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A value proposition for trough level-based anti-TNFα drug dosing

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A B S T R A C T

Treatment of inflammatory bowel diseases and rheumatic disorders with anti-tumor necrosis factor alpha (TNFα) drugs is expensive, while a significant proportion of patients does not show adequate clinical response. Therapeutic drug monitoring (TDM) enables patient-specific anti-TNFα therapy. The role of laboratory tests in clinical care has recently been described in a value proposition framework. It describes care processes, stakeholders, costs, risks, benefits and patient outcomes based on the use of a laboratory test in a clinical care pathway. We have applied this concept to the use of TDM for anti-TNFα drugs, describing evidence that supports the intervention and its cost effectiveness, steps that need to be adjusted in the care pathway, possible treatment algorithms and measures to assess adoption of this framework into clinical practice.

For effective TDM, an assay for measurement of drug levels together with appropriate target ranges and an anti-drug-antibody assay have to be implemented. Also, instead of only reporting the drug concentration, laboratorians, pharmacists and clinicians should deliver added value by introducing a TDM-based treatment algorithm into clinical practice. Thus, to maximize effectiveness of TDM of anti-TNFα therapy in routine care, adjustment of current care pathways and cooperation of many stakeholders are needed.

1. Introduction

Therapeutic proteins targeting tumor necrosis factor alpha (TNFα) have greatly improved the management of chronic inflammatory diseases, such as inflammatory bowel diseases (IBD) and several rheumatic disorders. Anti-TNFα monoclonal antibodies (MAb's) have been proven to induce and maintain remission in many patients who did not respond well to conventional treatment and are thus widely used for treatment of chronic inflammatory disorders, despite high treatment costs [1]. However, primary non-response or loss of response during treatment can occur in up to 50% of patients [2,3]. This can be due to formation of anti-drug-antibodies (ADA), which increase clearance of the drug and thereby lead to inferior clinical outcome [4–8]. Lack of response may also be due to high disease burden [9], or pharmacodynamic factors such as the (re)activation of inflammation by alternative pathways [10].

Different causes of non-response to anti-TNFα drugs require distinct approaches to treatment optimization. In current clinical practice, dose intensification is often the first step in treatment optimization when loss of response occurs, while other options such as adding immunosuppressive co-medication, changing to a different anti-TNFα drug, and changing to a different class of immunosuppressive drug should all be considered [9]. Given the fact that up to 50% of patients do not respond optimally to expensive anti-TNFα treatment, there is a clear need for more efficient treatment optimization. Therapeutic drug monitoring (TDM) of anti-TNFα drugs and detection of ADA can differentiate between different causes of non/suboptimal response and thus enables therapy adjustment based on an individualized dosing advice (reviewed in e.g. [9]).

The implementation of TDM in routine care requires a change in the current care pathway: tests for measurement of anti-TNFα drug concentrations and ADA have to be performed according to a pre-defined diagnostic and therapeutic protocol. This requires collaboration of many stakeholders. Proper introduction and evaluation of the new care pathway is therefore essential, which considers all the consequences for all the stakeholders who are involved in the TDM pathway.

Price and colleagues [11] recently developed a value proposition framework for laboratory medicine which defines all relevant questions concerning choice and implementation of laboratory tests. Briefly summarized, this value proposition aims to provide all necessary information that enables all stakeholders to make decisions that increase the proportion of patients achieving optimal therapeutic levels as well as resource investment and disinvestment decisions. In this study, this framework was used to develop a value proposition for TDM in personalized treatment with anti-TNFα drugs.

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Box 1
Framework for a value proposition (based on [11]).

1. The unmet clinical need. This includes definition of the problem and the impact on clinical, operational and economic outcomes.
2. Patient population that will benefit. This includes e.g. gender, age and setting in which the problem arises.
3. Identity of the test and its properties. This includes the test name and the basic pathology with which it is associated, reference intervals or clinical decision cut-off values, biological variation and expected analytical performance.
4. Test intervention utility. This includes screening, diagnosis, prognosis, risk stratification and/or monitoring.
5. Expected outcomes. This includes clinical, process and/or resource utilization.
6. Location where test is performed. This includes laboratory and/or point of care setting.
7. Quality of evidence available. This includes results from formal trials, observational studies, systematic review and meta-analysis.
8. Part(s) of the care pathway in which the test will be used.
9. Benefits / disadvantages to each of the stakeholders involved in delivering and receiving the care.
10. Potential limitations and risks associated that might be associated with introduction of the test, and a proposed mitigation strategy. This could be relevant to all of the stakeholders and may cover clinical, operational and economic outcomes.
11. Resource/activity contributed by each of the service lines involved in the care pathway with and without the test intervention.
12. Statement of the reimbursement received for delivering the care pathway with and without (before and after) the test intervention.
13. A proposed implementation plan including the metrics for monitoring appropriate adoption.

