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REVIEW

Therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal disease: a systematic literature review informing EULAR points to consider

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ABSTRACT

The objectives of this review were to collect and summarise evidence on therapeutic drug monitoring (TDM) of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases and to inform the EULAR Task Force for the formulation of evidence-based points to consider. A systematic literature review (SLR) was performed, covering technical aspects and (clinical) utility of TDM, to answer 13 research questions. MEDLINE, Embase and Cochrane were searched until July 2020. American College of Rheumatology and EULAR abstracts were also considered for inclusion. Data were extracted in evidence tables and risk of bias assessment was performed. For the search on technical aspects, 678 records were identified, of which 22 papers were selected. For the clinical utility search, 3846 records were identified, of which 108 papers were included. Patient-related factors associated with biopharmaceutical blood concentrations included body weight, methotrexate comedication and disease activity. The identification of a target range was hampered by study variability, mainly disease activity measures and study type. Evidence was inconsistent for multiple clinical situations in which TDM is currently applied. However, for some particular scenarios, including prediction of future treatment response, non-response to treatment, tapering and hypersensitivity reactions, robust evidence was found. There is currently no evidence for routine use of proactive TDM, in part because published cost-effectiveness analyses do not incorporate the current landscape of biopharmaceutical costs and usage. This SLR yields evidence in favour of TDM of biopharmaceuticals in some clinical scenarios, but evidence is insufficient to support implementation of routine use of TDM.

Key messages

⇒ Therapeutic drug monitoring (TDM) refers to the principle of using biopharmaceutical blood concentrations and, optionally, antidrug antibodies to optimise treatment for an individual patient.
⇒ Guidance for the application of TDM of biopharmaceuticals in rheumatology practice is lacking since robust studies comparing TDM with current standard care are scarce.
⇒ Although the identification of a target range for biopharmaceutical blood concentrations is hampered by study variability and fixed dosing of biopharmaceuticals, we identified clear demographic, treatment-related and disease-related factors that are associated with biopharmaceutical blood concentrations.
⇒ There is currently insufficient evidence for the routine use of proactive TDM; however, reactive TDM should be considered in some specific clinical situations.

INTRODUCTION

Therapeutic drug monitoring (TDM) has been suggested as a clinical tool to optimise treatment with biopharmaceuticals in rheumatology. TDM refers to the principle of using biopharmaceutical blood concentrations and, optionally, antidrug antibodies (ADAbs) to optimise treatment for an individual patient, based on the assumption of a definable relation between dose and biopharmaceutical blood concentration and between concentration and therapeutic effects. TDM is usually applied to small molecular drugs with a narrow therapeutic window and potentially severe toxicity.[1 2] However, there is expanding interest in TDM for biopharmaceuticals to enable a more tailored and personalised treatment approach to prescribing these expensive drugs.[3 4]

There are several basic principles that should be met to support the usefulness of TDM of biopharmaceuticals in rheumatic diseases.[5] First, there should be a variability in biopharmaceutical blood concentration among patients; second, a relation between blood concentration and clinical response should be present; and third, either low or high blood concentrations might result in clinically meaningful situations for patients treated with biopharmaceuticals, such as decreased efficacy, side effects or an increased risk of immunogenicity. These principles are among the focus in the current study.

Observational data have suggested a rationale for TDM of biopharmaceuticals by demonstrating large variations in serum concentrations between individuals on standard dosing, as well as a concentration–effect relationship.[6–12] Although TDM has shown promise as a potential strategy to personalise treatment, several challenges remain and, in rheumatology, the use of TDM of biopharmaceuticals is still controversial.[13 14] Randomised clinical trials addressing the effectiveness of TDM are lacking in rheumatology; hence, the clinical benefit and cost-effectiveness remain uncertain. Furthermore, therapeutic blood concentration ranges and minimal effective concentrations of biopharmaceuticals that are essential to guide TDM in daily practice remain largely undefined. Finally, guidance for application of TDM in clinical rheumatology practice is lacking. To provide such guidance, many unanswered questions must be elucidated, for example: what assay(s) should be used to measure biopharmaceutical blood concentrations and ADAb? in which situations can TDM be applied in clinical practice? what is the optimal blood concentration?

The aim of this systematic literature review (SLR) was to inform the EULAR Task Force for the formulation of the first evidence-based points to consider on TDM of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases (RMDs). To this end, we assessed the current evidence on TDM of biopharmaceuticals in rheumatology, with respect to technical aspects, clinical utility, as well as aspects relevant for interpretation of results and implementation.

Box 1 Research questions

Technical aspects of TDM

1. Are the results of different assays for biopharmaceutical blood concentration measurement comparable?
2. Are assays for detecting ADAbs comparable?

