Table 1. The two Krieckaert (2022a; b) articles: systematic review (SR) - questions and results - and subsequent EULAR points-to-consider

Topics	SR Research questions	SR results	Associated EULAR Points-to-consider
Technical aspects of TDM	• Are the results of different assays for biopharmaceutical blood concentration measurement comparable?	Several assay formats are available. ELISA is the most widely used. Based on 20 studies (correlations with ELISA best studied): Good correlation, comparable: Direct ELISA with sandwich ELISA, (coef.>0.9), RIA and IFMA with ELISA (80-98%), RGA with RIA, LC-MS/MS with an electrochemiluminescence-based assay, point-of-care tests Quantum Blue and lateral flow assay with ELISA and each other. Weak correlation, conflicting results, less comparable: RGA with HMSA, ELISA, and LC-MS/MS.	• Measurement of biopharmaceutical blood concentrations should be performed in a validated laboratory. • Measurement of ADAb should be performed in a validated laboratory, preferably using a consistent assay over time. Measurement should be performed and interpreted alongside contemporaneous biopharmaceutical blood concentrations
	• Are assays for detecting ADAbs comparable?	Based on five studies: NB: Search was confined to drug-sensitive assays, relevant for clinical practice (drug-tolerant assays, which are less relevant, were excluded). Good correlation: ELISA with enzyme immunoassay, surface plasmon resonance, and other ELISA formats. Good correlation, but conflicting results: ELISA with RGA (>0.8), except for one study; absolute levels were not directly comparable between assays.	
Clinical utility and relevant aspects for inter-pretation of results of TDM	• What is the association between biopharmaceutical blood concentrations and disease activity?	Based on 43 prospective observational studies and post hoc analyses of RCTs (study duration +/- 1 year, outcomes vary widely): On a population level, higher biopharmaceutical blood concentrations correlated with better treatment outcome and/or lower disease activity. Best evidence for TNF inhibitors in RA and axSpA. Infliximab-disease activity correlation not found for axSpA. Data lacking for PsA.	• Despite an association with clinical response, the use of biopharmaceutical blood concentrations to guide dosing is not recommended due to the lack of an identified optimal range for most biopharmaceuticals in most indications.
	• What is the optimal target range, on group level, for each individual biopharmaceutical for each disease (RA, axSpA and PsA)?	Based on 31 mainly observational studies with population-level data that cannot directly be translated to individual patients examining blood concentration ranges that are associated with clinical response: ADA range for RA 2–8 µg/mL, axSpA 2.5–8.0 µg/mL, PsA 1–8 µg/mL. ETN ranges: inconclusive. IFX ranges: inconclusive or no data. GLM range for all: >1 µg/mL. CZP range for all: 20–39.9 µg/mL. TCZ intravenous range for RA: >1 µg/mL, TCZ subcutaneous range for RA: inconclusive.	
	• Which factors influence biopharmaceutical blood concentrations? • What are the requirements to interpret biopharmaceutical blood concentrations?	• Duration of therapy - Four studies on IFX: Trough blood concentrations induction phase > maintenance phase. In RA patients with stable disease activity, low intrapatient variability of two consecutive infliximab blood concentration and ADAb measurements. • Timing of sampling – two studies: Unknown: Importance of through vs. random sampling, and which concentration (through, peak, under the curve) correlates best with clinical response. For ADA-treated RA patients, a weak inverse association was found between the blood concentration and the number of days after the previous injection. However, not confirmed in a second study that showed comparable blood concentrations of adalimumab at peak, intermediate and trough timing of sampling. For ETN-treated patients, trough blood concentrations were significantly lower than peak and intermediate blood concentrations. With subcutaneous administered therapeutic monoclonal antibodies, there is little variance in concentrations during steady state. • Route of administration – four studies: For ABC and TCZ, intravenous and subcutaneous differences shown in three/four studies in blood concentrations; higher trough concentrations for subcutaneous.	• Biopharmaceutical blood concentrations are dependent on the dose, administration interval and date of last dose. When interpreting biopharmaceutical blood concentrations, patient-specific factors that influence pharmacokinetics should be considered, which include body weight, methotrexate co-treatment, disease activity and adherence to therapy.

