

# EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases

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## ABSTRACT

**Objective** To develop EULAR points-to-consider for therapeutic drug monitoring (TDM) of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases (RMDs).

**Methods** The points-to-consider were developed in accordance with EULAR standardised operation procedures by a multidisciplinary task force from eight European countries, based on a systematic literature review and expert consensus. Level of evidence and strength of the points-to-consider were determined, and mean levels of agreement among the task force were calculated using a 10-point rating scale.

**Results** Six overarching principles and 13 points-to-consider were formulated. The level of agreement among the task force for the overarching principles and points-to-consider ranged from 8.4 to 9.9. The overarching principles define TDM and its subtypes, and reinforce the underlying pharmacokinetic/pharmacodynamic principles, which are relevant to all biopharmaceutical classes. The points-to-consider highlight the clinical utility of the measurement and interpretation of biopharmaceutical blood concentrations and antidrug antibodies in specific clinical scenarios, including factors that influence these parameters. In general, proactive use of TDM is not recommended but reactive TDM could be considered in certain clinical situations. An important factor limiting wider adoption of TDM is the lack of both high quality trials addressing effectiveness and safety of TDM and robust economic evaluation in patients with RMDs. Future research should focus on providing this evidence, as well as on further understanding of pharmacokinetic and pharmacodynamic characteristics of biopharmaceuticals.

**Conclusion** These points-to-consider are evidence-based and consensus-based statements for the use of TDM of biopharmaceuticals in inflammatory RMDs, addressing the clinical utility of TDM.

## INTRODUCTION

Therapeutic drug monitoring (TDM) of biopharmaceuticals refers to the principle of using biopharmaceutical blood concentrations and, optionally, antidrug antibodies (ADAb), to guide therapeutic

decisions. TDM could be helpful in several clinical situations such as loss of response to therapy, the interpretation of side effects to therapy and to determine dose adjustments. TDM is common practice with certain small molecule drugs used in epilepsy, psychiatric disorders and infections.<sup>1,2</sup> It is also applied increasingly to biopharmaceuticals, especially in the field of gastroenterology.<sup>3,4</sup> In rheumatology, interest in TDM of biopharmaceuticals is increasing, alongside a growing body of evidence. Validated assays for TDM, both for measuring biopharmaceutical blood concentrations and ADAb, are becoming widely available. However, little guidance exists as to whether, or how, to apply TDM in clinical practice.

Use of biopharmaceuticals at the per-label dose results in a huge variation in serum levels of the biopharmaceutical. These real-life data have been published for several biopharmaceuticals.<sup>5–7</sup> A proportion of patients have very high or very low biopharmaceutical blood concentrations, suggesting there is a potential benefit for dose optimisation.<sup>8–11</sup> Such optimisation could improve efficacy, while possibly reducing the potential risk of adverse events related to high blood concentrations, such as infections.<sup>12</sup>

Understanding whether TDM would improve ownership of patient health decisions is important. Equally, many rheumatologists are unaware of the pharmacokinetic properties of biopharmaceuticals and whether TDM-informed dosing may improve outcomes. There are also knowledge gaps around the potential use of TDM. For example, if trough blood concentrations alone are informative; identification of the optimal frequency of TDM within clinical practice, and whether or not TDM should be proactive (regularly, in all patients) or reactive (only under prespecified circumstances).

Therefore, a multidisciplinary task force was created with the aim of developing EULAR overarching principles and points-to-consider on whether, when, in whom and how to perform TDM of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases (RMDs) and how to interpret the outputs. This manuscript reports the final

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overarching principles and points-to-consider agreed on by the task force.

### METHODS

The process adhered to the 2014 updated EULAR standardised operation procedures (SOPs).<sup>13</sup> After approval by the EULAR Executive Committee, a steering committee was established, comprising the convenor (JDI), a methodologist (AvT), a junior methodologist (VN-C), four fellows (CLMK, GLM, BH-B and JEG) including a representative of the Emerging EULAR Network (EMEUNET) and four rheumatologists (DM, MJ, GW and AB). The multidisciplinary task force also included a further seven rheumatologists, one bioanalytical scientist, one health economist with background in clinical pharmacy, one health professional, one additional EMEUNET representative and three patient representatives, altogether representing eight European countries.