Clinical utility and relevant aspects for interpretation of results of TDM

3. What is the association between biopharmaceutical blood concentrations and disease activity?
4. What is the optimal target range, on group level, for each individual biopharmaceutical for each disease (RA, axSpA and PsA)?
5. Which factors influence biopharmaceutical blood concentrations?
6. What are the requirements to interpret biopharmaceutical blood concentrations?
7. What is the clinical utility of TDM compared to standard clinical care with regard to outcome?
8. In which clinical situations could TDM influence clinical decision making?
   - To predict outcome in patients in remission or with low disease activity who taper or discontinue biopharmaceutical treatment.
   - To predict successful dose escalation in the case of biopharmaceutical treatment failure.
   - To predict response to the subsequent biopharmaceutical treatment when switching between biopharmaceuticals (in case of treatment failure).
   - Early prediction of a later response to a biopharmaceutical.
   - To predict persistence of a flare.
   - To reduce overexposure to minimise infection risk.
9. In which situations should ADAbs be measured?
10. What are the incremental costs and consequences (benefits and harms) of TDM compared to standard practice?
11. What factors have been identified to influence cost-effectiveness of TDM?
12. What evidence is available on patient perspectives regarding acceptability and preferences of TDM?
13. What evidence is available on clinicians' perspective regarding acceptability and preferences?

ADAb, antidrug antibody; axSpA, axial spondyloarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TDM, therapeutic drug monitoring.

METHODS

For this SLR, two searches were performed in accordance with the EULAR standardised operating procedures (SOPs),[15] one on the technical aspects of TDM and one on the (clinical) utility of TDM. Inclusion criteria for both searches were literature published until July 2020 that was found through MEDLINE, Embase and Cochrane; relevant international congress abstracts from 2018, 2019 (American College of Rheumatology (ACR) and EULAR) and 2020 (EULAR); English, Spanish, Dutch or French language (as spoken by the authors); and all study designs. Additionally, the search on clinical aspects and utility was confined to adult patients with rheumatoid arthritis (RA) and spondyloarthritis (SpA) including psoriatic arthritis (PsA). Exclusion criteria were case reports on single patients, grey literature such as theses or reports from specific healthcare organisations, and congress abstracts other than from ACR/EULAR congresses. The search on the clinical aspects and utility of TDM was extended with a specific search for research questions (RQs) 6 and 8 (box 1) since these were more exploratory RQs and we might have missed relevant evidence without this additional search (online supplemental file 1 and figure 1B). Thirteen RQs were formulated and approved by the entire Task Force (box 1) during its first meeting. These RQs were structured and framed according to the EULAR SOP. Search terms (online supplemental file 1) were formulated with the help of experienced librarians.

Rayyan software was used to organise the different phases of the SLR.[16] All identified records were imported in Rayyan and duplicates were removed. Title and abstract screening, followed by full-text reading, was performed in pairs. Arguments for exclusion were recorded. The Task

