Therapeutic Drug Monitoring for MAbs: What Does the Future Hold?

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Background

Inflammatory diseases (Rheumatoid arthritis (RA), ankylosing spondylitis (AS), inflammatory bowel disease (IBD) and psoriasis) are typically treated using "step-up" approaches, starting with chemical anti-inflammatory agents and immunomodulators. Patients failing conventional therapies require treatment with monoclonal antibodies (MAbs). While MAbs are effective for induction and maintenance of clinical remission, many patients fail or lose response over time. A retrospective assessment of treatment failures in RA [1] found 33.7% and 26% of patients discontinued their first MAb for loss of response (LOR) or adverse events, respectively. Overall 12-year drug survival was 23.4%. In a larger assessment [2], overall discontinuation at 4 years of etanercept was 41%, infliximab was 46% and adalimumab was 52%. In IBD, approximately one-third of patients show no response to induction therapy, and up to 50% of responders, lose response over time [3]. Failure rates are similar for psoriasis.

Factors associated with LOR include immunogenicity (production of anti-drug antibodies (ADAs)) along with factors including gender, body size, concomitant immunosuppressive agents, disease type and severity, and serum albumin with substantial unexplained variability. Thus, subtherapuetic concentration may cause of LOR [4] and ADA [5]. A retrospective study showed maintaining trough infliximab concentrations above a threshold value was important for successful therapy [6], which echoed earlier work by Maser [7]. This problem was not solved using empirical dosing approaches, prompting use of therapeutic drug monitoring (TDM) to determine need for dose adjustments. Steenholdt et al. [8] reported a TDM-based dose adjustment algorithm was non-inferior to traditional dose escalations. A larger prospective trial [9] showed TDM-based dosing maintained response and sometimes reduced treatment costs. However TDM utility has been questioned, partly because of lack of powered prospective studies using TDM-based dosing [10], 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 [11] 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 [12]. These deficiencies are reasons that US insurance companies will generally not reimburse for MAb TDM [13]. The lack of reimbursement, together with the cost of the assays (US$250.00 to US$2500.00) has compromised TDM applicability.

Dashboards

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 [14]. Dashboard systems facilitate personalized dose adjustments using modeling, making better use of TDM [15]. 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 [16]. 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 [17].

Conclusions

TDM has potential benefit in reducing LOR and combined with dashboard systems, may improve patient outcomes.

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