Therapeutic drug monitoring in autoimmune and oncological diseases

by Dr Jacqueline Gosink

Therapeutic drug monitoring (TDM) supports optimized use of biologic therapies in the treatment of immune-mediated inflammatory diseases and some cancers. By guiding clinical decision-making on individualized dosage, treatment intervals or the need to switch therapies, TDM contributes to improved patient outcomes. Circulating drug concentrations and anti-drug antibody levels can be measured rapidly and with high precision using fully automated immunoassays.

Biologic therapies

Biologic therapies are a cornerstone of treatment for a range of inflammatory diseases, including inflammatory bowel disease (IBD), rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, psoriasis and multiple sclerosis, as well as various cancers. These therapies are typically based on monoclonal antibodies or fusion proteins that block disease-promoting molecules, such as pro-inflammatory cytokines. Tumour necrosis factor alpha (TNFα) is among the most widely targeted molecules in this context. Other biologic targets include CD20, interleukins, integrins and growth factors (Table 1).

Variable responses

Patient responses to biologic therapies can be highly varied due to differences in pharmacokinetics, immune responses and disease activity. Primary non-response or secondary loss of response occur in a significant proportion of patients. For example, up to a third of IBD patients treated with anti-TNFα fail to show an initial response, while up to 50% of responders lose their response, especially during the first year [1]. Drastic decreases in drug responses can occur when patients produce antibodies against the therapeutic drugs. These antibodies can block the action of the agent or accelerate its clearance, reducing the effectiveness of the therapy.

Importance of therapeutic drug monitoring

Therapeutic drug monitoring (TDM) involves the measurement of drug levels and anti-drug antibodies in patient blood samples to assess if the drug is being absorbed, distributed, metabolized and excreted as expected. Patients with slower pharmacokinetics may experience drug bioavailability levels above the therapeutic window (supratherapeutic), increasing the risk of side effects. Conversely, patients with accelerated pharmacokinetics, for example due to the presence of anti-drug antibodies, may exhibit drug bioavailability levels below the therapeutic window (subtherapeutic), leading to reduced drug effectiveness. TDM can guide decisions on type of drug, timing and dosage, allowing for a personalized treatment approach.

Reactive and proactive TDM

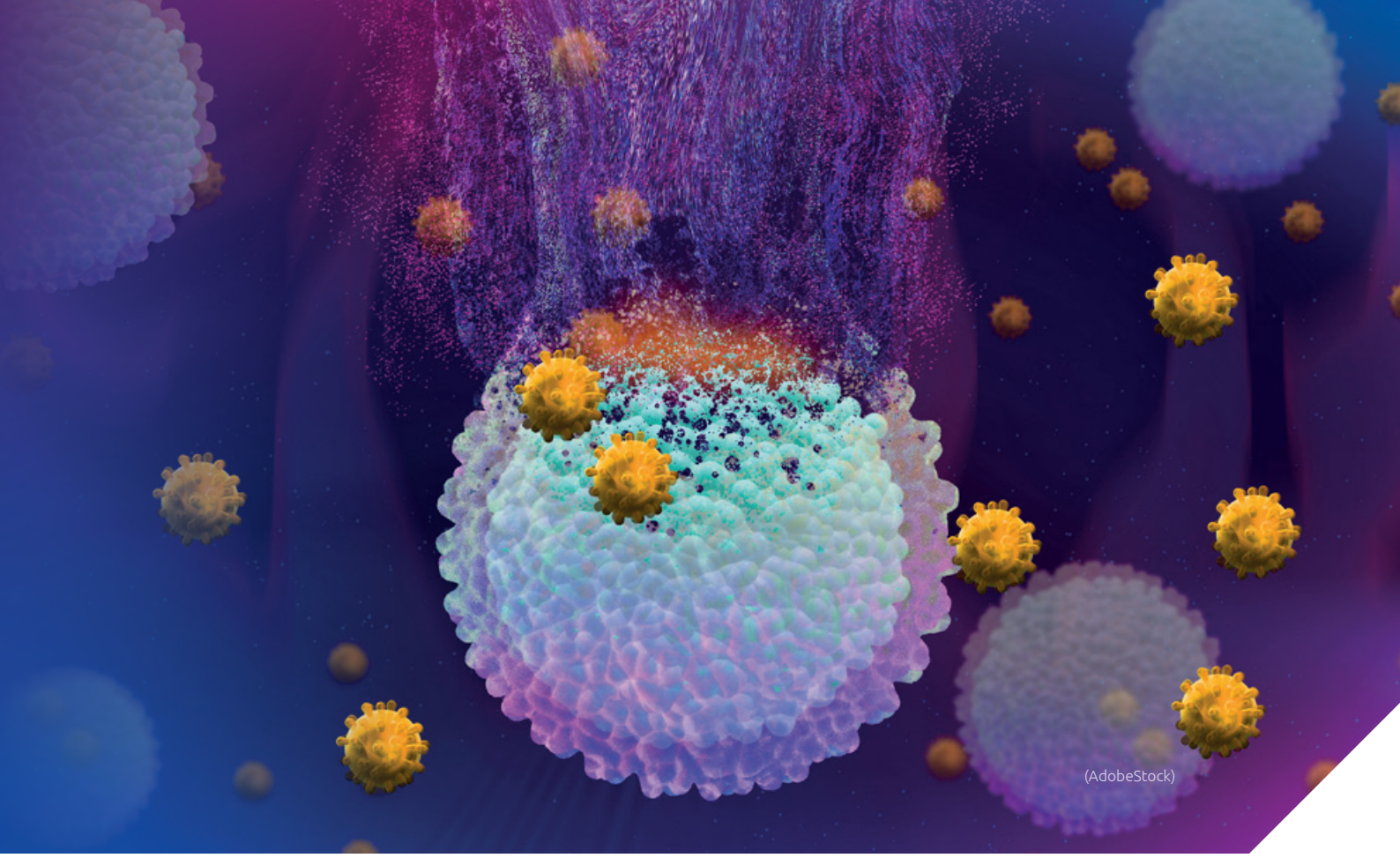
Reactive TDM is performed when clinical symptoms suggest a non-response or loss of response. Based on these results, clinicians may adjust the dose, switch to another drug of the same class or select an agent with a different mechanism of action (Fig. 1) [1]. TDM-based management helps to optimize patients' responses and avoid over- or under-exposure to the drugs.