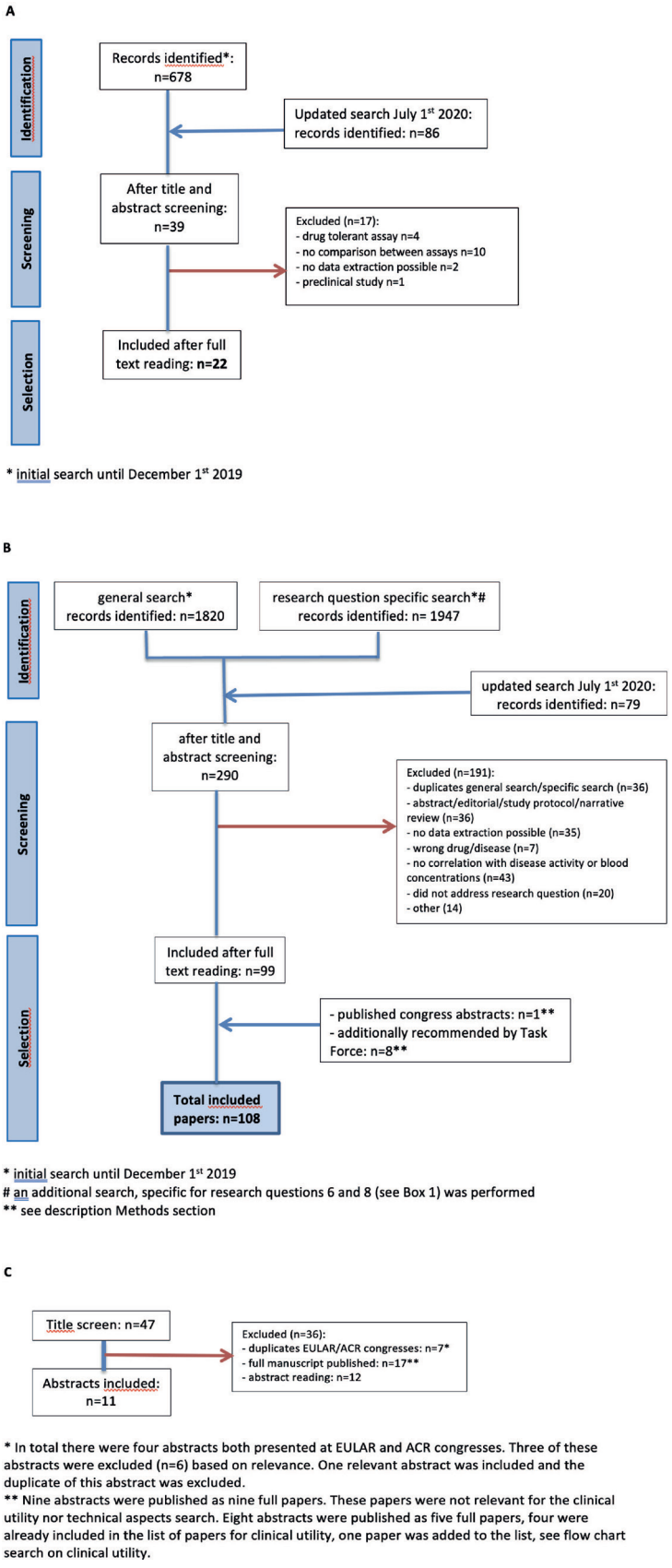

Figure 1 (A) Flowchart of selected article search on technical aspects of TDM. (B) Flowchart of selected articles search on clinical utility of TDM. (C) Flowchart selected of Congress Abstracts (abstracts from ACR and EULAR congresses 2018 and 2019 and EULAR 2020 Congress were considered for inclusion). ACR, American College of Rheumatology; TDM, therapeutic drug monitoring.

Force checked the list of papers and abstracts included for correctness and completeness and could add relevant papers not retrieved during the search. Additionally, snowballing was performed. Details on the search strategy are displayed in figure 1A–C.

Data were extracted from eligible papers using a standardised extraction form and listed in summary of evidence tables (see online supplemental file 2) by one reviewer and checked by a second reviewer. Disagreement between the reviewers was discussed with the methodologists.

Risk of bias assessment of individual studies was performed using the A Measurement Tool to Assess Systematic Reviews 2 for systematic reviews,[17] Cochrane Risk of Bias 2 tool for randomised controlled trials (RCTs),[18] the Quality in Prognosis Studies tool[19] and the Newcastle-Ottowa Scale for observational (cohort and case–control) studies,[20] the Quality Assessment of Diagnostic Accuracy Studies[21] for diagnostic studies and the Consensus on Health Economic Criteria[22] for economic evaluations (online supplemental files 2 and 3). Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting guidelines were followed.

RESULTS

Technical aspects of TDM

Biopharmaceutical blood concentration measurements (RQ 1)

Several assay formats are available to measure biopharmaceutical blood concentrations, of which ELISA is the most widely used. In total, 20 studies were identified that compared two or more formats for biopharmaceutical blood concentration measurement.[23–42] In 12 studies, agreement between different assay formats and ELISA formats was investigated.[23–27 29 34 36 37 40–42] There are two types of ELISAs available: direct ELISA, characterised by non-specific detection of the analyte, and sandwich ELISA, characterised by specific detection of the analyte. In studies where these ELISA formats were compared, a good correlation between them was shown (correlation coefficients >0.9).[26 27 29 40 41] Other assay formats also correlated well with ELISA. In four studies, ELISA was compared with homogenous mobility shift assay (HMSA).[23 25 37 42] Four studies compared reporter gene assay (RGA) with ELISA, with conflicting results.[24 29 34 37] Furthermore, the measurement of biopharmaceutical blood concentrations was comparable between ELISA and radioimmunoassay (RIA) and also between ELISA and immunofluorometric assay (IFMA), showing an agreement of 80%–98%.[34 36] RGA correlated weakly with HMSA and with liquid chromatography–mass spectrometry (LC-MS/MS) assay, RGA correlated well with RIA and was less comparable to IFMA.[33 34 36 38] Lastly, LC-MS/MS correlated well with an electrochemiluminescence-based assay.[32]

Overall, ELISAs intercorrelate well and also correlate well with other assay formats, although some studies reported modest discrepancies in absolute biopharmaceutical blood concentrations. Correlation between other assay types is less well studied and weaker in some cases.

Regarding point-of-care tests, two types were widely studied, namely, Quantum Blue and lateral flow assay. Both showed a good correlation with ELISA in seven observational studies.[27 28 30 31 35 39 41] In one study, both point-of-care methods are compared with each other and demonstrate good correlation.[41]

Detection of ADAb (RQ 2)

