotherapy

that drop was actually the

less with the pegulated than it was with

the nonpagalated

okay which again suggests that

the difference in halflife that this

nonpercolate has such a short halflife

that it does not cover all the

postchemotherapy

myosuppression

if we look at the

uh clearance values again to illustrate

how nonlinear the kinetics has become

if you look at those those were the

patients that i just reviewed for you

with small nonsmall cell lung cancer

before chemotherapy and lets just look

at the clearance

with increasing doses the clearance

declines from to

so this is a sign of the

concentration or dosedependent kinetics

are saturating the

pathways via the white blood cells

after chemotherapy so this is when the

chemotherapy now has reduced the white

blood cells

the clearance across all doses is

further reduced

because we basically have

reduced their elimination pathway we

still have

those dependents

and what ive done here is ive actually

plotted

the area under the curve this is for the

drug in plasma versus dose

and ive plotted the area under the

effect curve which is the anc count

versus those as well so lets look at

the

kinetics the in blue

and you can see that this is not a

straight line but it is a

super proportional

relationship meaning with increasing

doses the area increases more than

proportion to those this is true for the

kinetics

and the reason for that is that we have

saturation

however if we do the same plot for the

pharmacodynamic response you can see

that the pharmacodynamic response is

actually

infraproportional so increasing the

dose we get a less than proportion

increase in

the area of the anc count that has to do

with the fact that those doses are

already saturating the maximum possible

response

so

for the purposes of those selection

as the

paper that i have included with my

handouts

points out they looked at the

relationship based on a model between

the

maximum effect okay

as a function of the concentration of

phil graston

they defined it uh im sorry by an ec

0 value of about nanograms per ml and

you can see the various doses the top

two doses basically fall into the

plateau portion

and you can see those original doses in

the studies that i just reviewed for you

were body weight

corrected and they actually then picked

a nonbody weight corrected dose that

allowed them across a fairly large range

of body weights to fall into the plateau

all right so phil grassland has a

reduced total clearance relative to

field grassland because were taking out

the renal elimination pathway and it

depends exclusively on the

neutrophilmediated elimination pathway

as a result the pharmacokinetics becomes

strongly nonlinear and searchable after

single doses

however as far as the dynamics is

concerned

we can select doses that fall into the

plateau

and as a result we get those

effects that were talking about here

and preventing uh the chemotherapy and

use modern suppression

the tnf blockers uh well talk about

that uh after the end of my lecture

so let me now wrap up

my presentation by talk about

biosimilars

so biosimilars are the equivalent in the

biotech world of generic drugs

the idea basically is if we can

uh classify a biosimilar to a reference

protein drug they are therapeutically

substitutable

okay another term that you find in the

literature further that i follow

on biologics

now just to give you a reference no pun

intended generic drug products

for small molecular weight drugs

basically depend on a

comparison of the area under the curve

and bioequivalence assessment

okay in order to

[Music]