		• Dosing (interval) – seven studies: ADA blood concentrations in RA dropped with interval prolongation and increased with dose increase following non-response. ETN blood concentrations in RA, axSpA or PsA dropped with interval prolongation. Comparable results for IFX in RA in maintenance phase. ABC and TCZ trough blood concentrations higher with higher dose keeping interval constant. • Immunogenicity of biopharmaceuticals -22 studies: Evidence for the association of low biopharmaceutical blood concentrations with the presence of ADAb detected using a drug-sensitive assay for all anti-TNF therapeutic monoclonal antibodies, certolizumab pegol, sarilumab and RTX. Insufficient data for TCZ and other biopharmaceuticals. • Body weight or BMI – 11 studies: Lower TCZ intraven & subcut, ABC subcut, ADA, ETN blood concentrations in patients with higher body weight/higher BMI and in overweight/obese compared to normal BMI. • Concomitant medication – eight studies: In RA or PsA, higher ADA blood concentrations in ADA+MTX compared with ADA mono. Conflicting results for axSpA. • Inflammation parameters – eight studies: IFX, ADA, ETN, GLM, RTX blood concentrations inversely associated with pretreatment CRG and/or ESR. • RF and anti-CCP – two studies: In RA patients with high levels of both RF and anti-CCP, association with lower IFX blood concentrations in induction and maintenance phase, compared with patients with low levels of both RF and anti-CCP.	
	• What is the clinical utility of TDM compared to standard clinical care with regard to outcome?	Based on one EULAR RCT abstract with only IFX induction phase data in IMIDs, comparing TDM to standard care in the achievement of remission after 30 weeks of treatment: TDM was not superior to standard care, although a reduced number of infusion-related reactions were observed with TDM. Result of one small (N=32) observational study lacking a standard care comparator: knowledge of IFX blood concentration in SpA altered treatment decisions in 31% of patients without apparent influence on subsequent disease activity.	• Routine use of *proactive* TDM* is not recommended in the management of inflammatory RMDs.
	• In which clinical situations could TDM influence clinical decision making? Prediction of treatment response: – Early prediction of a later response to a biopharmaceutical. *Reactive* TDM, in the following predefined clinical situations: 1. To predict outcome in patients in remission or with	Early biopharmaceutical blood concentration measurement predictive of (non)response - Based on eight observational studies: • IFX better treatment response in RA or axSpA at 6 and 12 months predicted by higher week 6 (cut-off ranging from 2.5 µg/mL to 4.4 µg/mL) and week 14 (cut-off ranging from 4.7 µg/mL to 6.7 µg/mL) trough blood concentrations. • ADA week 12 non-response in axSpA predicted by blood concentrations of <3.3 µg/mL at week 2 or <4.3 µg/mL at week 4. • ADA month 12 non-response in RA predicted by blood concentrations of <5 µg/mL 3 months after initiation of treatment. • ETN response in RA, conflicting results: 3-month concentrations did not predict 12 month response in 171 patients, but a concentration of ≥3.1 µg/mL at 3-month predicted response at 6 months in 19 female patients. • CZP 6-month treatment response in RA, axSpA or PsA predicted by 3-month blood concentrations of ≥20 µg/mL. *Reactive* TDM, in the following predefined clinical situations:	• Measurement of biopharmaceutical blood concentrations up to 3 months after commencement of treatment could be considered to predict future efficacy. • *Reactive* TDM* could be considered in the management of inflammatory RMDs. • Measurement of biopharmaceutical blood concentrations could be considered to identify those with high biopharmaceutical blood

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	low disease activity who taper or discontinue biopharmaceutical treatment. 2. To predict successful dose escalation in the case of biopharmaceutical treatment failure. 3. To predict response to the subsequent biopharmaceutical treatment when switching between biopharmaceuticals (in case of treatment failure). 4. To predict persistence of a flare. 5. To reduce overexposure to minimize infection risk.	1. To predict successful tapering or discontinuation in remission or low disease activity: • Based on one small study in axSpA, numerically more patients with suboptimal GLM blood concentrations (<0.7 µg/mL) before tapering had a disease flare after tapering. • Based on five studies in RA: ○ Based on one modelling study: suggested no added benefit of TDM-guided tapering of TCZ over empirical-dose tapering; comparable flare rates ○ Based on one RCT post-hoc analysis: ADA trough concentrations did not predict patients that flared after discontinuation ○ Based on one RCT in patients all with high ADA blood concentrations: No difference in flare rate between interval prolongation group and normal continuation-control group. ○ Based on one post-hoc analysis of RCT and observational study: ADA, ETN, IFX blood concentrations did not predict successful discontinuation or dose reduction, except for subgroups with high ADA (cut-off >7.8 µg/ mL) and lower ETN (cut-off <2.6 µg/mL; NB: inverse association) and successful dose de-escalation. ○ Based on one observational study: higher ADA was associated with persistent remission (baseline cut-off of 6.4 µg/mL) and persistent low disease activity (cut-off 1.9 µg/mL). 2. To predict successful dose escalation in treatment failure: • Based on four observational studies and one RCT post-hoc study: TNF-inhibitor blood concentration measurement did not predict successful dose escalation in RA or SpA cases of clinical non-response; similar pre-escalation blood concentrations in responders and non-responders. 3. To predict successful response when switching biopharmaceutical in case of low blood concentrations or presence of ADAb: • Based on eight observational studies: Conflicting results, with ADAb at time of IFX failure not predicting successful switch to ADA or ETN in three RA studies and ADAb predicting successful switch from 1st to 2nd TNF inhibitor in two RA and SpA studies. Conflicting results also for predictive value of both biopharmaceutical blood concentrations and ADAb in two other studies. In one study, very low ADA levels (<0.5 µg/mL) associated with moderate-good response to ETN at 52 weeks after switch. 4. To predict persistence of a flare: • Based on one prospective study: Patients with detectable blood concentrations of RTX, IFX or ETN at first sign of a flare had lower disease activity during follow-up at 2-6 months compared with patients with undetectable blood concentrations. 5. To reduce overexposure to minimize infection risk - Based on two observational studies: • In SpA, those having IFX trough blood concentrations in the highest tertile (>15.5 µg/mL) had a higher risk of infection (requiring hospitalization, anti-infective treatment or IFX treatment delay) compared to having IFX concentrations in the lower two tertiles (HR 2.61, 95% CI 1.3 to 5.4). • In RA, those with high TNF inhibitor or TCZ concentrations had a higher risk of any infection in first treatment year compared with those with low/normal blood concentrations (HR 1.51, 95% CI 1.14 to 2.01). Risk of serious infection unknown.	concentrations in whom tapering may be indicated. • Measurement of biopharmaceutical blood concentrations should be considered to understand clinical non-response.

