Hello

Im ready to review for you the exercise thatI had asked you to do on the TNF antagonist

So let me just briefly review what I hadasked you to do

So I had posted the prescribing informationfor those five TNF blockers and I wanted

you to look at different sections: sections and in order to summarize the

differences between the products: their molecularorigin mechanism of action recommended dosing

regimen use in the geriatric populationnotable drugdrug interactions basic quantitative

information and immunogenicity

So what I have put together for you as akey is a summary

So lets just look at across from left toright you can see we have Adalimumab Infliximab

Etanercept Golimumab Certolizumab Pegolas the five TNF blockers

So what they all have in common they aretargeting tumor necrosis factor which is

an inflammatory protein involved in autoimmunediseases

So lets see how they compare in terms ofthe type

And you can see two of them Adalimumab andGolimumab they are recombinant IgGs

They are targeting TNF and they are completelyhuman humanized

Okay

So they are human completely human proteins

Compare that to Infliximab and you can seethere is an exing [spelled phonetically]

so this is a chimeric protein

So here we have the IG kappa chain connected this is human then connected to the

murine variable

So there is a mouse component to this butits still a monoclonal antibody

Then we have Etanercept

But Etanercept is not a monoclonal antibody

Its what they call a decoy receptor

It is a fusion protein where the TNF receptoris combined with FC of IgG

So theyre taking receptor the human receptorthat is available recombinantly and they

are bioengineering then a protein where theyrecombining it with the FC receptor

Why would they combine it with the FC receptor?

Well remember the FC receptor is responsibleamong other things for FCRNmediated recycling

So theyre basically doing this and takeadvantage of the FCRN to prolong the halflife

Otherwise the TNF receptor by itself thatprotein would be degraded very quickly

And then last one the Certolizumab thatsa humanized so its not human but humanized

So it has some human sequences and itsconjugated with Polyethylene glycol

Why did they conjugate it with Polyethyleneglycol?

Again to prolong the halflife

So this is a monoclonal antibody but theyare trying to prolong the halflife

So if you just switch down and look at the well lets look at the mechanism of action

first

So all these monclonals they are inhibitingthe receptor both soluble and membrane bound

The one exception is the decoy receptor

Okay

So that is the receptor that you are givingexogenously that is competing for TNF

And its sucking it up and its preventingit from doing its damage

Other than that they are all TNF bindingneutralizingmolecules

How do they compare in terms of their differentpharmacokinetic properties?

Well the first thing Infliximab is the onlyone that is given intravenously

So we obviously dont have to worry aboutbioavailability

The ones that are given subcutaneously youcan see the bioavailability ranges from 0

to about 0 percent

Eighty percent is the highest for Cimzia

Their peak concentration is achieved fivedays two days two to six days days

So it takes a couple of days because of theslow subcutaneous absorption

For Infliximab the Cmax is obviously theend of the infusion

You can see that all at least the ones thatwe have information on follow linear PK

How can that be after I tried to convinceyou that you have to worry about nonlinear

PK for maps and for proteins in general?

What that means is the doses are so high thatthey are exceeding the levels that you achieve

exceed by far the levels of TNF in thebody

Okay

So the binding to the target really has becomea small the nonlinear receptor binding

has become a small part of the overallPK

So the overall PK across the board is linearwhich obviously makes life easier

If you look at the volumes of distributionyou can see they range somewhere from five

to maybe 0 liters

So theyre all large proteins that have atough time leaving the intravascular space

just like you would have expected

The big difference is in their clearance andtheir halflife

So you can see what I would call the standardmonoclonals: Adalimumab and Golimumab humanized

ones they have halflives about two to threeweeks and similar clearances

So thats basically what an androgynous IgGdoes

So their clearance is primarily via the FCRNmediated recycling

Lets look at the chimeric

Okay

And you can see the chimeric one has a shorterhalflife

So because of the fact that it has a murinecomponent to it its eliminated more quickly

Okay

On the other hand the Etanercept the decoyreceptor has an even shorter halflife despite the fact that its combined or conjugatedwith an FC segment

Okay

So although its bioengineering it helpedit 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 PEGylationof Certolizumab gives it about a twoweek halflife

Okay

Now if we look at the various doses youcan see accordingly the Adalimumab is given biweekly subcutaneously

The Infliximab is given loading dose and thenbasically every two to four weeks two to eight weeks

The Etanercept the one with the shortesthalflife has to be given every week

Golimumab every four weeks and Certolizumabevery two weeks

So the short halflife translates into thehighest dose frequency for the Etanercept

Okay

So the decoy receptor has to be given veryfrequently because it has the highest clearance and the shortest halflife despite the FCconjugation

Now if you look at the major drugdrug interactionsyou can see this is not what you typically find for a small molecular weight drug whereyou look at other metabolic inhibitors drug transport inhibitors

But here you basically have a pharmacokineticpharmacodynamic interaction that methotrexate which is typically given for the autoimmunediseases before you would start patients on those monoclonal antibodies on those TNFantagonists

Methotrexate reduces the clearance for prettymuch all of them with the exception of Etanercept

And the mechanism behind that is that methotrexatereduces immune cells and immune cells are involved in the clearance via the FC effectorfunction

So by coadministering therapeutically methotrexateyou are reducing the clearance for at least four out of five

Pharmacodynamically as a result of coadministrationof methotrexate being an immune suppressor you would expect and you can see the labelstates that that the immune suppression is enhanced

Okay

So no major differences as I said withthe possible exception of the fusion protein

Now the last thing to look at is the immunogenicity

So this is whats the incidence of eitherADAs or infusion reactions signs of allergic response?

And Ive highlighted here the two that stickout because you can see lets start with the ones that are basically very similar

Adalimumab five percent ADA incidence maybelowering plasma concentrations and reduce efficacy

About the same incidence in Certolizumab andGolimumab; again the incidence is very similar

But then you look at the two problem childrenif you like

Infliximab and Etanercept

Okay

So Infliximab has a fairly high incidenceof infusion reaction

That means during the infusion people developrashes things like that that may require treatment

Okay

That is a direct consequence of the fact thatwere using a different species other than the humans as part of the molecule

And if you look at the fusion protein thatincidence is even higher

Okay

So you see those two are not only hamperedby the fact that they have a fairly short halflife they also as a result of thefact that theyre either artificial construct or that they contain a chimeric meaning miRNAsequences they also have a high incidence of immunogenicity

And I think thats it

I hope you not only enjoyed doing the exercisebut enjoyed listening to my lecture

I appreciate your paying attention to meand if youve got any questions as always contact the program coordinator

Thank you