conclude that they are therapeutically

substitutable unless they are locally

acting drugs

however for uh biosimilars

because of the complexity of the

molecule itself thats not sufficient so

the approach is different

and you can see this is the pyramid that

you find lots of time thats supposed to

help understand how we conclude that a

biosimilar is

biosimilar or highly similar to the

reference product

most of this permit

refers to analytical tools that allow us

to characterize the

molecular structure the physical

chemical properties the in vitro

properties in terms of the fc

and the fe part of monoclonal antibodies

for example

so this is all based on analytical work

then theres there are nonclinical

studies to show that the

pk and if possible the pd in animals are

comparable

what i want to focus on are the top two

parts of the pyramid

we want to show so in order for a

biosimilar to demonstrate bias

similarity

the reference and the potential by a

similar have to show that they are

biequivalent kinetically biequivalent

dynamically and that they are clinically

not

distinguishable so as we move up

we are reducing uncertainty uncertainty

meaning we are convincing ourselves more

and more that those two products are

truly therapeutically substitutable

and as i point out here pkpd including

immunogenicity studies

they are intended so thats the top part

here they are intended to show that any

differences between the two products are

not clinically significant

between the proposed biosimilar and the

reference product

and thats all part of the

totalitarianity of totality

of evidence which would be the entire

pyramid

all right now for uh the pkbd part

uh typically we have clinical

pharmacology studies in healthy

volunteers

so those are

not patients but study subjects

in order to demonstrate pk and pd if

possible by equivalence

in addition to that uh the this is

required in the united states per

guidance in a phase three study with

patients

uh we have to demonstrate or it has to

be demonstrated that there is no

clinical difference between outcomes

or for outcomes between test and

reference products

and as part of those studies theres

usually a sub study where the pk in

patients will be assessed

and lastly

clinical immunogenicity should be

comparable

so what ive done in the next few pages

i have summarized

the four biosimilars that as of right

now are approved in the us and you can

see one of them is

a gcsef that weve already talked about

and three of them are on monoclonals

okay so we have

phil them

just talked about that thats one

biosimilar approved and then we have

three

uh

tnf blockers that are part of the

exercise that also have been approved

and you can see how were they studied

well

they all underwent uh pharmacokinetic

study in healthy volunteers

either as a crossover or parallel group

so there was washout involved for the

crossover studies to make sure

that the two treatments didnt carry

over

you can see that

in all across the board

both us and eu sourced reference

product was used so those are all

multinational companies they wanted to

target approval in both the eu and the

united states

you can see fairly large sample sizes to

demonstrate by equivalence

on the next page uh ive listed

according to the label whether the drugs

follow linear or nonlinear pk

and as we talked about for

phil graston

it is subject to a strongly

superproportional pk all the other

at least two of them are known to be

linear in the therapeutic range the

third one is not stated in the label

as a result you can see that for the fur

grassed empire similar

different doses and different routes

were studied

to deal with the fact that they are

super proportional pk

on the other hand if you look at the

monoclonals

pretty much straight single doses and a

fixed dose of therapeutic dose was

studied

all those studies used by equivalence so

the area and the cmax

ratios between biosimilar and reference

had to be within 0 to percent

in addition to that and i think this is

kind of tough to see

for all of those

four biosimilars that are approved

uh phase three studies were done

in patients

the dosing regimen that was used was

obviously a therapeutic dosing regimen

and in subgroups of patients

at least informally the pharmacogenetics

was

assessed using either areas under the

curve during a dosing interval

or trough levels

other than the anc count for

fear grass stem for any of the tnf

blockers no pd matrix was assessed

as far as immunogenicity is concerned

you can see that

of of the four approved

the imaginicity rates were quote similar

meaning in the uh eyes of the fda and

the swans are not different between by

the uh by a similar and the reference

for one of the two of one of the four a

postmarketing study actually was

required because their birth differences

that could have been

clinically significant

so let me walk you through an example

and i picked the saxio which was the

first us approved biosimilar i picked

that as

my

example

okay so the biosimilar needed to

demonstrate by similarity for the us

approved reference product neupogen

included pkpd studies so lets walk

through them

one of the uh phase one studies one of

the pk bioequivalent studies that i

alluded to in my uh summary sheet

uh now looks at the concentrations of uh

field grad stem versus thyme

for the xoxia which is now the

