Discussion Summaries

Do pharmacokinetics justify dose-optimization for loss of response to Vedolizumab in IBD?

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Discussion Summaries

Main Text

Abstract

Knowledge surrounding therapeutic drug monitoring (TDM) in inflammatory bowel disease is growing, especially for tumor necrosis factor- α inhibitors class of drugs. Yet, TDM for the $\alpha 4\beta 7$ integrin antibody vedolizumab (VDZ) has not been equally established, as real-life data on VDZ pharmacokinetics, VDZ drug level and treatment response are scarce.

We summarize the @GIJournal discussion held on July 14, 2021 during which the article by Ungar et al. “Dose-optimization for loss-of-response to vedolizumab - pharmacokinetics and immune mechanisms” was critically reviewed by our expert Dr. Aline Charabaty (AC), and moderated by Dr. Asad ur Rahman (AR).

Discussion Summaries

Introduction

Therapeutic drug monitoring (TDM) involves the practice of measuring the blood concentration of drugs whose efficacy and/or toxicity are associated with a well-defined drug level range, with the intent to adjust the dose and/or frequency of the drug to reach safely the desired therapeutic effect. In the field of inflammatory bowel disease (IBD), TDM of tumor necrosis factor- α inhibitor drugs (TNFi) has been used in recent years to guide treatment optimization or modification, with real-world evidence showing that higher trough levels of infliximab (IFX) and adalimumab (ADA) correlate with higher rates of clinical and endoscopic remission and with decreased incidence of long-term complications.¹⁻⁴ Vedolizumab (VDZ), an $\alpha 4\beta 7$ integrin antibody, has showed similar modest correlation between drug levels and clinical outcomes, yet the evidence is somewhat contradicting, and the pharmacokinetic (PK) mechanisms to support the evidence are lacking.⁵⁻⁹

The recent article “Dose-optimization for loss-of-response to vedolizumab - pharmacokinetics and immune mechanisms” is the first multicenter observational study that evaluated the pharmacokinetic mechanisms that could justify dose-optimization of VDZ after loss of response to VDZ in patients with IBD.¹⁰ In the study, the authors used a multi-pronged approach to find both clinical and cellular biology evidence for VDZ dose-optimization. First, they hypothesized that pre-escalation VDZ levels should correlate with the outcomes of dose-optimization such as clinical, inflammatory biomarker and endoscopic remission; this was assessed in 16 patients treated with VDZ who had primary nonresponse or secondary loss of response. The method of dose-optimization was interval shortening of VDZ dosing from 8 weeks to 4 weeks. Second, the authors assessed whether VDZ saturation of $\alpha 4\beta 7$ -receptors at trough-time points on several peripheral blood and intestinal-lamina-propria tissues will correlate with mucosal healing among

Discussion Summaries

43 patients. Finally, the authors investigated whether VDZ levels would affect the innate immune system axis, particularly M2 macrophage subsets which express $\alpha 4\beta 7$ -receptors. This was assessed by studying integrin-receptor saturation, receptor trafficking and recycling, as well as anti-inflammatory cytokine secretions as a function of VDZ levels. (**Figure 1**)

Figure 1. Study hypotheses and methods, adopted from *Ungar et al.*

There was no difference (or higher levels) in pre-intensification trough-levels of VDZ among patients who achieved post-optimization clinical, biomarker and endoscopic remission, compared with non-remitting patients. This finding was seen whether the dose-optimization was done during maintenance ($p=0.09$, 0.25 , 0.04 , respectively), or during induction (week 6, $n=32$). In the immune sub-study ($n=43$), $\alpha 4\beta 7$ -receptors at trough time-points were maximally saturated in all patients, whether they had mucosal healing or not, on peripheral blood T-cells ($p=0.15$) or eosinophils ($p=0.88$) and on lamina-propria T-cells ($p=0.88$). Similarly, integrin-receptors on M1

Discussion Summaries

and M2-macrophages were saturated by low levels of vedolizumab and no distinct anti-inflammatory cytokine secretion change was noted across different VDZ levels. This multi-pronged study suggested that higher pre-escalation (or post-escalation) VDZ levels may reflect less protein (and drug) loss from the inflamed gut, and hence higher chances of mucosal healing and response, regardless of dose-escalation. The clinical and immune findings of the study could not support pharmacokinetics as the mechanism responsible for non-response or loss of response to VDZ, nor support the concept that higher drug concentrations are needed to achieve/regain response to vedolizumab (**Figure 2**).