Two task force meetings were held. During the first (face-to-face) meeting, in September 2019, the task force consensually formulated 13 research questions. This process was followed by a systematic literature review (SLR) conducted by the fellows and guided by the methodologists. A detailed description of the methodology and results of the SLR will be published separately. In brief, the literature published until July 2020 was searched through PubMed, Embase and Cochrane, and relevant international congress abstracts from 2018, 2019 (American College of Rheumatology and EULAR) and 2020 (EULAR) were considered for inclusion. Two different searches were performed: one search on the technical aspects of TDM, and one on the (clinical) utility of TDM, the latter confined to adult patients with rheumatoid arthritis (RA) and spondyloarthritis (SpA) including psoriatic arthritis (PsA)—these being the RMDs in which TDM has been studied to date. Title and abstract screening, followed by full text reading was performed in pairs (two pairs of two fellows). Data were extracted from selected papers and presented in evidence tables. The second (virtual) meeting took place in October 2020. Here, the task force reviewed the SLR results and discussed preliminary overarching principles and points-to-consider, which had been formulated by the steering committee ahead of the meeting, based on the evidence tables. Consensus on the final formulation was achieved through voting in accordance with the aforementioned SOP. In addition, a scientific and educational agenda were developed. After the second meeting, the level of agreement on each overarching principle and point-to-consider was assessed via e-mail, by anonymous rating (via an independent third party), on a scale from 0 (no agreement) to 10 (full agreement). The mean and SD of the levels of agreement were calculated. The level of evidence and grade of recommendation were based on the Oxford Centre for Evidence-Based Medicine Levels.<sup>14</sup> Risk of bias was assessed using the Cochrane Risk of bias 2 tool for randomised controlled trials (RCT),<sup>15</sup> the Quality In Prognosis Studies tool<sup>16</sup> and Newcastle-Ottawa Scale for observational (cohort and case-control) studies,<sup>17</sup> the Quality Assessment of Diagnostic Accuracy Studies<sup>18</sup> for diagnostic studies and the Consensus on Health Economic Criteria<sup>19</sup> for economic evaluations. The final manuscript was reviewed and approved by all task force members and approved by the EULAR Executive Committee.

### RESULTS

After reviewing the results of the SLR, and following a consensus process, 6 overarching principles and 13 points-to-consider (table 1) were formulated.

### Overarching principles

The six overarching principles are relevant to all points-to-consider. These overarching principles refer to the application of pharmacodynamic and pharmacokinetic principles in TDM, which are relevant to all biopharmaceutical classes, and contrast proactive versus reactive TDM. Most research in the field relates to RA but the principles can be extrapolated to other diseases, alongside evidence that is already available for conditions such as SpA and PsA. Lastly, the task force emphasise that the points-to-consider should always be considered in the context of (inter)national and local guidelines, underpinned by shared decision making.

### Points-to-consider

#### Measurement of biopharmaceutical blood concentrations should be performed in a validated laboratory

The measurement and interpretation of biopharmaceutical blood concentrations should be performed in a validated laboratory. There are several assay types available for measurement. The most widely used method is ELISA, with different ELISAs demonstrating good correlation.<sup>20–23</sup> There are several other assay types (such as Homogenous Mobility Shift Assay, immunofluorometric assay or Reporter Gene Assay) available that correlate well with ELISAs<sup>20 24–27</sup>; however, comparability among these other assay types is less widely studied. Point-of-care testing methods increase the accessibility of measurements and provide rapid and reliable results.<sup>21 23 28–31</sup>

The task force advises that the laboratory performing the assay should be familiar with biopharmaceutical blood concentration measurement and the specific test characteristics. Assays must be validated in accordance to (inter)national standards of practice.<sup>32</sup>

#### 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

The measurement and interpretation of ADAb is more complex than biopharmaceutical blood concentration measurement, in part due to interference by heterophilic antibodies such as rheumatoid factor. Interpretation of the results of an ADAb test for clinical purposes should be in the context of the biopharmaceutical blood concentration. Drug tolerant assays allow the detection of ADAb in the presence of the biopharmaceutical. These assays are preferably used for scientific purposes and their value in clinical practice remains unclear. These assays should, therefore, not be used for clinical purposes. In clinical practice, the presence of ADAb is usually only relevant if biopharmaceutical blood concentrations are low or absent, as a consequence of the ADAb. Drug sensitive assays only detect ADAb under these circumstances and the task force focused on these assays, which are also simpler to perform and interpret. Therefore, the task force advises to first measure the biopharmaceutical blood concentration and, only in the case of absent or very low drug concentrations, ADAb testing could be performed.