2. Methods

To clarify the value of laboratory testing in health care, Price and colleagues [11] described a value proposition framework (see Box 1). It requires initial consideration of the current clinical problem, how decision making in clinical care should be guided, what the process of the care delivery should look like and what the required resources are. In the current study, those questions are answered for TDM of anti-TNFα drug levels and measurement of anti-drug-antibodies (ADA) to facilitate personalized treatment of chronic inflammatory diseases. The main focus of this study is on infliximab, since this anti-TNFα drug has been studied most extensively. Data was gathered from studies and consensus documents, compared to clinical practice without use of TDM and changes that would result from use of TDM were identified and are reported here.

3. Results

3.1. The unmet clinical need

Treatment with anti-TNFα MAb's is very expensive [1], while a large proportion of patients do not show adequate clinical response to this treatment. This can be due to various reasons [2], namely the formation of anti-drug-antibodies (ADA), increased clearance of the drug, an ongoing inflammatory response without TNFα or a wrong diagnosis. This makes empiric therapy optimization, often done by dose escalation, inefficient. Also, the majority of patients do not receive doses that lead to trough levels within the proposed therapeutic concentration range [12,13]. This is illustrated in Fig. 1, which shows that only one third of patients has trough levels within the desired range. Patients with high drug levels are at risk of side effects such as serious infections [14,15] or unintentional and unnecessary high costs, while low drug levels are associated with loss of clinical response [16]. Therefore, a means to tailor anti-TNFα therapy to the need of the individual patient is highly desired.

3.2. Patient population that will benefit

All patients who receive anti-TNFα therapy could benefit from this personalized therapy. Five different categories of anti-TNFα MAb's are currently available: infliximab, a chimeric IgG MAb; adalimumab, a fully human MAb; golimumab, also a fully human MAb; etanercept, a fusion protein of TNF receptor 2 with an IgG1 Fc domain; and certolizumab pegol, a PEGylated Fab fragment. Several of these original drugs (also called reference products or innovator drugs) have experienced patent expiration, which has led to introduction of biosimilars [17] to the market. Currently, biosimilars are available for infliximab and etanercept and are expected soon for adalimumab. The anti-TNFα drugs are prescribed for the following indications: (pediatric) Crohn's disease, (pediatric) ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. Not all drugs are available for all indications in every country.

3.3. Identity of the test and its properties

Different analytical tests are available for quantification of anti-TNFα MAb's. Usually, enzyme-linked immunosorbent assays (ELISAs) are used. Other tests include homogeneous mobility shift assays (HMSA) [18,19] and mass spectrometry (MS) based assays [20–22]. An advantage of the HMSA and MS assays is that both the anti-TNFα MAb's and anti-drug antibodies (ADA) can be measured and that potentially all anti-TNFα MAb's can be quantified with the same assay. Currently, however, these more novel assays are less suited for routine clinical use due to the need of expensive analyzers and highly-specialized personnel.

Different ELISAs have to be used for all the different anti-TNFα drugs, except for biosimilars, which can be measured with the same assays as the innovator biologics [23]. Several ELISA kits are available

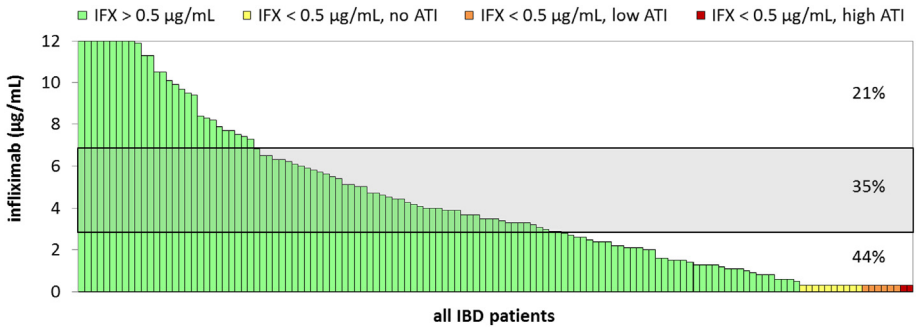

Fig. 1. Infliximab (IFX) trough levels and antibodies-to-infliximab (ATI) in a cohort of inflammatory bowel disease patients. The therapeutic range of 3–7 µg/mL is depicted with the light grey rectangle. The percentage of patients with IFX levels within, below or above the therapeutic range are indicated. ATI levels are shown with yellow, orange and red bars (modified from reference [13]). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

for each anti-TNFα MAb. It has to be noted that there is no standardization, so different kits may yield different drug concentrations [24,25].