Figure 2. Multi-pronged results and discussion, adopted from *Ungar et al.*

Discussion

A pre-discussion poll was run by AR about how to approach a patient with ulcerative colitis (UC) who had primary or secondary nonresponse to VDZ with every 8 weeks protocol: 46.5% of

Discussion Summaries

99 votes elected to increase the frequency to every 4 weeks, 43.4% elected to check a VDZ trough level, and only 10.1% decided to switch to a different drug.

AR: Q1: *As we continue to optimize our medical therapeutics for IBD patients, how does this data compare to the pharmacokinetic-pharmacodynamic (PK-PD) data for anti TNFi agents?*

AC: We have a good sense of PK-PD of TNFi in IBD & how adjusting drug level optimizes outcome.

As a reminder, PK = what the body does to the drug. This translates into “TNFi clearance”, which is affected by albumin level, inflammatory burden, male gender, thiopurine use, etc. PD = What the drug dose to the body, with the intensity of a drug effect being associated to its serum level.

Most exposure-response relationship studies for TNFi are retrospective or post-hoc analysis of RCT. Overall, they show a positive correlation between increased TNFi drug concentrations & favorable therapeutic outcomes (and decreased drug levels are associated with a decreased response and a decreased remission rate). (**Figure 3**)

So, if a patient has partial or loss of response (LOR) to TNFi and adequate or high TNFi levels, the next step would be to switch to a biologic with a different mechanism of action (MOA) and not to increase dose/frequency of TNFi. Meanwhile, if the same patient had low drug levels (and no significant antibodies), then the dose/frequency of TNFi should be increased to achieve higher TNFi trough levels and recapture response.

In this study, surprisingly, there was no difference in pre-escalation VDZ levels between those who achieved clinical remission vs remained active after frequency escalation. In other words,

Discussion Summaries

high or low pre-escalation VDZ levels do not preclude the option to escalate drug frequency. In fact, those who started with higher VDZ levels had higher rates of clinical remission and endoscopic healing after VDZ dose-escalation. Thus, this study highlights the fact that the PK-PD for VDZ in IBD is different than what we learned with TNFi.

Suggested Trough Targets for IFX and ADA			
	AGA Guidelines ¹	Bridge Consensus ²	Other Recommendations/Comments
IFX	Maintenance: ≥5 µg/mL	Induction: WK 2: > 20-25 µg/mL WK 6: > 10-15 µg/mL WK 14: ≥ 7 µg/mL	Recommendation: 10-15 µg/mL with biomarker, endo, & radiographic co-monitor Previous study findings: <ul style="list-style-type: none"> > 8µg/mL or ≥ 11.3µg/mL associated with EH^{3,4} ≥ 11.1µg/mL associated with histological remission⁴ Increase of IFX conc >0.5 µg/mL associated with EH (not completely clear)⁵
		Maintenance: >3 µg/mL response/remission >7 µg/mL for MH	
ADA	Maintenance: ≥7.5 µg/mL	WK 4: > 5 µg/mL response/remission >7-8 µg/mL for MH (Don't switch until > 10 µg/mL)	Recommendation: 10-15 µg/mL with biomarker, endo, & radiographic co-monitor Previous study findings: <ul style="list-style-type: none"> >6 µg/mL associated with clinical remission/EH⁶

EH, endoscopic healing; MH, mucosal healing.