Several assay formats are available and, in accordance with drug concentration measurement, ELISA is the most straightforward method. Test results of other assay formats are comparable to ELISA results<sup>24 25 33 34</sup> but a consistent assay type should preferably be used over time, since different assay types might express results with different arbitrary units (eg, ug/L, AU/mL) and have different cut-off values. The radioimmunoassay, an ADAb assay that is mildly drug tolerant and used in some

**Table 1** EULAR-endorsed overarching principles and points-to-consider for therapeutic drug monitoring (TDM) of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases

		Grade of recommendation	Level of evidence	Level of agreement (0–10, mean (SD))	% of votes $\geq$ 8/10
<b>Overarching principles</b>					
A	Pharmacokinetic and pharmacodynamic principles underpin the interpretation of TDM for biopharmaceuticals	NA	NA	9.7 (0.9)	100
B	TDM refers to the principle of utilising pharmacokinetic data (biopharmaceutical blood concentrations and, optionally, ADAb, to optimise treatment for an individual patient	NA	NA	9.7 (0.5)	100
C	There are two broad categories of TDM: Proactive TDM refers to scheduled testing irrespective of the clinical situation and reactive TDM refers to testing in response to particular clinical scenarios	NA	NA	9.7 (0.5)	100
D	Most research in the field relates to TNF-inhibitors but the underlying principles can be extrapolated to other biopharmaceutical classes	NA	NA	8.4 (1.4)	76
E	Therapeutic approaches to treating patients with inflammatory RMDs should be in line with international and national guidelines for the management of the respective disease. Consideration of TDM should be taken within the context of such guidance	NA	NA	9.5 (1.1)	96
F	TDM should be part of a shared decision making process between the patient and healthcare professionals, incorporating the patient's experiences and preferences	NA	NA	9.5 (1.3)	96
<b>Points-to-consider</b>					
1	Measurement of biopharmaceutical blood concentrations should be performed in a validated laboratory	C	2b	9.9 (0.3)	100
2	Measurement of ADAb should be performed in a validated laboratory, preferably using a consistent assay over time. Measurement should be performed and interpreted alongside <u>contemporaneous</u> biopharmaceutical blood concentrations	B - C	2b	9.8 (0.5)	100
3	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	B	2b	9.6 (0.6)	100
4	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.	B	2b	8 (2.2)	72
5	Routine use of proactive TDM is not recommended in the management of inflammatory RMDs	D	2b	9 (1.6)	88
6	Measurement of biopharmaceutical blood concentrations up to 3 months after commencement of treatment could be considered to predict future efficacy	B	2b	8.8 (1.3)	92
7	Reactive TDM could be considered in the management of inflammatory RMDs	B	2b	9.5 (1.0)	84
8	Measurement of biopharmaceutical blood concentrations could be considered to identify those with high biopharmaceutical blood concentrations in whom tapering may be indicated	B	2b	9.3 (1.2)	88
9	Measurement of biopharmaceutical blood concentrations should be considered to understand clinical non-response	B	2b	9.5 (1.0)	96
10	Measurement of ADAb should be considered in the case of immunogenic biopharmaceuticals, alongside biopharmaceutical blood concentrations, at the time of clinical non-response	B	2b	9.4 (1.0)	96
11	Measurement of ADAb should be considered in the case of a hypersensitivity reaction, mainly related to infusions	B	2b	9.4 (1.4)	96
12	Measurement of ADAb is not recommended in the case of an injection-site reaction	D	5	8.8 (2.0)	84
13	Cost-effectiveness of TDM should be considered according to local context and standard of care	D	2c	8.8 (2.4)	80

ADAb, antidrug antibodies; NA, not applicable; RMDs, rheumatic and musculoskeletal diseases; TNF, tumour necrosis factor.

clinical laboratories, was not included in the SLR. While the task force recognises the potential utility of radioimmunoassay, the requirement for radioisotopes limits its widespread use.

