Pharmacokinetics and therapeutic drug monitoring of monoclonal antibodies for inflammatory bowel diseases

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Scope of the lecture:
According to the classical step-up therapy approach, use of monoclonal antibodies (mAbs) is considered to be the last medical treatment option before surgery is needed. MAbs targeting Tumor Necrosis Factor-\(\alpha\) (TNF\(\alpha\)) cover the majority of the registered therapeutic mAbs used in the treatment of inflammatory bowel diseases (IBD). Infliximab, an intravenously administered chimeric IgG1 antibody was the first anti-TNF agent approved for treatment of IBD. Adalimumab and golimumab are both fully human subcutaneously administered IgG1 antibodies registered for treatment of Crohn’s disease (CD) and ulcerative colitis (UC), and UC respectively. Efficacy of these agents have been proven for both induction and maintenance treatment.

Therapeutic mAbs are given parenterally since oral administration of mAbs is precluded because of their high molecular weight (~ 150kDa), hydrophilicity, and gastric degradation. Intravenously given mAbs allow administration of large volumes and after absorption immediate systemic distribution is reached. For subcutaneously administered mAbs, absorption takes place via lymphatic drainage and maximum concentration is reached after several days. Systemic absorption and presystemic catabolism determine bioavailability. Reported bioavailabilities for ADL after subcutaneous administration ranges from 50-100\% and 51\% bioavailability is reported for GLM. Because of their high molecular weight and hydrophilicity, distribution of mAbs takes place mainly within the central compartment. A volume of distribution of 4.5 – 6 L have been reported for IFX at steady state, approximately equal to the extracellular fluid volume. Elimination of mAbs does not occur via regular
hepatic or renal clearance because of their high molecular weight. The exact mechanisms by which mAbs are eliminated from the body are not fully understood, but the primary route is via proteolytic catabolism after receptor-mediated endocytosis in the reticuloendothelial system (RES). IgG1 mAbs also interact with the Brambell receptor (FcRn) thereby increasing half-life. FcRn is functionally expressed in monocytes, macrophages, and dendritic cells. After endocytosis into vascular endothelial cells, FcRn binds the IgG antibody within the acidic environment of the endosome. Binding to FcRn results in protection from degradation and thereby prolonging half-life. The bound IgG antibody is returned to the cell surface and dissociates from FcRn in a physiologic environment (pH 7.4) and is released in the systemic circulation again[1–5].

Higher serum anti-TNF trough concentrations have been related to positive therapeutic outcomes e.g. clinical response, clinical remission and mucosal healing in patients with IBD and lower concentrations have been demonstrated to be associated with the formation of anti-drug antibodies (ADAs). Although proven efficacy for anti-TNF agents, still 30% of the patients have no clinical improvement after initiation of anti-TNF therapy (primary non-responders) and up to 50% of the patients loses response over time after initial clinical improvement (secondary non-responders). Therapeutic drug monitoring (TDM) can be applied in order to prevent loss of response. Population PK models of anti-TNF agents in IBD patients explain some interpatient variability, mainly attributed to body weight, ADAs and disease activity (albumin). Based on these population PK models, dashboard systems can be developed to implement adaptive-dosing strategies. Dashboard systems use Bayesian approaches where a priori information is combined with a posteriori information to predict individual concentrations. Model-based dosing for infliximab has been compared to other dosing strategies by simulating a virtual population with time-varying covariates[6]. This in silico assessment showed that model-based approaches were superior to other strategies (label
recommendations, TDM-guided stepwise dosing, TDM-guided proportional dosing). This application of model-based dosing during maintenance phase resulted in more patients reaching target trough concentrations and additionally decreased interpatient variability in infliximab serum concentrations.

References

Learning objectives:
1. Clearance mechanisms monoclonal antibodies in IBD patients
2. Factors influencing PK of monoclonal antibodies in IBD patients
3. Added value of applying TDM for biologicalss in IBD patients