Journal of Inflammatory Bowel Diseases & Disorders

Srinivas, J Inflam Bowel Dis & Disord 2018, 3:1
DOI: 10.4172/2476-1958. 1000e105

Editorial Open Access

Infliximab Trough Concentrations and Risk of Infection in Patients-Developing a Consensus

Srinivas NR*

Department of Drug Metabolism and Pharmacokinetics, Zydus Research Centre, Gujarat, India

***Corresponding author:** Nuggehally R Srinivas, Department of Drug Metabolism and Pharmacokinetics, Zydus Research Centre, Gujarat, India, E-mail: nuggehally.srinivas@zyduscadila.com

Received date: February 05, 2018; **Accepted date:** February 13, 2018; **Published date:** February 17, 2018

Editorial

The approval of infliximab, a monoclonal antibody, paved the way for the treatment of moderately to severely active ulcerative colitis (UC) and Crohn's disease (CD) in both adult and pediatric patients. Despite being a monoclonal antibody with a low volume of distribution limited to central compartment only (i.e., blood volume), infliximab was shown to exhibit high inter and intra-subject variability in its pharmacokinetic disposition [1]. Many covariates have been suggest that would explain the observed variability in the clearance of infliximab in patients and such covariates include antibodies to infliximab, co-medications, body weight, concentration of serum albumin and the degree of disease itself [1]. The application of reliable pharmacokinetic modeling tools has enabled development of guidance to achieve certain trough concentrations of infliximab for a desirable efficacy measure and/or optimization of the dose during maintenance therapy to achieve the desirable outcome [2]. In this context, Frymoyer et al. have performed population pharmacokinetic model of infliximab for achieving individualized dosing strategy for treating pediatric CD. Accordingly, the effective disease management has been linked to the attainment of desired trough concentrations in the patients [3]. Rolandsdotter et al. have further examined the trough levels of infliximab in children with inflammatory bowel disease (IBD). In this work, it was reported that a serum trough concentration of >7.2 ug/mL was achieved in IBD pediatric patients that showed clinical remission [4].

In a recent publication, Papamichael et al. have shown a direct correlation of improved endoscopic/histologic outcome in adult ulcerative colitis (UC) patients with trough concentrations of infliximab. Accordingly, the highest healing rate in UC was observed when infliximab trough concentration was ≥ 12.3 µg/mL for endoscopic (78%) and histologic (67%) evaluation. The rate of healing decreased as the trough concentration reduced with minimal rate of 17% observed for endoscopic/histologic evaluations at a trough concentration of <2.8 µg/mL. This was not the first report showing the existence of a strong correlation of trough concentration versus infliximab efficacy in adult patients [5]; in a previous study performed in both UC and IBD adult patients, mucosal healing rate occurred at infliximab trough concentration of 12-15 µg/mL (70%) and 6-10 µg/mL (80-90%), respectively [6]. Based on the severity of UC, there has been a recommendation to achieve higher trough concentration of infliximab since fistula healing is complex because on one hand it endures colonic inflammatory reversal and on the other fecal loss of infliximab is inevitable [7].

The intent of this communication is to build a consensus of the desired trough concentration levels of infliximab in the given indication versus the adverse event profile attributed to infliximab, applicable to the general class tumour necrosis factor-α (TNF-α) inhibitors [8]. In particular, recently published data of infliximab trough concentration versus rate of infections brings to light the serious nature of the situation in UC and CD patients who are desperate to get a better healing rate for a clinical remission. Although the patients involved in this study were not suffering from either UC or CD, the use of infliximab for a long term therapy provided the information on rate of infections which could be extrapolated to other disease management areas involving infliximab for a retrospective risk assessment [9].

Based on the above discussion, the range of infliximab trough concentration required for mucosal healing varies between Crohn's diseases (CD) and UC; and within CD/UC based on the severity of the inflammatory burden a higher infliximab trough concentration need to be targeted. Despite individualized dosing based on body weight, the variability in pharmacokinetics (i.e., trough concentrations) exists within the same cohort of patients. This may lead to the achievement of much higher infliximab trough concentrations in some individuals.

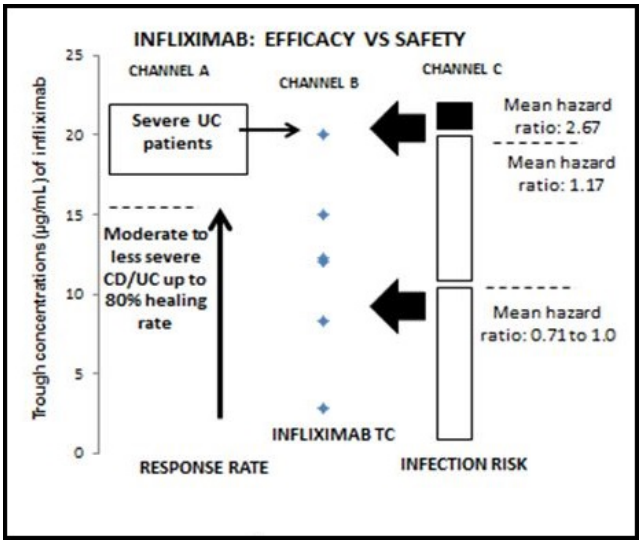

Figure 1: A composite pooled schematic representation of pharmacokinetic; efficacy and safety data of infliximab from various studies involving different patients and diseases demographics-intent to create awareness on possibility of infection risk at higher trough concentrations of infliximab.