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 cotreatment, disease activity and adherence to therapy

Pharmacokinetics describe the course of blood concentration over time, reflecting absorption, distribution and elimination. When requesting a biopharmaceutical blood concentration test, information regarding dose, dosing interval, route of administration and date of last dose enables interpretation of the result. With intravenous dosing, blood concentrations show a high peak postinfusion, subsequently falling as biopharmaceutical distributes into tissues and extracellular space. With subcutaneous dosing, blood concentrations reach a steady state with less peak-to-trough variation. The task force advises that blood sampling for biopharmaceutical blood concentration (and ADAb)

measurements should preferably be performed prior to the next administration when concentrations are at, or close to, trough. This is especially important, and easier to operationalise, with intravenous dosing. For subcutaneous dosing, trough measurement is less critical,<sup>35</sup> nonetheless, the task force recommends measurement as close as possible to the next administration.

Some patient-related factors influence pharmacokinetic parameters, such as body weight, methotrexate cotreatment, disease activity and adherence to therapy. With both fixed and body weight adjusted dosing of biopharmaceuticals (subcutaneously or intravenously administered), blood concentrations are lower in patients with higher body weight, especially for patients with a body weight >100kg or obesity (body mass index  $\geq$ 30 kg/m<sup>2</sup>).<sup>35–41</sup> For patients (with RA, PsA and potentially with axial SpA) treated with tumour necrosis factor (TNF)-inhibitors, blood concentrations are higher when methotrexate is co-prescribed from the start of treatment.<sup>10 39 42–45</sup> For adalimumab, this effect may be methotrexate dose-dependent.<sup>10 39 42</sup> The effect of methotrexate on pharmacokinetics of biopharmaceuticals is largely related to the suppression of the formation of ADAb. Immunogenicity has an important influence on

pharmacokinetics because ADAb form immune complexes with biopharmaceuticals, accelerating clearance. Regarding disease activity, biopharmaceutical blood concentrations correlate inversely with baseline C reactive protein (CRP) or erythrocyte sedimentation rate levels.<sup>8 46–50</sup> Thus, patients with lower disease activity tend to have higher biopharmaceutical blood concentrations although the mechanism(s) underpinning this relationship remain a question of debate. For example, with high inflammatory burden (high disease activity, high CRP), there is likely to be more target to bind the biopharmaceutical and therefore, blood concentrations will be lower. Conversely, with low biopharmaceutical blood concentrations, the target may be less neutralised, with less dampening of inflammation and higher CRP. Poor adherence to therapy also leads to lower biopharmaceutical blood concentrations.<sup>35 51</sup> Concentrations will also be lower than expected when patients postpone infusions or injections due to suboptimal adherence or concomitant medical issues, such as infections.

When interpreting biopharmaceutical blood concentrations, and based on the pharmacokinetic properties of biopharmaceuticals, the task force advises to consider dose, administration interval and route of administration, date of last dose and, especially in case of therapeutic monoclonal antibodies, co-administration of methotrexate.

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

In patients with RA or axial SpA, an association has been demonstrated between biopharmaceutical blood concentrations and clinical response.<sup>9 11 36 39 40 47 49 52–66</sup> Most data are available for adalimumab, etanercept and infliximab. In patients with peripheral SpA (including PsA) and patients treated with biopharmaceuticals other than adalimumab, etanercept or infliximab, less data are available. On average, patients with better treatment response or lower disease activity have higher biopharmaceutical blood concentrations.

The current licensed, generally fixed doses of biopharmaceuticals were selected in clinical trials to improve disease activity in the majority of patients, and concentrations in many patients may exceed those necessary for optimal target neutralisation. Similarly, with current dosing regimens, just a small proportion of patients will be underdosed. The specificity of biopharmaceuticals avoids off target (side) effects at high concentrations, in contrast to small molecule drugs. Therefore, relative overdosing of biopharmaceuticals is not associated with obvious short-term adverse events, although immunosuppression is likely to be higher. Relative overdosing also complicates analysis of the association between biopharmaceutical blood concentration and disease activity, particularly identification of a therapeutic range and minimal efficacious concentration. Nonetheless, clinical response is not solely a result of target blockade and other factors (both patient related and disease related) should be considered.

