Why Use TDM and Dashboards for Monoclonal Antibodies? The Promise of Individualized Therapy

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Scope of the lecture:
Therapeutic monoclonal antibodies (MAbs) have emerged as a major component of treatment for a wide variety of diseases including inflammatory diseases and oncology. With generally better safety profiles than chemical agents, MAbs have also demonstrated therapeutic failures that in some cases appear to be due to pharmacokinetic (PK) variability. This lecture will cover the primary factors that are predictive of between-patient variability for MAb PK, and will look at efforts to improve outcomes using therapeutic drug monitoring (TDM). This lecture will also introduce the concept of dashboard based dosing, which is a way of individualizing therapy based on the patients specific PK behavior and the promise of MAb therapy when TDM and dashboard guided individualized therapy is implemented.

Learning objectives:
1. Understand the pharmacokinetics of MAbs and factors that are commonly associated with MAb PK variability
2. Learn the relationships between MAb exposure and response and possible causes for therapeutic failure
3. Learn about the concept of dashboard guided dosing in conjunction with therapeutic drug monitoring

Extended abstract:

Background: Monoclonal antibodies (MAbs) exhibit complex pharmacokinetics (PK). Many factors impact anti-TNF MAb PK, altering MAb clearance and therefore the half-life: albumin, weight (particularly obesity), disease (severity, stage, co-morbidities), and concomitant administration of immunosuppressants (e.g. methotrexate). In addition, the pharmacodynamics or response to treatment can also impact MAb PK, and anti-drug antibodies (ADA) can be considered a pharmacodynamic response. These factors can alter MAb exposure, impacting on the likelihood of clinical response or subsequent loss of response (LOR) following an initial response. A potential cause of therapeutic failure and LOR is between-subject variability in exposure, which can arise from several sources, particularly MAb clearance and, for subcutaneously administered MAbs, from variability in the extent of absorption.

Clearance describes how a drug is removed from the body; and is inversely related to half-life with slower clearance resulting in longer half-life. Clearance determines trough concentrations – higher clearance is associated with lower trough levels for the same dose interval. Unlike small molecule drugs, which are often cleared by cytochrome P450 enzymes, MAbs are primarily cleared through proteolysis, although specific sites of catabolism have not been identified [1]. Proteolytic clearance is generally related to patient weight, with higher weight subjects having more rapid proteolytic clearance [2, 3]. Renal elimination generally does not contribute to MAb clearance, owing to their high molecular weight which limits glomerular filtration [4] although patients with focal segmental glomerulosclerosis (FSGS) have been found to have increased MAb clearance [5], which is a form of atypical clearance. Atypical clearance is often associated disease type and severity resulting from altered catabolic pathways or organ function. For example Beeken et al [6] and later, Kaplan et al [7] reported increased intestinal IgG clearance in patients with inflammatory bowel disease (IBD) that correlated with lesion severity. Similarly, Brandse [8] reported infliximab concentrations in feces from severe IBD patients that were associated poor response. Protein losing enteropathy was also noted in patients with systemic lupus erythematosus [9].

Target mediated clearance (TMC) is a saturable route of elimination that can be a substantial component of MAb clearance. The fraction of TMC to overall clearance depends on MAb concentration and target antigen expression, including MAb-antigen internalization and receptor turnover rate [10], which can result in both nonlinear and time dependent changes in clearance [11] and can also result in disease related differences in MAb PK. Antigens on cell surfaces may be shed into circulation as free antigen which can bind with MAbs. Thus extensive receptor shedding may accelerate clearance or decrease free MAb through competitive binding [12]. TMC is generally dependent on disease type and severity. Thus patients with more extensive disease and higher antigen burden will tend to have a higher fraction of MAb clearance through TMC. Even infliximab clearance, which does not exhibit TMC, has reported different clearances for different diseases which reflect the extent and degree of inflammation [13]. Faster MAb clearance in IBD is typically associated with low albumin which is also associated with more severe disease [2, 3]. Similarly diabetes is associated with faster MAb clearance. Diabetic comorbidity resulted in a 28% increase in ustekinumab clearance [14] which may be related to non-enzymatic glycation of proteins, which are cleared faster than non-glycated proteins [15].

Endogenous antibodies, MAbs, and albumin are protected from proteolysis by the Brambell

neonatal receptor (FcRn) [16], prolonging half-life [17]. FcRn receptors can be saturated at high IgG concentrations, resulting in shorter half-life [18]. Thus, albumin is often identified as being predictive of MAb clearance. In some disease states, such as multiple myeloma, high production of IgG M proteins results in a shortened half-life through FcRn saturation [19]. FcRn binding is species specific, so half-life generally increases as MAb structure becomes more human, with murine MAbs having a very short half-life (1-2 days); chimeric MAbs having a half-life of approximately 10-14 days, and fully human MAb having half-lives generally greater than 15 days [20]. Three additional Fc gamma receptors (FcγRI, FcγII and FcγIII) have been identified [21] which are expressed by macrophages, natural killer cells, B and T cells, and platelets. Fc gamma receptor binding elicits complement or antibody dependent cell cytotoxicity [22] which can form an additional route of clearance. MAb clearance through the reticuloendothelial system (RES) is partly regulated through interactions with FcγRs. The co-administration of methotrexate has been reported to reduce adalimumab clearance by 29-44% [23] in patients with rheumatoid arthritis. While methotrexate reduces immunogenicity-related clearance of adalimumab [24], it has been reported to reduce Fcγ receptor expression *in vitro* [25].