Unfortunately, the safety aspects of the infliximab treatment need to be considered because adverse events occurrence is primarily driven by

the therapeutic concentrations of infliximab but not by the treatment indications and/or chronicity of either UC or CD. In order to drive this critical point, a composite schematic was created with pharmacokinetic, pharmacodynamics and safety data acquired in different studies (Figure 1). Although the data were not derived in the same study and/or in the same pool of patients, the intent was to showcase the real difficulty in terms of safety issues for treating IBD patients beyond a certain threshold trough concentration of infliximab.

Figure 1 provides composite trough levels of infliximab (Channel B) versus mucosal healing rate (A) and the risk of infection (C) (note: infection rate data was taken from a cohort of patients being treated with infliximab for management of spondyloarthritis). The risk of infection is in particular an important safety parameter for infliximab and other TNF-α inhibitors [4,5]. A quick visual comparison suggests that slight shift in trough concentration of infliximab above certain threshold can push the patient to a substantial risk of infection as the hazard ratio (HR) significantly jumps from 1 to >2 (Figure 1).

While the work of Papamichael et al. [5] and other researchers [6-10] in the field is very important to accumulate data and generate a rich database for a formal pharmacokinetic-safety meta-analysis, the author cannot stress the importance of collecting relevant safety data in a prospective manner including the infection rates during therapy of infliximab or other anti-TNF α drugs, if any. Such informative analysis would enable an informed decision for targeting a higher infliximab trough concentration in difficult to treat UC or CD patients accounting for safety risks with appropriately planned risk mitigation strategies including the use of co-medications and/or controlling other factors impacting clearance of infliximab that may further exacerbate the safety risks. In addition, therapeutic drug monitoring of infliximab is of paramount importance to keep the balance of efficacy versus safety.

References

1. Hemperly A, Casteele VN (2018) Clinical pharmacokinetics and pharmacodynamics of infliximab in the treatment of inflammatory bowel disease. Clin Pharmacokinet 1: 1-14.
2. Ternant D, Passot C, Aubourg A, Goupille P, Desvignes C, et al. (2017) Model-based therapeutic drug monitoring of infliximab using a single serum trough concentration. Clin Pharmacokinet 1: 1-12.
3. Frymoyer A, Hoekman DR, Piester TL, de Meij TG, Hummel TZ, et al. (2017) Application of population pharmacokinetic modeling for individualized infliximab dosing strategies in Crohn disease. J Pediatr Gastroenterol Nutr 65: 639-645.
4. Rolandsdotter H, Marits P, Sundin U, Wikström AC, Fagerberg UL, et al. (2017) Serum-infliximab trough levels in 45 children with inflammatory bowel disease on maintenance treatment. Int J Mol Sci 18: 575.
5. Papamichael K, Rakowsky S, Rivera C, Cheifetz AS, Osterman MT (2018) Infliximab trough concentrations during maintenance therapy are associated with endoscopic and histologic healing in ulcerative colitis. Aliment Pharmacol Ther 47: 478-484.
6. Ungar B, Levy I, Yavne Y (2016) Optimizing anti-TNF-α therapy: serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 14: 550-557.
7. Yarur AJ, Jain A, Hauenstein SI (2016) Higher adalimumab levels are associated with histologic and endoscopic remission in patients with Crohn's disease and ulcerative colitis. Inflamm Bowel Dis 22: 409-415.
8. Harrold LR, Litman HJ, Saunders KC (2018) One-year risk of serious infection in patients treated with certolizumab pegol as compared with other TNF inhibitors in a real-world setting: data from a national U.S. rheumatoid arthritis registry. Arthritis Res Ther 20: 2.
9. Bejan-Angoulvant T, Ternant D, Daoued F (2017) Brief Report: Relationship Between Serum Infliximab Concentrations and Risk of Infections in Patients Treated for Spondyloarthritis. Arthritis Rheumatol 69: 108-113.
10. Roblin X, Boschetti G, Duru G, Williet N, Deltedesco E, et al. (2017) Distinct thresholds of infliximab trough level are associated with different therapeutic outcomes in patients with inflammatory bowel disease: A prospective observational study. Inflamm Bowel Dis 23: 2048-2053.