A number of studies have attempted to identify a therapeutic range for each biopharmaceutical and indication. However, due to large variation in blood concentrations, different clinical outcome measures between studies, and differences in timing of blood sampling in relation to dosing, no clear optimal therapeutic range could be identified in most cases. Most evidence relates to patients with RA treated with adalimumab where, with blood concentrations of at least 1 mg/L, some clinical efficacy is evident in most patients.<sup>35 58 65 67</sup> With increasing blood

concentrations efficacy improves further until approximately 8 mg/L, beyond which no additional benefit is seen at a population level.<sup>10 39</sup> Data from individual patients must, of course, be interpreted in the context of these group level data.

**Routine use of proactive TDM is not recommended in the management of inflammatory RMDs**

Proactive TDM refers to scheduled testing irrespective of the clinical situation. Two studies have compared proactive TDM to standard clinical care.<sup>68 69</sup> In each case, TDM did not provide additional benefit with regard to clinical outcome. In the Norwegian Drug Monitoring (NOR-DRUM) A trial, which evaluated TDM of infliximab, there was no difference in remission rates between the TDM arm and standard care arm, although fewer infusion reactions were observed in the TDM arm.<sup>69</sup> Results from the maintenance phase of treatment (NOR-DRUM B) are awaited.

A smaller prospective observational study also failed to demonstrate clinical utility of proactive TDM.<sup>68</sup> In this study, preliminary treatment decisions were made based on disease activity during the first study visit, and these were subsequently re-evaluated when blood concentration measurements were available. Although treatment decisions changed after re-evaluation, control of disease activity did not improve. In light of the existing evidence, the use of proactive TDM is therefore currently not supported by the task force.

**Measurement of biopharmaceutical blood concentrations up to 3 months after commencement of treatment could be considered to predict future efficacy**

The measurement of blood concentrations up to 3 months after the start of treatment could be considered to predict future efficacy of a biopharmaceutical. This point-to-consider is based on the results of observational studies investigating the predictive value of early biopharmaceutical blood concentrations for later clinical response. Most evidence is available for 3 months after the start of treatment with some evidence for measurements at 6 weeks or even earlier. Three of four infliximab studies (two in RA, one in SpA) showed low circulating blood concentrations predicting a lesser response.<sup>53 70 71</sup> One study in RA showed that combining infliximab blood concentration with disease activity slightly increased the predictive value for response after 6 months, compared with disease activity alone.<sup>72</sup> In adalimumab treated patients, biopharmaceutical blood concentrations at weeks 2 and 4 of treatment were associated with clinical response at week 12,<sup>61</sup> and week 12 blood concentrations were predictive of week 52 response.<sup>35</sup> For etanercept, two studies showed contradictory results and, for certolizumab, a single study showed an association between 3-month blood concentrations and response at 6 months.<sup>35 46 73</sup> Based on this evidence, the task force agreed that the measurement of biopharmaceutical blood concentrations early during treatment with infliximab or adalimumab may predict future efficacy; however, more data are needed in order to embed such a strategy into routine clinical practice.

**Reactive TDM could be considered in the management of inflammatory RMDs**

Reactive TDM refers to testing in response to particular clinical scenarios. For example, TDM might help to identify a reason for lack or loss of response to treatment, by detecting low biopharmaceutical concentrations in association with ADABs. Accordingly, these data may also be helpful in deciding on subsequent

treatment choices. On the other hand, in patients with low disease activity or in remission, results of TDM might suggest tapering or discontinuation of the biopharmaceutical. In this way, reactive TDM can be relevant for personalised approaches to patient care. Having discussed multiple scenarios, the task force agreed on the robustness of evidence for some of these, which form the basis of points-to-consider 8–12.

**Measurement of biopharmaceutical blood concentrations could be considered to identify those with high biopharmaceutical blood concentrations in whom tapering may be indicated**

Tapering of biopharmaceuticals in patients with high blood concentrations addresses overexposure. Notably, the dose of a biopharmaceutical needed to achieve a treatment response when disease activity is high, probably is higher than the dose needed to maintain that response once inflammation has been dampened. This point-to-consider relates to patients on established treatment with a biopharmaceutical and is not applicable to blood concentrations during induction phase of treatment or early after commencement of treatment. Tapering of biopharmaceuticals appears not to destabilise disease activity in patients with high biopharmaceutical blood concentrations.<sup>6 74</sup> Therefore, the task force recommends considering measurement of biopharmaceutical blood concentrations in patients in whom tapering could be appropriate.