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	• In which situations should ADAbs be measured? *Reactive* TDM, in predefined clinical situations considered potentially relevant for ADAb measurement alone: infusion or hypersensitivity reactions, injection-site reactions, switching or discontinuing biopharmaceutical treatment, treatment failure, and consideration of dose increase.	*Reactive* TDM, in predefined clinical situations considered potentially relevant for ADAb measurement alone: • Based on one study in TCZ iv or subcut: no association between ADAb and adverse events or loss of efficacy. • Based on eight studies in IFX: ADAb associated with infusion reactions (statistically significant in six studies). • Based on two studies in ADA: ADAb associated with very low incidence of adverse reactions. No evidence of an association with injection-site reactions was found. • Based on nine studies: Detectable ADAb was associated with higher disease activity, lack or loss of response to treatment, higher risk of treatment discontinuation, compared to no-ADAb. Dose increase in case of ADAb detection did not have a beneficial effect.	• Measurement of ADAb should be considered in the case of immunogenic biopharmaceuticals, alongside biopharmaceutical blood concentrations, at the time of clinical non-response. • Measurement of ADAb should be considered in the case of a hypersensitivity reaction, mainly related to infusions. • Measurement of ADAb is not recommended in the case of an injection-site reaction.
	• What are the incremental costs and consequences (benefits and harms) of TDM compared to standard practice?	Based on two Markov modelling studies and one microcosting study: - simulations showed better effectiveness and reduced costs for the TDM-based approach, both from a societal and healthcare perspective. NB: lack of clinically based dose adaptations in the standard care comparator in this study. - TDM can be cost saving if it prevents between 2.5-5.0 patients out of every 100 being treated non-optimally for 3–6 months. - UK: Cost for monitoring was £153 p/patient: 67% costs attributable to acquisition of trough blood sample, 23% for consumables (e.g., ELISA kits, laboratory consumables), 10% for staff costs.	• Cost-effectiveness of TDM should be considered according to local context and standard of care
	• What factors have been identified to influence cost-effectiveness of TDM?	Based on two Markov modelling studies and one microcosting study: Cost-effectiveness is influenced by: target disease activity, the level of biopharmaceutical blood concentrations that triggered treatment decisions, the biopharmaceuticals chosen as alternative treatment options. Also, by the number of: samples studied per patient, (additional) visits per patient, samples analyzed simultaneously in the laboratory.	
	• What evidence is available on patient perspectives regarding acceptability and preferences of TDM?	No evidence.	• -
	• What evidence is available on clinicians' perspective regarding acceptability and preferences of TDM?	Based on two EULAR abstracts: Barriers to TDM were costs and a lack of recognition of a clinical problem, understanding of the purpose of testing, evidence for effectiveness of TDM, test capacity. Reasons to request a test: suspicion of immunogenicity, consideration of tapering and switching, mainly between originator and biosimilar.	• -

Therapeutic drug monitoring (TDM); antidrug antibodies (ADAbs); enzyme-linked immunosorbent assay (ELISA); homogenous mobility shift assay (HMSA); reporter gene assay (RGA); radioimmunoassay (RIA); immunofluorometric assay (IFMA); liquid-chromatography–mass spectrometry (LC-MS/MS); tumor necrosis factor (TNF); rheumatoid arthritis (RA); axial

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spondylarthritis (axSpA); psoriatic arthritis (PsA); adalimumab (ADA); etanercept (ETN); infliximab (IFX); golimumab (GLM); certolizumab (CZP); tocilizumab (TCZ); abatacept (ABC); rituximab (RTX); body mass index (BMI); methotrexate (MTX); C reactive protein (CRP); erythrocyte sedimentation rate (ESR); rheumatoid factor (RF); anticyclic citrullinated peptide (anti-CCP); immune-mediated inflammatory diseases (IMIDs)

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