biosimilar and the reference product the

neupogen

so here you can see that the profiles

seem to

overlap nicely

the format by equivalence assessment

tells us that both the area under the

curve

and the cmax their 90 confidence

interval falls within 0 to percent

so they passed

the pharmacokinetic by equivalence

in addition to that because we have a

markup a pharmacodynamic marker

as part of this study they also measured

the pharmacodynamic by equivalence

and in order to do that they for the

same study now they measured over time

the

anc the absolute neutrophil count versus

time again you can see the profiles

are virtually superimposable

using the by equivalence criteria for

both the area under the effect curve and

the peak effect

fall within the bike ruins goal post

check

then i mentioned before given the fact

that there is a relatively complicated

dose

dependence they also looked at and

0 milli micrograms per kilogram

sub q

again you can see without any formal

testing that the dose dependence for

both the

soxial biosimilar and the neupogen

reference

are basically superimposable

so in all the clinical uh the phase one

pkpd by equivalence was

uh achieved

and then to confirm that this translates

in patients in

any

or in

no clinically significant difference

between the two

so they did a study in patients with

breast cancer that underwent

chemotherapy

and they receive two doses of fear grass

stem so just like we talked about before

this is the first dose of fibroglastin

then somewhere here they received

chemotherapy you can see the white blood

cell count declines

and then they get the second dose

and you can see again if you compare the

soxial the biosimilar and the neupogen

the reference

the profiles

are virtually

superimposable

and the uh clinically

uh

relevant outcome that was used to assess

the study

was the duration of severe neutropenia

so if you look at for the both

treatments

the mean and the 90

percent confidence interval

they basically overlap and they could

conclude that the true treatments are by

equivalent

so based on the totality of the evidence

they were able to show that soxyu and

neupogen were biosimilar and soxia in

00 became the first

biosimilar ever

now that concludes my formal

presentation

ill give you a chance to work on the

exercise

and if youd like to you can listen to

me again and ill tell you what you

should have gotten in the exercise

hello this is jurgen reynolds again im

ready to review for you the exercise

that i had asked you to do

on the tnf antagonist so let me just

briefly uh review what i had asked you

to do

so i had posted the uh prescribing

information for those five tnf blockers

and i wanted you to look at different

sections section six seven

eleven and twelve

in order to summarize uh the differences

between the products the molecular

origin mechanism of action recommended

dosing regimen

use in the geriatric population notable

drug dog interactions

basic quantitative information and

immunogenicity

so what i have put together for you as a

key

is a summary

so lets just look at the cross

from left to right you can see we have a

linear map

inflexi map turner set

glimmer map and certainly the map pijo

or pigol

as the

five tnf blockers so what they all have

in common

they are targeting tumor necrosis factor

which is an inflammatory protein

involved in autoimmune diseases

so lets see how they compare in terms

of the type and you can see two of them

at limu map and garlic map

they are recombinant igg ones

they theyre targeting tnf and they are

completely human

um and um

okay so they are human

uh completely human proteins

compare that to inflexi infliximab and

you can see theres an xc so this is a

chimeric

protein

so here we have the

ig kappa chain

connected this is human then connected

to the murian variable

so theres a mouse component to this but

its still a monoclonal antibody

then we have a turner set but a

ternacept is not a monoclonal antibody

its what they call a decoy receptor

it is a fusion protein where the tnf

receptor

is combined with fc

of igg so theyre taking the receptor

the human receptor that is available

recombinantly

and theyre bioengineering then a

protein where theyre combining it with

the fc receptor

why would they combine it with the fc

receptor well remember the fc receptor

is responsible among other things for

fcrn mediated recycling so theyre

basically doing this

and take advantage of the fcrn to

prolong the halflife otherwise the tnf

receptor by itself that protein would be

degraded very quickly

and then the last one the cetoluzy map

thats a humanized so its not human but

humanized so it has some urine sequences

and its conjugated with polyethylene

glycol

why did they

why did they conjugate it with

polyethylene glycol again to prolong the

halflife

so this is a monoclonal antibody

but theyre trying to prolong the

halflife

so if we just switch down and look at

the uh

well lets look at the mechanism of

action first so

all the monoclonals they are inhibiting

the receptor both soluble and membrane

bound

the one exception is the decoy receptor

okay so that is the receptor that youre

giving exogenously that is competing for

tnf

and its uh

sucking it up and its preventing it

from doing its damage other than that

theyre all tnf

binding slash neutralizing

molecules

how do they compare in terms of their