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Figure 3. Suggested trough targets for infliximab (IFX) and adalimumab (ADA), adopted from @MondaynightIBD. AGA: American gastroenterological association; WK: week; EH: endoscopic healing; MH: mucosal healing.

AR: Indeed, this is very interesting to note that the drug levels may be a marker of disease severity and not necessarily a marker to guide treatment intensification.

Discussion Summaries

@Lou_Skolnick: Do we know if there are safety concerns with higher levels? Or is it a guessing game? I also don't understand how TDM wasn't something that was done from the start. It's like driving a car without a gas gauge. How was it not obvious to start doing this 10 years ago?

@Empoweringpts9: @Lou_Skolnick, we've had testing levels for some of our medications for many years. Some other medications are newer and the measurement tests hadn't been fully developed. As I'm sure you're aware, insurances give us a hard time to pay for the test too.

AR: Q2: *When starting a patient on VDZ, do you routinely check a trough level during the induction of therapy? What level do you aim for?*

AC: There are a few studies in favor of proactive TDM for TNFi, with the idea that optimizing TNFi levels at induction & early during therapy is key to optimizing long term outcomes.¹¹ The prospective PANTS study suggests that TNFi levels at induction affect long term outcomes in CD, with low IFX or ADA levels at week 14 being associated with non-remission at week 54, and IFX levels > 7 mcg/mL or ADA levels > 12 mcg/mL at week 14 being both associated with clinical remission at week 54, respectively (**Figure 4**).¹² I am half-sold on proactive TDM at induction for TNFi. However, for VDZ, I don't routinely check VDZ levels proactively during induction, since it is not yet clear what level we should aim for or if PK-PD of VDZ are similar to TNFi¹³. When I do check the level, it is for patients at higher risk for

Discussion Summaries

drug loss, meaning IBD with high inflammatory burden, low albumin, or multiple prior drugs failure. In that case, I use VDZ levels of 24-35 during induction, and 11-15 during maintenance.

Figure 4: relation of infliximab and adalimumab drug concentrations at week 14 with remission outcomes in Crohn's disease at week 54), adopted from @MondaynightIBD.

AR: Those are great points! At what point do you recommend checking a drug level during induction? Week 6 versus week 10?

Discussion Summaries

AC: With IFX I would do TDM at week 6, so I know what to do next (escalate dose, prepare for q4wks vs q8wks maintenance regimen). How about @IBDdoc_BattatMd @mchiorean4 @IBD_Afzali @P_DeepakIBDMD @waqqasafif?

@EdwardLoftus2: Spot on as usual — I agree that, during maintenance, I'm usually hoping to see levels in low to mid-teens or higher.

@IBDdoc_BattatMd: Similarly, to above. It is worth noting that this is all based on observational data and we need to interpret such data with caution. That being said, in high-risk patients, I will check week 6 IFX levels strictly to avoid late treatment changes (next dose 8 weeks later). Often, I don't give VDZ in these pts, so generally I wait until the maintenance phase. Of note, there is an association between VDZ drug concentrations (at least >20 at week 6 and >12 during maintenance) and outcomes, but it is unclear if it works exactly the same way as TNFi¹⁴. As opposed to the important work @waqqasafif did on TNFi TDM, which showed positive outcomes with dose-escalation in patients with low drug levels, *Ungar et al* showed different results for VDZ¹⁰. I still dose escalate, but I select low risk patients for VDZ and do not do aggressive TDM. I am interested to hear the thoughts of @ShomronH on this.

@ShomronH: The MOA of biologic drugs requires binding to a cognate antigen ($\alpha 4\beta 7$ 'receptor' in the case of VDZ), whether this inhibits migration or other functions. So, if the

Discussion Summaries

receptors are fully blocked, how does the extra drug work? It's like putting a sixth player to win a basketball game when Yanis blocks all shots anyway.

