Attendee Questions from PSP Webinar: "Pharmacokinetics and Dose Adjustments for Monoclonal Antibodies in IBD - Considerations and Applications in Clinical Practice"

To watch a recording of this webinar, click here.

Why was increasing the dose not as effective in maintaining the C_{trough} versus reducing the dosing interval?

Drugs with linear PK (which includes many of the anti-inflammatory MAbs) have a half-life that is independent of dose. For a drug administered via IV typically takes 4-5 half-lives for a drug to completely clear the system. Thus, increasing the dose doesn't make the concentrations last longer it just increases the concentrations (higher peak concentration, for example). In the case of these MAbs, patient clearance (and therefore half-life) is variable and dosing the drug over the proper interval is a better way of ensuring coverage of the drug (maintaining therapeutically appropriate concentrations) over the entire dose interval.

You have shown ADA increases clearance here. Have you ever observed ADA which prolongs exposure (i.e. non clearing)?

Yes, it's rare to see, but there are certainly patients who develop ADA whose PK is either not affected or it extends the half-life.

Why are physicians so reluctant to decrease the dosing interval?

The common reaction to an insufficient response to a drug is to increase the dose administered. For chemical agents, this is usually the correct response. Shortening the dose interval is something that is tried, but it is often the last thing that is attempted. Unfortunately the delay to an appropriate dose adjustment often results in patients developing ADA.

Since ADA response is heterogeneous, can you please comment on how to TDM based on ADA? Similar ADA titer may have different impact on PK.

This is an excellent question. The model includes terms for unexplained between subject variability, thus while on average a specific titer may cause some typical increase in clearance, the model allows for subjects to have greater or less than the typical expected increase in clearance.

Recently TAILORIX data was presented showing no significant advantage of TDM over Clinically adjusted regimen. Can you comment on that?

TAILORIX increased dose to 7.5 then to 10 mg/kg in patients that showed loss of response or low troughs but didn't address dose intervals which is the primary adjustment that should be considered. It was a small study and the duration was only the first year of maintenance (it did

not include induction therapy). Thus the study design was not sufficient to demonstrate the advantage (or lack) of TDM.

Are there insurance reimbursement issue in case of using shorter intervals based on TDM? Is it considered off-label usage?

In the US, patients do occasionally have their dose interval shortened or (more commonly) the dose increased due to lack of therapeutic response. Doses that are higher than 5 mg/kg usually require pre-approval from insurance. Dose intervals shorter than 6 weeks and doses higher than 10 mg/kg are not used often, but with approval from the insurance company may be reimbursed with pre-approval. The question of off-label is tricky. Physicians are not regulated by FDA and so can do what they feel is in the best interests of their patient but of course are guided by their institutional guidelines, their clinical experience and the ability to get the treatment costs reimbursed. From a regulatory perspective, only two maintenance doses are specifically mentioned in the package insert (5 mg/kg and 10 mg/kg) and the interval mentioned is 8 weeks. Thus, any other dose at any other interval is technically off-label.

Would you say that the principle benefit of personalized dosing is avoiding immunogenicity or of maintaining a 'therapeutic' drug level?

Hopefully both, and possibly that health care dollars are better spent because patients that can have lower doses or longer dose intervals wont have to spend money on drug they don't need, and patients who get too little drug to respond well will now get enough drug often enough to respond.

What type of model is underlying the dashboard system and how are the parameters of the model scaled with age, BW, sex, etc?

The dashboard infliximab model is a two compartment model with linear clearance. Clearance is affected by weight, albumin, concomitant immunosuppressants, antidrug antibodies, volumes of distribution are scaled by weight and intercompartmental clearance is scaled by weight and disease severity (CRP or score). We have never seen an effect of age or sex on IFX clearance once weight is included in the model. The effects of age and sex on MAb clearance are not commonly identified separately from body size.