Regardless of extent of humanization, MAbs are exogenous proteins and all MAbs can induce ADA [26]. Numerous factors can impact ADA formation, including the formulation, its stability, extent of humanization, dose regimen, and treatment duration [27]. The intravenous (IV) route of administration is generally least likely to induce an ADA response, although this is not always true [28]. Subcutaneous administration is generally more immunogenic than IV. ADA occurs more frequently following administration of low doses than with high doses [29], and has been associated with intermittent exposure during clinical care [30]. ADAs can be neutralizing, in which MAb binding is impaired, or can increase MAb clearance [4]. Concomitant administration of immunosuppressants generally reduces the likelihood that a patient will develop ADA [31]. Concomitant administration of infliximab and methotrexate resulted in significantly lower ADA prevalence and generally higher serum infliximab concentrations, although without significantly impacting efficacy [32]. A report on Crohn's Disease (CD) patients who developed LOR to infliximab accompanied by ADA, showed the addition of an immunomodulator resulted in restoration of clinical response, decrease in ADA titers and increased infliximab trough concentrations [33].

Inflammatory diseases (ID) (e.g. Rheumatoid arthritis (RA), ankylosing spondylitis, inflammatory bowel disease (IBD), and psoriasis) are treated using "step-up" approaches, starting with chemical anti-inflammatory and immunomodulatory agents. Patients failing these therapies require treatment with monoclonal antibodies (MAbs) generally targeting tumor necrosis factor (TNF). While MAbs are effective treatments for ID, many patients lose response over time. In a retrospective assessment [34], discontinuation at 4 years for etanercept was 41%, infliximab was 46% and adalimumab was 52%. Approximately 20-30% of initially responding patients lose response during the first year of therapy [35] and subsequently approximately 10% lose response annually [36]. Psoriasis has similar failure rates.

Post-hoc analyses from pivotal trials in IBD suggested maintaining measurable serum infliximab trough concentrations during maintenance was associated with improved outcomes. [37, 38]. In a prospective study in patients with CD with secondary LOR to infliximab Steenholdt *et al*. [39] showed using an individualized therapeutic drug monitoring (TDM)-based dosing algorithm was cost-effective versus clinical symptom-driven dose escalations. A larger 1 year prospective trial [40] provided evidence that TDM-guided dosing

may preserve clinical response in patients with IBD after baseline adjustment of infliximab serum trough concentrations to 3 to 7 μg/ml. However, the utility of TDM for MAbs has been questioned, partly because of lack of powered prospective studies using TDM-based dosing [41], together with a small prospective study (TAILORIX), investigating only dose increases in maintenance over 1 year, but not shortening dosing intervals, an important adjustment. The study design was insufficient to demonstrate the advantage (or lack) of TDM [42] but suggested no benefit. TDM utility for MAbs has also been questioned due to slow assay turnaround, analytical deficiencies, assay differences, and difficulties with interpreting TDM [43]. These deficiencies are reasons that US insurance companies will generally not reimburse for MAb TDM [44]. The lack of reimbursement, together with the cost of the MAb assays (US$250.00 to US$2500.00) has compromised TDM applicability in the ID setting.

Identifying an individual's effective dose is neither intuitive nor static owing to flux in patient status and associated factors over time. This is particularly true for pediatric IBD using infliximab, which uses weight-based resulting in lower drug exposure in pediatrics [45]. Dashboard systems facilitate personalized dose adjustments using modeling, making better use of TDM [46]. A retrospective study using a prototype dashboard demonstrated quicker identification of individualized optimal dosage and identified LOR in advance of observed sub-therapeutic trough concentrations based on increasing individual clearance [47]. Another retrospective assessment of this dashboard found treatment recommendations were substantially different from standard of care, but feasible, and showed that patients recommended to have a dose adjustment had lower probability of clinical remission [48].

Loss of response to anti-TNF treatment is very common, and should be avoided if at all possible. Many retrospective studies have shown that LOR is often associated with low MAb serum concentrations. Reasons for insufficient exposure can vary a great deal and include lack of compliance, increasing disease activity and inflammatory burden and, importantly, formation of ADA. The presence of ADA is closely associated with relatively lower serum concentrations of drug. ADA formation can occur as early as 18 days after the initiation of treatment [49]. As a consequence it is of paramount importance to the clinician to have information on circulating concentrations of both MAb and ADA to allow for a comprehensive decision on dose adjustments or to recommend a switch to a different treatment, within or outside the therapeutic class.

The application of Bayesian dashboard systems to therapeutic MAbs used to treat ID was selected owing to the current need to determine appropriate doses quickly to avoid intermittent exposure which can lead to ADA and LOR. In addition these agents are expensive and there is a strong desire to contain healthcare costs while improving patient outcomes. Dashboard systems make the transition from passive TDM to proactive therapeutic management taking into account between subject differences in both pharmacokinetics and pharmacodynamics, and as such are expected to show clinical benefit. A prototype system is currently undergoing testing in a clinical trials to determine its usefulness, and if useful, will result in the system being expanded to include other MAbs used to treat IBD. Application in other therapeutic areas including RA and psoriasis will also need testing although the failure rate for MAbs in RA is comparable to that in IBD and TDM is already being adopted by rheumatologists.

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