Interpretation of ADAb detection is less straightforward due to expression of different arbitrary units and different cut-off values. Furthermore, the presence of the biopharmaceutical in serum interferes with ADAb measurement, depending on the assay used. Therefore, the search was confined to drug-sensitive assays, which is relevant for clinical practice. With these assays, ADAb are solely detectable when there is very low/no concentration of biopharmaceutical present in the serum sample and, therefore, where they are potentially interfering with clinical efficacy. In contrast, drug-tolerant assays detect (sometimes transient) ADAb, even in the presence of circulating biopharmaceuticals, and are therefore less relevant for clinical practice. Five studies compared assays used for the detection of ADAb.[24 36 37 43 44] All studies compared ELISA with RGA and, except for one study,[24] measurements were comparable (correlation coefficients >0.8); however, absolute levels were not directly comparable between assays. ELISAs were additionally compared with enzyme immunoassay, surface plasmon resonance and other ELISA formats, with a high correlation.[36 43 44]

Clinical utility and relevant aspects for interpretation of results of TDM

Disease activity and biopharmaceutical blood concentrations (RQ 3)

The relationship between biopharmaceutical blood concentration and treatment outcome has been described in prospective observational studies and post hoc analyses of RCTs.[10 12 45–85] Study duration is generally up to 1 year, and treatment outcomes vary widely. On a population level, higher biopharmaceutical blood concentrations correlated with better treatment outcome and/or lower disease activity. Evidence is most robust for tumour necrosis factor (TNF) inhibitors in RA (adalimumab/infliximab/etanercept) and axial spondyloarthritis (axSpA) (adalimumab/etanercept/golimumab).[10 12 45–49 55 62–68 77 81–86] A clear relationship between infliximab blood concentrations and disease activity has not been demonstrated in axSpA, and for other biopharmaceuticals, especially in PsA, data are limited or lacking.[69 70 72–75]

Therapeutic range of biopharmaceutical blood concentrations (RQ 4)

Although there is a large interindividual variation in biopharmaceutical blood concentrations in patients

Table 1 Population-based blood concentration ranges that are associated with clinical response, per biopharmaceutical and disease

Drug	Rheumatoid arthritis	Axial spondyloarthritis	Psoriatic arthritis
ADA	~>8 µg/mL: remission (DAS-28 <2.6) ~>2 µg/mL: LDA (DAS-28 <3.2) <1 µg/mL: no response Range: 2–8 µg/mL[11 52–56 66 77 87 88 93]	~8 µg/mL: major improvement (ΔASDAS ≥2.0) ~5 µg/mL: low disease activity ~2.5 µg/mL: clinical improvement (ΔASDAS ≥1.1) Range: 2.5–8.0 µg/mL[9 63–65 95]	>1 µg/mL: clinical efficacy* >4 µg/mL: optimal efficacy* Range: 1–8 µg/mL[75 96]
ETN	Range: inconclusive[53 54 56 82 89 93]	Range: inconclusive[67]	Range: inconclusive[75]
IFX	Induction phase (week 6): ≥2.5 µg/mL: response Maintenance phase: >1 µg/mL: LDA (DAS-28 <3.2) Range: inconclusive [47 56 68 75 84 90 93]	No data	No data
GLM	Range: >1 µg/mL[80]	0.7–1.4 µg/mL: clinical improvement (ΔASDAS ≥1.1) Range: >1 µg/mL[12 80]	Range: >1 µg/mL[80]
CZP	23–28 µg/mL: remission (DAS-28 <2.3) Range: 20–39.9 µg/mL (largest improvement in DAS-28)[76 91 92]	Range: 20–39.9 µg/mL (largest improvement in ASDAS)[76]	Range: 20–39.9 µg/mL (largest improvement in DAS-28)[76]
TCZ	Intravenous: >1 µg/mL: DAS-28 ≥1.2 improvement Range: >1 µg/mL[6] Subcutaneous: range: inconclusive[94]	NA	NA

DAS-28: either erythrocyte sedimentation rate or C reactive protein.
*No clear definition of clinical or optimal efficacy with regard to disease activity measurement outcome.
.ADA, adalimumab; ASDAS, Ankylosing Spondylitis Disease Activity Score; CZP, certolizumab pegol; DAS-28, Disease Activity Score in 28 Joints; ETN, etanercept; GLM, golimumab; IFX, infliximab; LDA, low disease activity; NA, not applicable; TCZ, tocilizumab.

treated with a standard dose of a biopharmaceutical, available literature represents population-level data that cannot directly be translated to individual patients. In the absence of individual patient data, literature was searched for population-level biopharmaceutical blood concentrations that discriminated between response to treatment or remission and non-response or no remission for each biopharmaceutical for each indication (table 1).[6 9 11 12 47 52–56 63 64 66–68 75–77 80 82 84 87–96] There is a lack of pharmacokinetic/pharmacodynamic modelling studies and pharmacokinetic dose-finding studies that identify the minimal effective blood concentration or drug dose to achieve a certain treatment outcome in individual patients. The evidence available consists of mainly observational studies, indicating a therapeutic association between disease activity and biopharmaceutical blood concentration on a group level, using mainly standard dosing of therapy. Quality and quantity of the data contributing to the ranges in table 1 varied between drugs and conditions. For etanercept, blood concentrations tend to be lower and vary less widely (ie, 0–6 µg/mL) compared with blood concentrations of monoclonal anti-TNF antibodies.[53 54 56 67 68 75 82 89 93] Several studies failed to identify a target blood concentration range of etanercept, irrespective of the disease.[56 68 75 93] In other studies, cut-off values ranged widely from approximately 1.0 µg/mL to 3.1 µg/mL. Because of incomparable study designs, no target range was identified for infliximab.[53 54 67 82 89] For other biopharmaceuticals, data contributing to the identification of a target concentration are not available.