Previously, we evaluated several commercially available ELISA kits for infliximab (IFX) [24]. All kits tested were suitable for use on an automated ELISA processor, so little hands-on time is required. We found that the apDia IFX ELISA had the best analytical performance with a within-run imprecision of ≤6.1%, a between-run imprecision of ≤7.1% and acceptable accuracy (80% < X < 120%) for all concentrations tested. It was also shown that the apDia IFX ELISA measures higher levels than the three other ELISAs tested (Sanquin Diagnostics in house, Lisa Tracker and Promonitor kits). This has to be taken into account when dosing is adjusted using a therapeutic range (see below).

The desired therapeutic range for anti-TNFα therapy depends on the anti-TNFα drug administered and on the disease type, disease severity, complications (such as the presence of fistulas) and treatment goal (clinical remission vs mucosal healing) [9]. Most research on therapeutic ranges has been done for infliximab and adalimumab in inflammatory bowel disease (IBD) patients. Recently, an international team of experts reached consensus on therapeutic trough levels for IBD patients to obtain clinical remission, which were 3–8 μg/mL for infliximab and 5–12 μg/mL for adalimumab [9]. Since different ELISA assays measure different concentrations, the therapeutic range may need to be (re)defined depending on the assay used [24].

3.4. Test intervention utility

Therapeutic drug monitoring (TDM) of anti-TNFα drug levels can be applied as reactive TDM or as proactive TDM [26,27]. Reactive TDM includes measurement of trough drug levels and ADA in response to active disease or the occurrence of suspected side-effects and is done to guide treatment changes. Proactive TDM includes measurement of trough drug levels and ADA to guide ongoing maintenance treatment, regardless of clinical performance. Recent evidence shows that higher IFX levels during the start of treatment are associated with better clinical outcome [28], but target concentrations are unknown. Results from TDM (drug and ADA trough levels) are combined with the clinical state of the patient to guide treatment. In 2017, algorithms for both reactive and proactive TDM have been proposed (see Figs. 2 and 3) [9].

3.5. 3.5 Expected outcomes

3.5.1. I. Clinical effectiveness

Proactive monitoring and application of appropriate dose adjustment are expected to significantly reduce the number of patients with supra-therapeutic and sub-therapeutic anti-TNFα trough levels. This potentially leads to less side-effects and immunization. Also, patients who developed anti-drug antibodies (ADA) may be detected earlier and therapy may be adjusted accordingly. By reactive monitoring, the cause of disease worsening could be detected, leading to faster and more efficient therapy optimization. This, in turn, potentially leads to increased quality of life for the patients.

We recently investigated infliximab drug trough levels in an IBD (see Fig. 1) [13], and a rheumatic cohort [12]. In both cohort studies, we found that about one-third of patients had supra-therapeutic IFX levels, one-third had therapeutic IFX levels and one-third had sub-therapeutic IFX levels. Half of the patients with sub-therapeutic levels had detectable ADA. This indicates that current patient management is ineffective and could possibly be greatly improved applying either reactive or proactive TDM.

3.5.2. II. Cost effectiveness

Treatment optimization does not necessarily lead to overall cost reduction, (although this could be the case, as suggested by several studies [10,29–31]. However, it will make anti-TNFα therapy more cost efficient by providing individualized care and thus more health gained per euro spent. This could be due to reduced utilization of hospital resources, e.g. due to reduced hospital stays, more optimal dosing of the drug or adequate switching to other drugs if necessary. From our two study cohorts [12,13], we estimate average yearly drug costs for proactive trough-level based, individualized anti-TNFα therapy in the Netherlands to be at maximum equally expensive as current generic anti-TNFα dosing (data not shown). A recent review [32] that analyzed seven studies comparing cost-effectiveness of empirical dose management to TDM-based dosing reports major cost savings by using a TDM-based strategy in IBD and RA patients without a negative impact on efficacy. Two of those studies were RCT's, five were modeling studies. Although all studies found that TDM was more cost efficient than empiric dose optimization, the amount saved depended on the underlying disease, the clinical situation of the study population and the modeling approaches used.

3.5.3. III. Broader impact

Individualized treatment of patients could lead to an increased quality of life. For patients with supra-therapeutic levels, the interval between anti-TNFα administrations can be extended. Finally, patients on 'drug holiday' may stay in remission for prolonged periods without receiving any treatment.

3.6. Location where the test is performed

Currently, measurement of drug and ADA levels is done in central laboratories. Quick and quantitative point-of-care tests are emerging on the market, but are not widely used yet. Those could also be suitable for anti-TNFα therapy monitoring, if they include ADA measurements and after appropriate clinical performance studies have been done.