**Measurement of biopharmaceutical blood concentrations should be considered to understand clinical non-response**

Measuring biopharmaceutical blood concentrations at the time of clinical non-response to treatment may provide insight into the underlying reasons for non-response, that is, to distinguish between pharmacokinetic (subtherapeutic blood concentrations, sometimes associated with ADAb), or pharmacodynamic (mismatch between drug target and disease mediators) factors. Therefore, the task force advises to consider the measurement of biopharmaceutical blood concentrations at the time of clinical non-response. Understanding the mechanism of non-response may then aid subsequent treatment decisions, although evidence is contradictory in this regard. For example, some observational studies indicate that patients with low TNF-inhibitor blood concentrations have better treatment response to a second TNF-inhibitor treatment, compared with patients with high blood concentrations at the time of treatment failure.<sup>75 76</sup> This is especially the case for patients switching from an immunogenic to a less immunogenic biopharmaceutical. However, another observational study could not confirm this relationship.<sup>77</sup>

**Measurement of ADAb should be considered in the case of immunogenic biopharmaceuticals, alongside biopharmaceutical blood concentrations, at the time of clinical non-response**

The presence of ADAb can be related to clinical non-response, including treatment failure, treatment discontinuation and shorter treatment survival. ADAb should be interpreted in the context of biopharmaceutical blood concentrations, and be measured with a drug sensitive assay, as described in point-to-consider 2. ADAb can interfere with biopharmaceutical target binding as well as reducing blood concentration by enhancing clearance, both negating clinical response.

The task force judges that the presence of ADAb can provide insight into the reasons of clinical non-response to treatment. However, there is contradictory evidence that the presence of ADAb to a first TNF-inhibitor predicts better treatment response to a second TNF-inhibitor.<sup>75 77–82</sup> Switching from an

immunogenic to a less immunogenic TNF-inhibitor might be considered, as patients might also be more likely to develop ADAb to a second immunogenic TNF-inhibitor.<sup>79</sup>

**Measurement of ADAb should be considered in the case of a hypersensitivity reaction, mainly related to infusions**

Hypersensitivity reactions refer to all types of reactions that appear immediately or shortly after administration of a biopharmaceutical, and can have varied manifestations. Most typically, infusion reactions relate to the presence of ADAb to an intravenously infused biopharmaceutical, such as infliximab.<sup>83–85</sup> Manifestations of an infusion reaction can be chills, generalised rash, fever, (angio)oedema, dyspnoea or hypotension. Such reactions are a response to complexes formed between ADAb and the biopharmaceutical. Most immune complexes formed are small (2–4 immunoglobulins) and tend not to cause infusion reactions. A single study has shown that the induction of infusion reactions is related to the size of the immune complexes. During intravenous infusion of a biopharmaceutical, large amounts of immunoglobulin enter the patients' bloodstream. If the patient has previously developed a large amount of ADAb, large immune complexes will form, and may induce an infusion reaction.<sup>86</sup>

In the specific case of hypersensitivity reactions, the task force could justify measuring ADAb without biopharmaceutical blood concentrations. In the case of severe hypersensitivity reactions, ADAb measurement is unlikely to alter clinical decision making as treatment will stop regardless. With less severe reactions, however, if treatment is effective and ADAb are absent, the task force advises that there is no absolute reason to stop treatment, as long as the patient feels informed and agrees to continue treatment. This scenario especially accounts for reactions with more general symptoms such as headache, arthralgia and fatigue.

**Measurement of ADAb is not recommended in the case of an injection-site reaction**

There is no robust published evidence of a causal association between the presence of ADAb and injection-site reactions with subcutaneously administered biopharmaceuticals. The task force considers such an association unlikely and advises against measurement of ADAb under these circumstances.