Factors that influence biopharmaceutical blood concentrations (RQs 5 and 6)

Factors that influence biopharmaceutical pharmacokinetics and/or interpretation of blood concentrations were reviewed in order to provide guidance on aspects that should be considered to be provided on request forms and when interpreting test results or providing advice. These aspects are related to patient, disease, biopharmaceuticals and technology.

Duration of therapy

It has been shown that infliximab trough blood concentrations are higher during the induction phase compared with the maintenance phase of treatment.[49 90 97] For most other biopharmaceuticals in rheumatology, there is no induction phase. Intrapatient variability of consecutive infliximab blood concentration and ADAb measurement is low, as shown in patients with RA with stable disease activity on two consecutive measurements.[85]

Timing of sampling (trough vs non-trough)

In an effort to standardise sampling and to theoretically aid interpretation of results, samples for biopharmaceutical blood concentrations are often collected as trough.

However, little evidence exists for the importance of trough sampling, compared with random sampling, of subcutaneous biopharmaceuticals. In addition, whether trough or peak concentrations or area under the concentration curve correlates best with clinical response is unknown. With subcutaneous administered therapeutic monoclonal antibodies, there is little variance in concentrations during steady state. For adalimumab-treated patients with RA, a weak inverse association was found between the blood concentration and the number of days after the previous injection.[98] This could not be confirmed in a second study that showed comparable blood concentrations of adalimumab at peak, intermediate and trough timing of sampling.[52] For etanercept-treated patients, trough blood concentrations were significantly lower than peak and intermediate blood concentrations.[52]

Route of administration

Abatacept and tocilizumab are biopharmaceuticals available as intravenous and subcutaneous formulations. Three out of four studies with these agents (subanalyses of RCTs) showed numerical (no statistics performed) differences in blood concentrations, with higher trough concentrations for the subcutaneous formulations.[94 99–101]

Dosing (interval)

Data for adalimumab and etanercept showed that changing the dosing interval influences blood concentrations. In patients with RA treated with adalimumab, median blood concentrations dropped from 10.6 µg/mL to 6.0 µg/mL with interval prolongation from once every 2 weeks to once every 3 weeks.[7] In patients in whom the adalimumab dose was increased to once a week because of non-response to treatment, median blood concentrations increased from 2.0 µg/mL to 15.0 µg/mL.[10] In patients with either RA, axSpA or PsA treated with etanercept, median blood concentrations decreased from 1.50 µg/mL to 0.46 µg/mL after interval prolongation from once a week to every fortnight.[102] Comparable results were observed in infliximab-treated patients with RA. Here, both dose and interval correlated with infliximab trough concentrations during the maintenance phase of treatment.[8 103] For example, with a 100 mg increase in dose, the trough blood concentration increased from 0.8 µg/mL to 1.8 µg/mL, whereas shortening the interval from 8 weeks to 6 weeks in patients receiving 3 mg/kg infliximab increased the trough blood concentration from 0.8 µg/mL to 2.8 µg/mL.[8] For abatacept and tocilizumab, higher dosages (5 mg/kg vs 10 mg/kg and 4, 6 or 8 mg/kg, respectively) resulted in consistently higher trough blood concentrations when dosing intervals remained constant.[104 105]

Immunogenicity of biopharmaceuticals

Immunogenicity is an important pharmacodynamic factor in treatment with most biopharmaceuticals, especially with therapeutic monoclonal antibodies. There is 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 rituximab.[10 51 53 56 63 65 67 71 76 91 96 106–116] For tocilizumab and other biopharmaceuticals such as secukinumab or ixekizumab, there are some data available; however, data in these papers were presented with insufficient amount of detail to properly extract these from the papers. Receptor constructs such as etanercept and abatacept do not appear to be immunogenic.