3.7. Quality of evidence available

Currently, implementation of reactive and proactive TDM for anti-TNFα drugs is debated in literature. Many retrospective and observational studies showed that anti-TNFα drug trough levels correlate with clinical outcomes [5,6,33–41]. Prospective observational studies [12,13] have shown that the majority of patients do currently not reach levels within the proposed therapeutic concentration ranges. Thus, many patients potentially benefit from TDM. Furthermore, simulation studies [29,30] and randomized controlled trials [10,31,42] showed that optimizing anti-TNFα therapy using TDM leads to better clinical outcomes and is more cost-effective than empiric dose-escalation for patients who have lost response to anti-TNFα therapy.

Only one randomized controlled trial (RTC) [10] and three observational studies [38,43,44] in patients with IBD showed that reactive TDM was superior to empirical dose escalation or switching therapies, while several other observational studies showed no clinical differences [45,46]. One RCT showed that there was no difference in outcome between reactive and proactive TDM for IBD patients [47], while an observational study did show differences for infliximab but not for adalimumab [48]. No RCTs or comparative observational studies have been performed to evaluate the role of routine proactive TDM for achieving remission. Indirect evidence can be derived from one RCT (the TAXIT trial [42]), in which the therapy for IBD patients were randomized to receive proactive TDM or no TDM during one year. This trial showed that there was no difference between TDM and empiric therapy optimization. However, in this study all patients were first optimized by TDM to obtain trough levels within the therapeutic range before randomization.

Despite the limited number of studies comparing TDM vs empiric dose optimization a 2017 consensus statement [9] supports the implementation of both reactive and proactive TDM, see Figs. 2 and 3. Also, a guideline [26] and a technical review [27] of the American Gastroenterological Association (AGA) recommend reactive TDM in adults with active IBD and, due to a knowledge gap, makes no recommendation regarding the use of routine proactive TDM in patients