@IBDdoc_BattatMd: This is an amazing analogy! You must have subconsciously known I'm a basketball nut! Unless there is an unknown MOA of VDZ other than $\alpha 4\beta 7$, this clearly differs from TNFi, in which such a large TNFi burden can exist.

AR: Q3: *For patients who secondarily lose response to VDZ during maintenance therapy, do you routinely check drug levels prior to escalating therapy to every 4 weeks?*

AC: I Usually change the frequency to q4wks without checking levels. This is based on the fact that antibodies against VDZ are rare & often not neutralizing. I reassess clinical & biomarker response after 3 doses of VDZ q4wks, and if no improvement then I change to a drug with different MOA.

AR: Great practical points about being proactive while monitoring for disease response during induction therapy, and how this gives insight into how the disease will behave down in the future. ***And as a slight offshoot for this question, in your practice, do payers need a drug level prior to approval for dose escalation of VDZ to every 4 or 6 weeks?***

AC: Levels don't necessarily convince payers to cover higher doses & patients might get stuck with the bill. After this study, it will be hard to justify to payors that patients with high

Discussion Summaries

VDZ trough levels will benefit from dose-escalations (which is counter-intuitive/ opposite to the experience with TNFi).

AR: The authors of this study must be congratulated by going the extra mile and obtaining $\alpha 4\beta 7$ receptor occupancy testing to test the hypothesis of molecular basis of VDZ. **Q4: Do you see a role for $\alpha 4\beta 7$ receptor occupancy in colonic tissue specimens to help us in the future? This may be a question for #AI in #IBD.**

@EdwardLoftus2: In short, no.

AC: I will keep this one simple: I am not sure I do! It doesn't seem that the receptor occupancy is affected by drug level, and it is not different in responders versus non-responders.

@bverstockt: Agree, there is no link between receptor occupancy, trough levels and response. MOA of VDZ is much more than originally anticipated!

AR: Thanks. It sure looks like this based on this study's data set. So **Q5 and bottom line: should we change our practice by ordering a trough VDZ level early in induction to assess likelihood of long-term response to VDZ?**

AC: The authors of this study did a good job to answer this question. Based on their data, a patient with IBD & a low or (even more so) a high VDZ level can benefit from dose-

Discussion Summaries

escalation. So, at this point, I won't be checking levels but will be optimizing frequency when needed. Thoughts? @fudmanMD @DrJordanAxelrad.

@fudmanMD: I agree, not just this study, but overall, the value of VDZ levels in maintenance is not clear to me. I have moved away from checking levels in maintenance and I escalate based on response. I've never seen a clinically relevant anti-VDZ Ab; has anyone else?

@EdwardLoftus2: I have seen a couple including one person who had infusion reactions.

@IBDimmunology: Interesting @EdwardLoftus2. Infusion reactions with VDZ are new to me.

@bverstockt: I don't check VDZ levels proactively, but I do check them reactively. In case of loss of response, I do check levels before considering q4wks. Immunogenicity to VDZ is extremely rare, both in trials as in real-practice. In the current study by @ibdleuven @SeverineVermei1 @gils_ann #Vandenberghe, we looked at immunogenicity in VDZ failures: hardly any antibody ¹⁵!

Conclusion

Optimization of therapeutics is vital for our patients with IBD and we still have a long way to go in #precisionmedicine. Based on this study, there is no strong support for pharmacokinetics as the mechanism responsible for non or loss of response to vedolizumab. In addition, the higher pre-escalation levels of VDZ may indicate less clearance (less severe disease) and a higher

Discussion Summaries

likelihood of subsequently re-gaining response, regardless of therapy escalation. This favors dose-escalation in selected patients, without checking trough levels prior to optimization. Finally, there is no data supporting the need for higher drug concentrations to enhance vedolizumab's immune effects, as most $\alpha 4\beta 7$ receptors on cells of interest are saturated with the smaller drug concentrations and there is no difference on the effect on the innate immune axis with higher drug levels.

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Discussion Summaries

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