Body weight or body mass index (BMI)

In tocilizumab-treated patients, blood concentrations were lower in patients with higher body weight, both for intravenous and subcutaneous formulations.[58 94 105] In patients treated with abatacept subcutaneously, overweight (BMI 25–30 kg/m^2) and obese (BMI >30 kg/m^2) patients had numerically lower blood concentrations compared with patients with normal BMI.[117] For adalimumab and etanercept, patients with higher BMI, especially >30 kg/m^2, had lower biopharmaceutical blood concentrations.[55 56 67 68 81 83 107]

Concomitant medication

Patients with RA or PsA cotreated with adalimumab and methotrexate had higher biopharmaceutical blood concentrations compared with patients treated with adalimumab monotherapy.[11 55 96 118–120] In patients with axSpA treated with infliximab, results were contradictory.[121 122]

Inflammation parameters

Biopharmaceutical blood concentrations were inversely associated with pretreatment C reactive protein (CRP) levels and/or erythrocyte sedimentation rate (ESR) in patients treated with infliximab, adalimumab, etanercept, golimumab and rituximab.[9 49 50 75 81 82 116 123]

Rheumatoid factor and anticyclic citrullinated peptide (CCP) antibodies

In infliximab-treated patients with RA, the presence of high titres of both rheumatoid factor and anti-CCP was associated with lower infliximab blood concentrations during both the induction as well as the maintenance phase of treatment, compared with patients with low levels of both.[103] It was speculated that high titres might reflect an enhanced humoral immunity with increased risk of ADAb development and subsequent lower biopharmaceutical blood concentrations. Another study could not confirm this association.[82]

Proactive TDM (RQ 7)

Proactive TDM refers to regular, scheduled testing and subsequent dose adaptations guided by a therapeutic range, irrespective of the clinical situation. Only the Norwegian Drug Monitoring (NOR-DRUM) trial compared TDM to standard care in an RCT in patients with inflammatory diseases; part A was included in this SLR as a EULAR congress abstract.[124] This study focusses

on the induction phase of treatment with infliximab and compares TDM to standard care in the achievement of remission after 30 weeks of treatment. Patients with different immune-mediated inflammatory diseases were enrolled, including RA, PsA and SpA. TDM was not superior to standard care, although a reduced number of infusion-related reactions were observed with TDM. The authors conclude that TDM is not indicated in the induction phase of treatment with infliximab. Results of the maintenance phase (NOR-DRUM B) and cost-effectiveness analyses were not available within the search period of this SLR.

Several observational studies addressed proactive TDM. Only one study included sufficient data for this SLR; however, it was a small study and lacked a standard care comparator.[79] In 32 patients with SpA treated with infliximab, knowledge of blood concentration altered treatment decisions in 31% of patients but with no apparent influence on subsequent disease activity.

Prediction of response to treatment (RQ 8D)

In eight observational studies, the predictive value of early biopharmaceutical blood concentration measurement for later treatment response was investigated.[56 63 76 82 84 90 97 122]

Higher week 6 (cut-off ranging from 2.5 µg/mL to 4.4 µg/mL) and week 14 infliximab trough blood concentrations (cut-off ranging from 4.7 µg/mL to 6.7 µg/mL) were predictive of better treatment response at 6 and 12 months in RA or axSpA.[84 90 97 122] Adalimumab blood concentrations of <3.3 µg/mL at week 2 or <4.3 µg/mL at week 4 were predictive of week 12 non-response in axSpA.[63] In RA, adalimumab blood concentrations of <5 µg/mL 3 months after initiation of treatment were predictive of 12 months of EULAR non-response.[56] For etanercept, contradictory results were found in RA. In a study including 171 etanercept-treated patients, 3 month blood concentrations did not predict response at 12 months, whereas a study of 19 female patients suggested a concentration of ≥3.1 µg/mL at 3-month predicted response at 6 months.[56 82] In certolizumab treated with RA, axSpA or PsA, 3 month blood concentrations of ≥20 µg/mL were associated with response to treatment after 6 months.[76]

Reactive TDM (RQ 8A–C and E and F)

Reactive TDM refers to testing triggered by particular clinical scenarios. The Task Force predefined five situations for which evidence was searched.