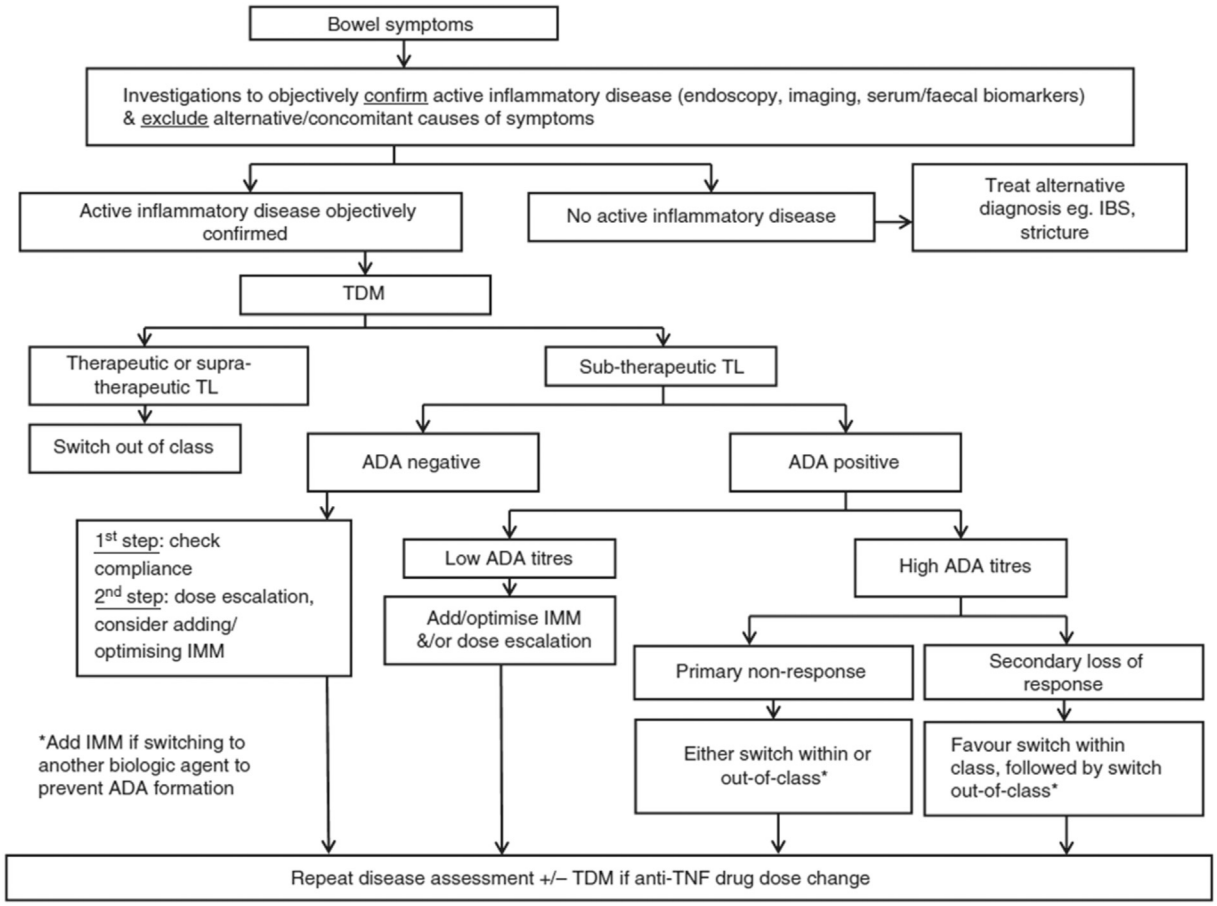

Fig. 2. *Proposed treatment algorithm for reactive TDM in inflammatory bowel disease (IBD)* patients experiencing bowel symptoms while on anti-TNFα treatment. ADA, anti-drug antibodies; IBS, irritable bowel syndrome; IMM, immunomodulators; TDM, therapeutic drug monitoring; TL, trough level. *Figure reprinted with permission from* (9).

with quiescent IBD [26].

3.8. Part(s) of the care pathway in which the test will be used

Monitoring of anti-TNFα therapy can be used in each patient population that may be treated with anti-TNFα MAb's, as described in section 3.2. Monitoring is part of the pharmacological treatment of these patients, mainly in the outpatient setting.

3.9. & 3.10 Benefits / disadvantages / risks to each of the stakeholders

The patient. The main potential benefit to the patient is earlier or longer remission times using a personalized dosing approach. The patient is assured that an adequate dose is administered, which may be lower or higher than the standard dose, and that infusion of anti-TNFα is stopped timely once loss of response or prolonged complete remission occurs.

The physician / pharmacist. Both enable the implementation of personalized medicine. A disadvantage to the physician / pharmacist might be that anti-TNFα level-based administration schemes are more time consuming. In a health care system that is financed based on activities, extra activities are a source of income for the care provider.

The laboratory. Laboratory medicine facilitates personalized drug therapy by measuring drug and ADA levels. Depending on how a laboratory is financed, testing may pose a financial burden or be a source of income.

Health care institution. In case anti-TNFα is purchased by and administered in a hospital or private practice, finances and resources (e.g. beds and nurses) are used more efficiently. If the institution is financed based on activities, day clinic visits and thus income may decrease. If the institution receives a fixed price to deliver care to a certain patient category regardless of the number of visits, expenses may be saved. The increased costs experienced by clinical laboratories as a consequence of TDM activities might be balanced within the same institution by reduced treatment costs.

Insurers. Insurers providing reimbursement for anti-TNFα therapies are certain that patients receive effective pharmacotherapy, because under- and over-dosing are minimized. Anti-TNFα testing incurs extra costs. Personalized treatment may increase or decrease costs spent on the drug.

3.10. Resource/activity contributed by each of the service lines involved in the care pathway with and without the test intervention

If anti-TNFα based drug-dosing is taken into clinical practice, laboratories have to validate anti-TNFα and ADA tests and establish therapeutic ranges for the anti-TNFα test chosen and either should implement drug and ADA measurements in routine practice or send samples to other specialized laboratories. Per treatment regimen, the physician and pharmacist have to agree on a reactive or proactive monitoring regime and on treatment algorithms, for example as shown in Figs. 2 and 3. For every individual patient, physician and pharmacist have to invest extra time to interpret drug and ADA levels for all patients before every infusion.

The nurse has to withdraw blood from patients before every infusion, physicians have to explain the new treatment regime to each patient. All care givers and the institution have to agree on how the additional costs for laboratory tests are financed and how potentially