different pharmacokinetic properties

well the first thing

infliximab is the only one that is given

intravenously so we obviously dont have

to worry about bioavailability

the ones that are given subcutaneously

you can see the bioavailability ranges

from 0 to about 0 0 percent is the

highest for simsia

their peak

concentration is achieved five days

two days two to six days days so it

takes a couple of days

because of the slow subcutaneous

absorption

for infliximab the tmax is obviously

the end of the infusion

you can see that all at least the ones

that we have information on

have

or follow linear pk

how can that be after i try to convince

you

that you have to worry about nonin apk

for

maps and for proteins in general what

that means is the doses are so high

that theyre exceeding the levels that

you achieve exceed by far the levels of

t and f in the body

okay so the

binding to the target really has become

a small the nonlinear the central

binding has become a small part of the

overall pk so the overall pk across the

board is

linear which obviously makes

life

easier

if you look at the volumes of

distribution you can see they range

somewhere from five to maybe 0 liters

so theyre all large proteins

that have a tough time leaving the

intravascular space just like you would

have expected

the big difference is in their clearance

and their halflife

so you can see the what i would call the

standard monoclonals

at limu map and colima map the humanized

ones they have halflifes about one to

two to three weeks

and similar clearances so thats

basically what an endogenous igg does

so their clearance is primarily via the

fcrn mediated recycling

lets look at the chimeric

okay and you can see the chimeric one

has a shorter halflife

so because of the fact that it has a

mirroring component to it its

eliminated more quickly

okay

on the other hand the eternal set the

decoy receptor has an even shorter

halflife despite the fact that its

combined or conjugated with an fc

segment

okay so all those by engineering it

helped it a little bit but the halflife

is still of all five of them it is the

shortest

on the other hand you can see that the

pendulation of certain lucid map gives

it about a two week half life

okay

now if we uh look at the various doses

you can see accordingly uh the the

those the um

a lima map is given biweekly

subcutaneously

the inflexi map

is given loading dose and then basically

every two to four weeks or two to eight

weeks

uh

the eternal sept the one with the

shortest halflife has to be given every

week

golem map every four weeks

and uh set the lucid map every two weeks

so the short halflife translates into

the

highest dose frequency for the eternal

set

okay so the decay receptor has to be

given very frequently

because it has the highest clearance and

the shortest halflife despite the fc

conjugation

now if you look at the major drug drug

interactions you can see

this is not what you typically find for

a small molecular weight drug where you

look at other

metabolic inhibitors drug transport

inhibitors

but here you basically have a

pharmacokinetic thermodynamic

interaction that methotrexate which is

typically given for the autoimmune

diseases before you would start patients

on those monoclonal antibodies on those

tnf antagonists

methotrexate reduces the clearance

for pretty much all of them with the

exception of eternal cell

and the mechanism behind that is that

methotrexate reduces

immune cells and the immune cells are

involved in the clearance via the fc

effector function

so by coadministering

therapeutically methotrexate

are reducing the clearance for at least

four order five

pharmacodynamically as a result of

coadministration of

methotrexate being an immune suppressor

you would expect and you can see the

label states that that the immune

suppression is

enhanced

okay

so no major differences as i said with

the possible exception of the fusion

protein

now the last thing to look at is the

immunogenicity so this is whats the

incidence of

either

adas or

infusion reactions signs of allergic

response

and ive highlighted here the two that

stick out

because you can see uh

lets start with the ones

that are basically very similar and

limit map five percent ada incidence

may be lowering uh plasma concentrations

and reduce efficacy

about the same

uh

incidents in uh said lucy map

and gloomy map again the incidence is

very similar

but then you look at the two problem

children if you like infliximab in a

ternacip

okay so infliximab has a fairly high

incidence of infusion reaction that

means during the infusion people people

develop

rashes

things like that that may require

treatment

okay

that is a direct consequence of the fact

that were using a different species

other than the humans as part of the

molecule

and if you look at the

fusion protein that incidence is even

higher

okay so you see those two are not only

hampered by the fact that they have a

fairly short halflife they also as a

result of the fact that theyre either

artificial construct or that they

contain chimeric minimurian

sequences they also have a high

incidence of immunogenicity

and i think that is thats it i hope you

not only enjoyed doing the exercise but

enjoyed listening to my lecture

i appreciate you uh

paying attention to me and if youve got

any questions as always contact the

program coordinator

thank you

you