Proactive TDM involves taking measurements on a scheduled basis, regardless of clinical status, to assess how an individual is reacting to a specific therapy. It aims to prevent disease flare-ups and treatment failure by proactively adjusting drug dosage to maintain target serum levels.

IBD, inflammatory arthritis and psoriasis

Patients with IBD, rheumatoid arthritis, spondyloarthritis, psoriatic arthritis and psoriasis are commonly treated with biologic therapies, although their usage varies across diseases and between countries. Infliximab and adalimumab, which both target TNFα, are the most used therapies [2].

Reactive TDM is a widely accepted clinical approach to manage patients with suspected treatment failure. For IBD patients with loss of response to anti-TNFα agents, reactive TDM is suggested



or recommended by the majority of gastroenterology associations [3]. In addition to its clinical benefits, reactive TDM has been shown to be a more cost-effective strategy than standard empiric dose escalation, helping to manage resources for these expensive therapies [1]. Proactive TDM is an emerging approach and has been adopted in clinical practice to varying degrees in different countries [3,4]. In the Australian guideline for anti-TNFα therapy in IBD, TDM is recommended following successful treatment induction, prior to a drug holiday, during clinical remission if results are likely to impact management, as well as in cases of treatment failure [5].

In the new BMJ clinical practice guideline, proactive TDM is recommended for patients with IBD, inflammatory arthritis and psoriasis receiving intravenous infliximab therapy [2,4]. >>

Table 1. Examples of biologics and biosimilars for different disease indications
IBD, inflammatory bowel disease

Drug/biologic	Disease					
	IBD	Rheumatoid arthritis	Ankylosing spondylitis	Psoriasis/ psoriasis arthritis	Cancer	Multiple sclerosis
Infliximab (anti-TNFα)	x	x	x	x		
Adalimumab (anti-TNFα)	x	x	x	x		
Certolizumab pegol (anti-TNFα)	x	x	x	x		
Etanercept (anti-TNFα)		x	x	x		
Golimumab (anti-TNFα)	x	x	x	x		
Vedolizumab (anti-integrin α4β7)	x					
Secukinumab (anti-IL17A)			x	x		
Tocilizumab (anti-IL6R)		x				
Ustekinumab (anti-IL12-IL23)	x			x		
Risankizumab (anti-IL23)	x			x		
Rituximab (anti-CD20)		x			x	
Bevacizumab (anti-VEGF)					x	
Trastuzumab (anti-HER2)					x	
Nivolumab (anti-PD1)					x	
Pembrolizumab (anti-PD1)					x	
Natalizumab (anti-integrin α4β1)						x
Ocrelizumab (anti-CD20)						x

>> A proactive approach during the maintenance phase was shown to increase the rate of sustained disease control or remission by around 14% [4,6]. Recommendations for other drugs may be added in the future based on further trial evidence.

The guideline emphasizes that proactive TDM can especially benefit patients with characteristics associated with a worse prognosis, such as high baseline disease activity, previous loss of response, obesity, lack of concurrent immunosuppression, high risk of non-adherence and, in the case of patients with IBD, persistent elevated fecal calprotectin [4].