1. *To predict outcome in patients in remission or with low disease activity who taper or discontinue treatment.* Six studies addressed this situation, one in axSpA and five in RA.[7 52 66 125–127] In a small study in axSpA, numerically more patients with suboptimal golimumab blood concentrations (<0.7 µg/mL) before tapering had a disease flare after tapering.[127] In RA, a modelling study with tocilizumab suggested no added benefit of TDM-guided tapering, with flare rates comparable to empirical dose tapering.[125] In a post hoc analysis of an RCT in which patients with RA were randomised to discontinue adalimumab, trough concentrations did not predict patients that flared after discontinuation.[126] In another RCT, in which patients with RA with high adalimumab blood concentrations were randomised to dose interval prolongation or continuation of treatment every 2 weeks, interval prolongation did not increase flare rate.[7] In another study combining data from post hoc analyses of an RCT and an observational study, no predictive value of adalimumab, etanercept or infliximab blood concentrations for successful discontinuation or dose reduction could be demonstrated, except for a subset of patients with high adalimumab blood concentrations (cut-off >7.8 µg/mL) and a small inverse association between lower etanercept concentration (cut-off <2.6 µg/mL) and successful dose de-escalation.[52] In a further observational study, patients with RA who remained in remission or in a state of low disease activity after dose halving of adalimumab had significantly higher adalimumab blood concentrations compared with those who flared, with a baseline cut-off of 6.4 µg/mL for persistent remission and 1.9 µg/mL for persistent low disease activity.[66]
2. *To predict successful dose escalation in case of biopharmaceutical treatment failure.* In four observational studies and one post hoc study of an RCT, TNF-inhibitor blood concentration measurement did not predict successful dose escalation in cases of clinical non-response in patients with RA or SpA.[79 128–131] Biopharmaceutical blood concentrations were similar prior to dose escalation in patients who did or did not respond to dose escalation.
3. *To predict subsequent response when switching between biopharmaceuticals (in case of treatment failure).* Results from eight studies on subsequent response to treatment after switching from one to another biopharmaceutical in case of low blood concentrations or presence of ADAb were conflicting.[132–139] In three observational RA studies, ADAb at time of infliximab failure did not predict success of subsequent adalimumab or etanercept treatment.[137–139] However, two other observational studies in RA and SpA suggested that ADAb predicted successful switching from a first to a second TNF inhibitor.[135 136] In two studies, both biopharmaceutical blood concentrations and ADAb were measured; these studies showed conflicting results.[132 134] In a study including adalimumab non-responders switching to etanercept, numerically more patients with very low adalimumab levels (<0.5 µg/mL) had EULAR moderate to good responses 52 weeks after switching.[133]
4. *To predict persistence of a flare.* A prospective study measured biopharmaceutical blood concentrations (rituximab, infliximab and etanercept) at the first sign of a flare (ie, increase in CRP or ESR or in disease activity).[140] Patients with detectable blood concentrations had lower disease activity during follow-up (2–6

months) compared with patients with undetectable blood concentrations.

5. *To reduce overexposure to minimise infection risk.* Two observational studies sought an association between high biopharmaceutical blood concentrations and infections.[141 142] In infliximab-treated patients with SpA, the risk of an infection episode that required hospitalisation, anti-infective treatment or infliximab treatment delay was higher in patients with trough blood concentrations in the highest tertile (>15.5 µg/mL) compared with the lower two tertiles (HR 2.61, 95% CI 1.3 to 5.4).[142] In patients with RA treated with TNF inhibitors or tocilizumab, those with high drug concentrations had a higher risk of any infection during the first year of treatment (HR 1.51, 95% CI 1.14 to 2.01) compared with those with low/normal blood concentrations. However, the study lacked power to assess the risk of serious infections.[141]

Clinical implications of ADAb (RQ 9)

Additional clinical situations considered potentially relevant for ADAb measurement alone were infusion or hypersensitivity reactions, injection-site reactions, switching or discontinuing biopharmaceutical treatment, treatment failure and consideration of dose increase. In a study of patients receiving tocilizumab (intravenous and subcutaneous formulations), only a small proportion of patients tested positive for ADAb, with no clear relationship with adverse events or loss of efficacy.[143] An association between the presence of anti-infliximab antibodies and infusion reactions was demonstrated in eight studies, which was statistically significant in six studies.[45 74 109 113 144–147] Two studies reported a very low incidence of adverse reactions in patients with antiadalimumab antibodies.[86 148] No evidence of an association between ADAb and injection-site reactions was found.

Nine studies investigated an association between ADAb and treatment discontinuation, treatment failure and dose increase.[45 64 74 109 113 136 144 145 149] Patients with detectable ADAb had higher disease activity and more often experienced lack or loss of response to treatment compared with ADAb-negative patients. Most of these studies additionally showed a higher risk of treatment discontinuation in patients with detectable ADAb.[45 74 113 136 145] No beneficial effect of dose increase in case of ADAb detection was found.

Costs-effectiveness of TDM (RQs 10 and 11)

Two modelling studies investigated the cost-effectiveness of TDM.[150 151] In one study, a Markov model was used to simulate a TDM-based strategy compared with standard practice.[150] The simulations showed better effectiveness and reduced costs for the TDM-based approach, both from a societal and healthcare perspective. Although there were major cost benefits to TDM, the lack of clinically based dose adaptations in the standard care comparator reduces the value of this study.

Another Markov modelling study evaluated the benefits of testing for biopharmaceutical blood concentration and ADAb.[151] The assumption was that testing could prevent ineffective treatment via early testing-based treatment adjustments. This study concluded that TDM can be cost saving if it prevents between 2.5 patients and 5.0 patients out of every 100 being treated non-optimally for 3–6 months.

In a microcosting study, direct medical costs were identified that are incurred by biopharmaceutical blood concentration and ADAb testing in clinical practice in the UK.[152] Cost for monitoring was £153 per patient. In total, 67% of costs were attributable to acquisition of a trough blood sample, 23% for consumables such as ELISA kits and laboratory consumables, and 10% for staff costs.

Costs of TDM are influenced by clinical, contextual and logistical factors. In the aforementioned studies, several factors were identified that influenced cost-effectiveness, including the target disease activity, the level of biopharmaceutical blood concentrations that triggered treatment decisions and the biopharmaceuticals chosen as alternative treatment options.[150 151] Other factors were the number of samples studied per patient, the number of visits per patient (additional appointment for blood sampling at trough) and the number of samples analysed simultaneously in the laboratory.[152] Some of these factors are strongly related to local context of care.