**Cost-effectiveness of TDM should be considered according to local context and standard of care**

There were a modest number of relevant economic analyses using decision-analytic modelling identified that investigated the cost-effectiveness of TDM.<sup>87 88</sup> The resource use and costs of implementing TDM are substantial and include test kits, additional blood draws and associated patient travel, laboratory costs and test interpretation.<sup>87–89</sup> These indicative studies suggest that TDM can potentially reduce costs with a gain in patient health measured using Quality Adjusted Life Years but, there is substantial uncertainty in these results. In addition, the context of the economic analysis, developing nature of the relevant biopharmaceuticals and evolution of clinical practice suggest that an iterative approach to economic analysis developing future evidence is required. Biopharmaceutical costs have become lower and clinical practice is evolving to incorporate clinically based dosing adjustments without the use of TDM. Economic analyses are needed to look at the impact of TDM on healthcare resources and patients. In terms of the impact on patients, TDM may improve clinical response and reduce treatment side effects with a subsequent impact on the health of the patient. The task force suggests that the impact of TDM on

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these factors should be taken into consideration in the context of local circumstances and guidelines. Robust economic analyses conducted in line with published recommendations specific to the relevant clinical situation<sup>90</sup> assimilating available data into decision-analytical models are required to quantify the incremental costs and consequences of TDM compared with the current practice of prescribing biopharmaceuticals for people with inflammatory RMDs.

### DISCUSSION

This paper reports EULAR-endorsed overarching principles and points-to-consider for TDM of biopharmaceuticals in inflammatory RMDs. The points-to-consider were developed using an evidence-based and expert opinion-based approach. The points-to-consider highlight the potential clinical utility of the measurement and interpretation of biopharmaceutical blood concentrations and ADAb, alongside factors that influence these parameters such as dose, administration interval, body weight, methotrexate cotreatment, disease activity and adherence to treatment. In general, proactive use of TDM is not recommended due to lack of data from clinical trials, but reactive TDM could be considered in certain clinical situations.

While an increasing volume of papers address TDM, the vast majority remain observational studies or post hoc analyses of RCTs with lower levels of evidence. High-quality clinical trials of TDM in rheumatology are sparse, and require the optimum biopharmaceutical therapeutic range to be known in advance. However, relevant data from the original, dose-finding, licensing trials are generally not available. Therefore, the task force appeals to biopharmaceutical companies to release these data into the public domain.

Although targeted towards enhancing personalised care for patients with inflammatory RMDs, these points-to-consider are derived from population-based data. In addition, their generalisability depends on (inter)national guidelines on patient management and on local context. Even within Europe, and despite the existence of EULAR recommendations, there remain differences regarding the use of biopharmaceuticals, which impact generalisability of these points-to-consider.

Patient and healthcare professionals views around TDM have not been widely explored. Future research and education should focus on stakeholder (including patients, rheumatologists and other health professionals) preferences and acceptability regarding TDM of biopharmaceuticals. The task force suggests a scientific agenda (table 2) and an educational agenda (table 3), which should help to increase awareness and knowledge of pharmacokinetics and pharmacodynamics relevant to biopharmaceuticals, especially concerning minimal effective blood concentrations. Regarding the scientific agenda, prospective studies are required, of the clinical utility of TDM in general and in specific scenarios such as tapering or switching. Registries could provide insight into potential adverse events related to immunogenicity and over-dosing of biopharmaceuticals. Regarding the educational agenda, three packages are proposed, for patients, rheumatologists/other health professionals, and third parties, such as healthcare administrators, policy makers, funders and governing bodies. These will support awareness of the current points-to-consider and scientific agenda, and will be developed in collaboration with all stakeholders, especially patients. Not all points in the educational agenda will be relevant for each stakeholder, namely patients and understanding better what patients wish to know about TDM is itself part of the agenda.