	Negative anti-drug antibodies	Positive anti-drug antibodies
Therapeutic level of drug	Mechanistic failure **Switch to out of class agent**	False positive or mechanistic failure **Retest. If consistent, switch to out of class agent**
Subtherapeutic level of drug	Non-immune-mediated pharmacokinetic failure **Dose escalate**	Immune-mediated pharmacokinetic failure **Switch agent within class**

Figure 1. Example of therapeutic decision algorithm in IBD patients with loss of response [1]

Multiple sclerosis

Biologic therapies play a central role in the treatment of multiple sclerosis, particularly in the relapsing–remitting form of the disease. For example, natalizumab blocks α4β1-integrin, inhibiting leukocyte migration across the blood–brain barrier and reducing both clinical relapses and active brain lesions. Measurement of drug concentrations and adjustment of dosing intervals may help to reduce treatment burden, manage costs and lower the risk of progressive multifocal leukoencephalitis, a serious treatment-associated complication [7,8]. CD20 is another key target in MS treatment. Anti-CD20 monoclonal antibodies deplete disease-promoting B-cells via complement-dependent cytotoxicity or antibody-dependent cellular cytotoxicity, leading to improved clinical outcomes. Ocrelizumab, a CD20-targeting agent, is currently the only approved therapy for the primary progressive form of MS [9].

Cancer

Anti-CD20 therapies are also employed in the treatment of malignancies such as non-Hodgkin's lymphoma. CD20 is highly expressed on malignant B cells, enabling the selective depletion of cancerous cells while sparing progenitor B cells to replenish the healthy population. Other cancer therapies target antigens that are overexpressed on solid tumours. For instance, agents directed at epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) are used to treat colorectal and breast cancers, respectively. The tumour microenvironment is a further therapeutic target. For example, inhibitors of vascular endothelial growth factor (VEGF) disrupt angiogenesis, thereby limiting tumour growth in certain cancers. Immune checkpoint inhibitors are therapies that block proteins responsible for regulating immune activity, thereby enhancing T cell ability to target and destroy tumour cells. Programmed death receptor-1 (PD-1) is a key checkpoint target [10,11].

Although antibody therapies have proven successful in treating cancer, dosing strategies may be suboptimal in some patients due to variable pharmacokinetics. TDM represents a promising tool in oncology to optimize drug doses within the patient's individual therapeutic window.

Immunoassay measurements

Drug and anti-drug antibody levels can be quantitatively measured in patient serum or plasma samples using immunoassays such as enzyme-linked immunosorbent assay (ELISA) or chemiluminescence immunoassay (ChLIA). ELISA is currently the most commonly used method. ELISAs can be processed manually or on fully automated systems, making them suitable for all levels of throughput. Fully automated ChLIAs offer the advantages of higher sensitivity, faster turnaround times and random-access processing.

Typically, measurements are taken at blood trough levels, corresponding to the lowest drug concentration prior to the next scheduled dose. Trough sampling minimizes variability due to timing inconsistencies and ensures that minimum drug levels do not dip below the therapeutic threshold. Importantly, the same assay should be used for longitudinal monitoring of individual patients to ensure comparability between measurements.

Comprehensive assay range

An extensive range of assays for measurement of drug and anti-drug antibody levels has been developed by Biosynex-Theradiag and is now available from Euroimmun and Immunodiagnostic Systems (IDS). The LISA TRACKER* range covers the therapies adalimumab, infliximab, etanercept, certolizumab, golimumab, rituximab, secukinumab, tocilizumab, bevacizumab, trastuzumab, ustekinumab and vedolizumab. The i-Tracker ChLIA* range includes adalimumab, infliximab, ustekinumab, vedolizumab, golimumab, rituximab, certolizumab, etanercept, tocilizumab, risankizumab and ocrelizumab. In addition, ChLIAs for natalizumab, nivolumab and pembrolizumab are available for research use only.

Biosynex-Theradiag assays are suitable for use with both the original drugs and biosimiliars. The dynamic ranges of the assays are adapted for clinical use and are suitable for monitoring both the induction and maintenance phases of treatment. Adalimumab, infliximab and etanercept assays are calibrated against the 1st WHO international reference standards. Ready-to-use internal quality control sera (IMMUNO-TROLs*) are available to aid determination of the pharmacological dosage of the biotherapies.

Clinical studies

Biosynex-Theradiag assays have been used in many studies published in peer-reviewed journals [12]. These publications have advanced the understanding of the pharmacokinetics, immunogenicity and cost-effectiveness of biologic therapies for Crohns's disease, ulcerative colitis, rheumatoid arthritis, spondyloarthritis and psoriasis. Theradiag assays have also contributed to the development of international decision algorithms.

Outlook

TDM is a vital component of precision medicine, allowing biotherapeutic treatments to be tailored to individual patient needs.

With biotherapies representing a large proportion of new medications, the demand for efficient and scalable TDM solutions is expected to grow. This need will be further driven by demographic shift, lifestyle factors and the increasing burden of chronic inflammatory and oncological diseases. Immunoassays such as ChLIA and ELISA provide the speed, cost-efficiency and automatability required for high-volume routine TDM measurements and are validated for a large range of biotherapies. Future development of the Biosynex-Theradiag TDM assay range aims to broaden the indication areas and incorporate emerging drug therapies.

** Regulatory status, precise intended use and product availability must be verified for the user's individual jurisdiction.*

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