Although including grey literature and congress abstracts (other than from ACR/EULAR) was beyond the scope of our search, it is also worth noting that the National Institute for Health and Care Excellence concluded in their report on TDM of TNF inhibitors in RA that, based on the poor quality of evidence for cost-effectiveness of TDM, there is limited evidence to support its use in clinical practice.[153]

Patient and clinicians' perspective on TDM (RQ 12 and 13)

Our search found no literature on the patients' perspective on TDM.

We found two EULAR congress abstracts of qualitative studies that explored clinicians' perspectives on TDM.[154 155] Barriers to TDM requests included lack of recognition of a clinical problem, lack of understanding of the purpose of testing, lack of evidence for effectiveness of TDM, lack of test capacity and costs. Reasons for clinicians to request a test included suspicion of immunogenicity, and consideration of tapering and switching, mainly between originator and biosimilar.

DISCUSSION

While there is an increasing body of literature on the topic of TDM, most relates to observational studies and post hoc analyses of RCTs, often using relatively small sample sizes. Robust studies comparing TDM with current standard care are scarce. Despite the lack of robust trials, we have identified studies that inform the types of assays to use for measurement of biopharmaceutical blood

concentrations and ADAb. There are also clear demographic factors as well as treatment and disease related factors that are associated with biopharmaceutical blood concentrations which provide important information for when interpreting TDM data. The identification of a target range for biopharmaceutical blood concentrations is hampered by study variability, particularly with regard to disease activity measures and, additionally, by mainly fixed dosing of biopharmaceuticals. The licensed dose of at least some biopharmaceuticals represents a relative overexposure for a significant proportion of patients, and this complicates the identification of a minimal effective blood concentration or therapeutic range. Pharmacokinetic studies, including several dosages of a biopharmaceutical and predefined outcome measures, will aid in the identification of a minimal effective blood concentration. These types of studies are scarce and are often not in the public domain. Additionally, disease activity itself influences clearance of a biopharmaceutical and complicates further the identification of a therapeutic range. Additionally, most evidence is for TNF inhibitors, and whether or how this evidence can be extrapolated to other biopharmaceuticals remains unclear.

Evidence was inconsistent for the use of biopharmaceutical blood concentrations to assist dose tapering/discontinuation or for interpreting cause of flare or treatment failure; similarly, a predictive value for successful dose increase could not be concluded. Furthermore, current evidence is also inconsistent with regard to the use of biopharmaceutical blood concentrations and/or ADAb measurement at the time of treatment failure to assist the choice of subsequent treatment. Data surrounding ADAb utility is particularly conflicting in this regard, although there is a strong association between the detection of ADAb and loss of response to treatment and some association with hypersensitivity reactions. Measurement of infliximab, adalimumab and, probably, certolizumab pegol blood concentrations early in the course of treatment may aid in predicting future treatment response. High biopharmaceutical blood concentrations may be associated with a higher risk of infections, although evidence is limited.

There is currently insufficient evidence for the routine use of proactive TDM, in part because published cost-effectiveness analyses do not incorporate the current landscape of biopharmaceutical costs and usage. The NOR-DRUM trials were the first RCTs to assess the effectiveness of proactive TDM, as compared with standard therapy, across patients with immune-mediated inflammatory diseases, including RA, SpA and PsA.[156 157] However, because of our inclusion date of 1 July 2020, we only included the abstract of NORDRUM A in our SLR[124]; meanwhile, full papers of both NOR-DRUM A and B have been published. The NOR-DRUM trial part A compared TDM of infliximab to standard care in the induction phase of treatment, whereas NOR-DRUM B compared TDM to standard care in the maintenance phase of infliximab treatment. NOR-DRUM A showed no additional benefit of TDM over standard care in the induction phase of infliximab treatment. In contrast, NOR-DRUM B showed an advantage of TDM during the maintenance phase of infliximab treatment in patients with immune-mediated inflammatory diseases, including RA, SpA and PsA. Sustained disease control, without worsening of disease, was observed more frequently in the TDM group as compared with the standard care group. These results may support the use of proactive TDM in the maintenance phase of infliximab treatment but were, due to date of publication, not yet available at the time of the current SLR.

In conclusion, this SLR, on technical and clinical aspects including clinical utility was performed to collect and summarise the evidence for TDM of biopharmaceuticals in rheumatology. This informed the Task Force on TDM of biopharmaceuticals for the formulation of the first EULAR-endorsed points to consider. Further implications of the results of this SLR and a scientific and educational agenda can be found in the 'EULAR points to consider for TDM of biopharmaceuticals in inflammatory RMD paper.[158]

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Correction: *Therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal disease: a systematic literature review informing EULAR points to consider*

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Author John D Isaacs was incorrectly listed as John Isaac.

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