**Table 2** Scientific agenda

1. Pharmacokinetic/pharmacodynamic models	
▶	What is the critical minimal blood concentration of a specific biopharmaceutical in inflammatory RMDs for efficacy of the drug and for optimal target binding?
▶	At what blood concentration does a specific biopharmaceutical reach its maximum pharmacodynamic effect?
▶	What pharmacokinetic models exist for biopharmaceuticals in inflammatory RMDs?
▶	What is the interpatient variability in pharmacokinetics and pharmacodynamics with biopharmaceuticals?
▶	Can patient characteristics or biomarkers predict ADAb development?
2. Prospective studies/RCTs	
▶	Prospective studies comparing TDM with standard of care with regard to clinical utility and cost-effectiveness of TDM, for a range of biopharmaceuticals in different inflammatory RMDs.
▶	Prospective studies comparing proactive and reactive TDM, with regard to clinical utility and cost-effectiveness of TDM.
▶	Prospective tapering studies comparing TDM and standard of care.
▶	Prospective switching studies comparing TDM and standard of care.
3. Adverse event studies	
▶	Cohort or registry studies to evaluate the role of high biological drug levels in risk of infections.
▶	Cohort or registry studies to seek association of ADAb with specific adverse events/side effects, for example, injection site reactions, infusion reactions, hypersensitivity reactions (immediate and delayed).
4. Economic evaluations	
▶	Economic analyses specific to the relevant clinical context to quantify the incremental costs and consequences of TDM compared with the current practice of prescribing biopharmaceuticals for people with inflammatory RMDs
5. International collaborative opportunities	
▶	Development of an international biobank/databank to facilitate guidance on recommended pharmacokinetic/pharmacodynamic parameters for distinct biopharmaceuticals in different inflammatory arthritides.
▶	What is the 'minimal data set' required to provide confidence around TDM of distinct biopharmaceuticals prescribed for different inflammatory RMDs?
▶	Can this 'minimal data set' be integrated into intuitive models suitable for remote monitoring (eg, via smartphone applications)?
6. The patient perspective	
▶	Exploration of patient knowledge and preferences about TDM, including how they view its usefulness as part of shared decision making?
ADAb, antidrug antibody; RCT, randomised controlled trial; RMDs, rheumatic and musculoskeletal diseases; TDM, therapeutic drug monitoring.	

**Table 3** Educational agenda

A. Educational package for patients, developed collaboratively with all stakeholders, particularly patients, caregivers and patient organisations.	
B. Educational package for rheumatologists and other health professionals, developed collaboratively with all stakeholders.	
C. Educational package for healthcare administrators, policy-makers, funders and governing bodies.	
These educational packages could include information about one or more of the following items:	
1. TDM	<ul style="list-style-type: none"> <li>▶ What is TDM? What aspects are simple? What aspects are more difficult?</li> <li>▶ What is proactive TDM and what is reactive TDM?</li> <li>▶ What do patients want to know about TDM before incorporating it into their care?</li> <li>▶ Why might it be helpful to perform TDM—in general and in particular circumstances?</li> <li>▶ What is the evidence to support implementation of TDM in rheumatological practice?</li> <li>▶ What are the additional costs of performing TDM versus standard practice?</li> <li>▶ How can TDM be useful for patients and healthcare professionals as part of shared decision making?</li> </ul>
2. Biopharmaceuticals	<ul style="list-style-type: none"> <li>▶ What is a biopharmaceutical? (including monoclonal antibodies vs soluble receptor constructs)</li> <li>▶ How is a biopharmaceutical metabolised? Are there differences between monoclonal antibodies and soluble receptor constructs?</li> <li>▶ What is pharmacokinetics and pharmacodynamics and what do we know of this with regard to biopharmaceuticals in inflammatory RMDs?</li> <li>▶ What do we understand about specificity vs selectivity in clinical pharmacology with respect to rheumatology medications, including biopharmaceuticals?</li> <li>▶ How do we measure biopharmaceutical blood concentrations?</li> </ul>
3. Immunogenicity	<ul style="list-style-type: none"> <li>▶ What is immunogenicity?</li> <li>▶ What is an ADA and why do they form?</li> <li>▶ How do we measure ADAs? (including drug tolerant vs drug sensitive assays)</li> <li>▶ What are the different types of ADAs (including neutralising, non-neutralising)?</li> <li>▶ How do ADAs influence biopharmaceutical pharmacokinetics and pharmacodynamics?</li> <li>▶ What are the consequences of ADA formation? Do ADAs cause adverse events/side effects? Do they interfere with treatment? What is the frequency of such interference (sometimes or always)?</li> </ul>
ADAb, antidrug antibody; RMDs, rheumatic and musculoskeletal diseases; TDM, therapeutic drug monitoring.	

In conclusion, these are the first set of EULAR-endorsed overarching principles and points-to-consider advising on whether, when, in whom and how to perform and interpret TDM of biopharmaceuticals in inflammatory RMDs in clinical practice. Given the rapidly progressing field of TDM and personalised medicine more broadly, it is anticipated that some of the unanswered questions highlighted in these points-to-consider will be answered, as more data become available, which may prompt for an update of these points-to-consider in the years ahead.

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