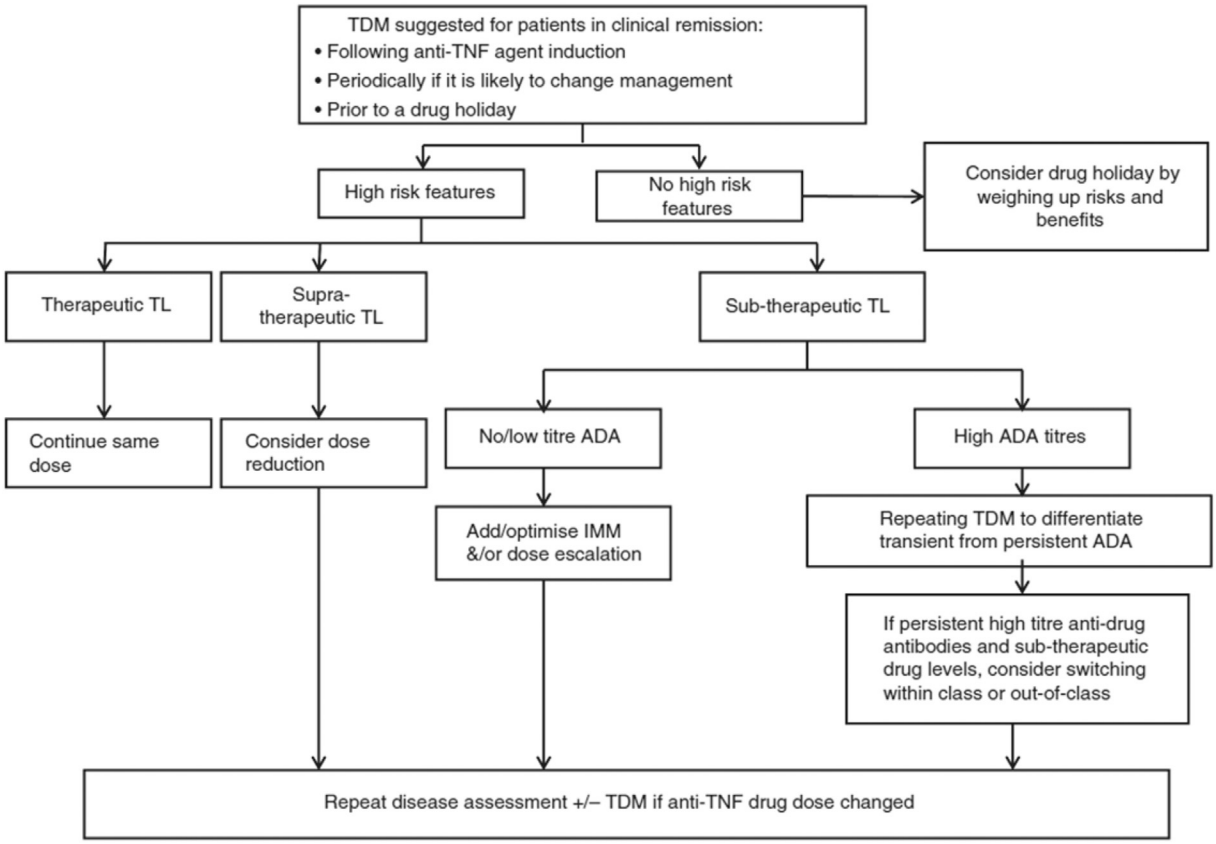

Fig. 3. *Proposed treatment algorithm for proactive TDM in inflammatory bowel disease (IBD)* patients on anti-TNFα treatment. ADA, anti-drug antibodies; IMM, immunomodulators; TDM, therapeutic drug monitoring; TL, trough level. *Figure reprinted with permission from*(**9**).

changing drug costs are handled. Finally, the caregiver has to agree with the insurer on reimbursement.

3.11. Statement of the reimbursement received for delivering the care pathway with and without (before and after) the test intervention

Introduction of TDM for anti-TNFα therapies leads to more laboratory testing to determine drug levels and ADA, leading to higher costs for testing. Health care professionals have to invest more time per drug prescription. Depending on the reimbursement system, this could lead to higher costs of income for the laboratory and/or hospital. However, costs for performing TDM are several fold lower than the anti-TNFα therapy itself. It is expected that on average the test costs are (over)compensated by savings through optimized therapy resulting from TDM, i.e. less anti-TNFα therapies being administered and less hospital visits.

3.12. A proposed plan for implementation and monitoring

As a first step, the caregivers must choose between proactive of reactive monitoring. Proactive routine measurement of anti-TNFα drug concentrations could be combined with already existing routine check-ups for patients. Once or twice a year, blood is drawn just before administration of the anti-TNFα drug. Anti-TNFα and, if indicated by low anti-TNFα concentration, ADA levels are measured. During the next outpatient visit to the physician or consultation by phone, test results are discussed. If warranted by the test results, anti-TNFα dose adjustment or other pharmacological changes are made.

Reactive TDM means that anti-TNFα drug concentrations are only measured when a patient experiences increased disease activity. Treatment algorithms need to be developed for proactive an reactive monitoring, see Figs. 2 and 3 for examples in inflammatory bowel disease.

Objective criteria for successful implementation of an algorithm-based dosing regimen should be established and tested. In case of proactive monitoring, a metric for appropriate adoption would be the percentage of patients that has trough levels measured after induction therapy. Metrics for both monitoring strategies would be the percentage of patients within desired ranges at introduction of the monitoring protocol and after e.g. 6 months. After successful implementation, one would expect the percentage of patients within the desired ranges to be markedly increased.

4. Discussion

The clinical care pathway is central to the value proposition as it describes the complete care process for a particular condition in a specific group of patients, including the use of a laboratory test (11). This discriminates the value proposition from consensus statements that only weigh medical evidence for a care pathway involving a laboratory test. The purpose of this study was to develop a value proposition for therapeutic drug monitoring (TDM) of anti-TNFα drugs.

Addressing the clinical questions in the framework showed that data from randomized controlled trials (RCT's) concerning TDM of anti-TNFα drugs are limited, and that almost all available data are derived from observational and modeling studies. The observational, retrospective and modeling studies support TDM of anti-TNFα drugs in clinical practice. From existing evidence, it is very likely that quantitation of anti-TNFα drug levels leads to more effective and efficient anti-TNFα treatment and faster treatment optimization [2,9,27,31,32]. A choice that needs to be made is whether a reactive of proactive monitoring regime is applied to individual patients. The choice may partly depend on history of disease and patient preference. The literature and our own experience (Fig. 1) show that a large percentage of

patients has anti-TNFα trough levels outside of the desired range. Therefore, we suggest to perform anti-TNFα monitoring at least after anti-TNFα agent induction, followed by dose adjustment (if indicated), and whenever a patient experiences symptoms of disease relapse while under anti-TNFα treatment. The latter is according to the reactive monitoring regime suggested in reference 9 and shown in Fig. 2. A personalized care approach, as just described, maximizes the gain in a patient's health in relation to the total amount of money spent.

The costs for TDM may vary between countries. On estimate, a measurement costs 30 to 50 euro if performed in-house using an ELISA kit, depending on whether only anti-TNFα concentration or also ADA need to be measured. In any case, the cost of one dose of anti-TNFα drug is several fold higher, in the Netherlands currently about 2000–2500 euro for an average dose of Remicade. Taken together with the high percentage of trough levels outside of the desired range, this illustrates that TDM is expected to be cost-efficient, since a large proportion of anti-TNFα doses can be adjusted. Although not (yet) backed-up by study results as these studies are difficult to perform, one would expect that more adequate dosing leads to lower incidence of ATI, less side-effects, longer periods in remission and thus better quality of life for the patient at lower treatment costs.

Target trough levels of anti-TNFα depend on the disease treated, but also on the test kit used for anti-TNFα measurement. So, communication between the laboratory and the physician/ pharmacist about the correct trough concentration is essential and we suggest that disease-specific trough ranges are reported together with a test result. In addition, caregivers should agree on treatment algorithms that take into account trough levels, clinical history, patient preferences, medication and symptoms of disease, e.g. as shown in Figs. 2 and 3, to assure standardized clinical practice.

While TDM of anti-TNF antibodies is a multi-disciplinary effort, it could well be initiated by laboratories and/or departments of clinical pharmacy since they are central in respectively providing suitable analytical and trough level information and giving an optimal dosing advice. We believe that the data provided in this report enable laboratorians to offer to caregivers and patients a proposition that is based on added medical value.

References

[1] M.E. van der Valk, M.J. Mangen, M. Leenders, G. Dijkstra, A.A. van Bodegraven, H.H. Fidder, et al., Healthcare costs of bowel disease have shifted from hospitalisation and surgery towards anti-TNFα therapy: results from the COIN study, Gut 63 (2014) 72–79.

[2] A. Dignass, J.O. Lindsay, A. Sturm, A. Windsor, J.F. Colombel, M. Allez, et al., Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 2: current management, J Crohns Colitis. 10 (2012) 991–1030.

[3] F. Schnitzler, H. Fidder, M. Ferrante, M. Noman, I. Arijs, G.V. Assche, et al., Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-Centre cohort, Gut 58 (2009) 492–500.

[4] Baert F, Noman M, Vermeire S, Van Assche G, D Haens G, Carbonez A, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N. Engl. J. Med. 2003;348:601–8.

[5] E.A. Maser, R. Villela, M.S. Silverberg, G.R. Greenberg, Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease, Clin. Gastroenterol. Hepatol. 10 (2006) 1248–1254.

[6] C.H. Seow, A. Newman, S.P. Irwin, A.H. Steinhart, M.S. Silverberg, G.R. Greenberg, Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis, Gut 59 (2010) 49–54.

[7] G.J. Wolbink, M. Vis, W. Lems, A.E. Voskuyl, E. de Groot, M.T. Nurmohamed, et al., Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis, Arthritis Rheum. 54 (2006) 711–715.

[8] G.M. Bartelds, C.A. Wijbrandts, M.T. Nurmohamed, S. Stapel, W.F. Lems, L. Aarden, et al., Anti-infliximab and anti-adalimumab antibodies in relation to response to adalimumab in infliximab switchers and anti-tumour necrosis factor naive patients: a cohort study, Ann. Rheum. Dis. 69 (2010) 817–821.

[9] N. Mitrev, N. Vande Casteele, C.H. Seow, J.M. Andrews, S.J. Connor, G.T. Moore, et al., Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases, Aliment. Pharmacol. Ther. 46 (2017) 1037–1053.

[10] C. Steenholdt, J. Brynskov, O.Ø. Thomsen, L.K. Munck, J. Fallingborg, L.A. Christensen, et al., Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial, Gut 63 (2014) 919–927.

[11] C.P. Price, A.S. John, R. Christenson, V. Scharnhorst, M. Oellerich, P. Jones, et al., Leveraging the real value of laboratory medicine with the value proposition, Clin Chim Acta Int J Clin Chem. 462 (2016) 183–186.

[12] E.M. Schmitz, S. Benoy-De Keuster, A.J. Meier, V. Scharnhorst, R.A. Traksel, M.A. Broeren, et al., Therapeutic drug monitoring (TDM) as a tool in the switch from infliximab innovator to biosimilar in rheumatic patients: results of a 12-month observational prospective cohort study, Clin. Rheumatol. 36 (2017) 2129–2134.

[13] E.M. Schmitz, P.J. Boekema, J.W. Straathof, D.C. van Renswouw, L. Brunsveld, V. Scharnhorst, et al., Switching from infliximab innovator to biosimilar in patients with inflammatory bowel disease: a 12-month multicentre observational prospective cohort study, Aliment. Pharmacol. Ther. 47 (2018) 356–363.

[14] F. Atzeni, L. Gianturco, R. Talotta, V. Varisco, M.C. Ditto, M. Turiel, et al., Investigating the potential side effects of anti-TNF therapy for rheumatoid arthritis: cause for concern? Immunotherapy 7 (2015) 353–361.

[15] T. Ali, S. Kaitha, S. Mahmood, A. Ftesi, J. Stone, M.S. Bronze, Clinical use of anti-TNF therapy and increased risk of infections, Drug Healthc Patient Saf. 5 (2013) 79–99.

[16] J.F. Brandse, D. Mould, O. Smeekes, Y. Ashruf, S. Kuin, A. Strik, et al., A Real-life Population Pharmacokinetic Study reveals Factors Associated with Clearance and Immunogenicity of Infliximab in Inflammatory Bowel Disease, Inflamm. Bowel Dis. 23 (2017) 650–660.

[17] FDA. Biosimilars > Information for Consumers (Biosimilars) [Internet]. [cited 2017 Sep 11]. Available from: https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm241718.htm

[18] S.-L. Wang, L. Ohrmund, S. Hauenstein, J. Salbato, R. Reddy, P. Monk, et al., Development and validation of a homogeneous mobility shift assay for the measurement of infliximab and antibodies-to-infliximab levels in patient serum, J. Immunol. Methods 382 (2012) 177–188.

[19] S.L. Wang, S. Hauenstein, L. Ohrmund, R. Shringarpure, J. Salbato, R. Reddy, et al., Monitoring of adalimumab and antibodies-to-adalimumab levels in patient serum by the homogeneous mobility shift assay, J. Pharm. Biomed. Anal. 78–79 (2013) 39–44.

[20] A. Guo, H. Gu, J. Zhou, D. Mulhern, Y. Wang, K.A. Lee, et al., Immunoaffinity enrichment and mass spectrometry analysis of protein methylation, Mol Cell Proteomics MCP. 13 (2014) 372–387.

[21] A.J. Kleinnijenhuis, M. Ingola, J.H. Toersche, F.L. van Holthoon, W.D. van Dongen, Quantitative bottom up analysis of infliximab in serum using protein a purification and integrated μLC-electrospray chip IonKey MS/MS technology, Bioanalysis 8 (2016) 891–904.

[22] J.F. Jourdil, D. Lebert, E. Gautier-Veyret, F. Lemaitre, B. Bonaz, G. Picard, et al., Infliximab quantitation in human plasma by liquid chromatography-tandem mass spectrometry: towards a standardization of the methods? Anal. Bioanal. Chem. 409 (2017) 1195–1205.

[23] A. Gils, R. Storme, E. Dreesen, T. Van Stappen, P.J. Declerck, P040. The biosimilars of infliximab are equally well quantified in a clinically validated infliximab assay, J Crohns Colitis. 9 (2015) S97.

[24] E.M. Schmitz, D. van de Kerkhof, D. Hamann, J.L. van Dongen, P.H. Kuijper, L. Brunsveld, et al., Therapeutic drug monitoring of infliximab: performance evaluation of three commercial ELISA kits, Clin Chem Lab Med CCLM FESCC. 54 (2016) 1211–1219.

[25] Wei Meng Lee, S. Connor, W. Ng, C. Mei-Ling Toong, Comparison of infliximab drug measurement across three commercially available ELISA kits, Pathology 48 (2016) 608–612.

[26] J.D. Feuerstein, G.C. Nguyen, S.S. Kupfer, Y. Falck-Ytter, S. Singh, American Gastroenterological Association Institute Clinical guidelines Committee. American Gastroenterological Association Institute Guideline on Therapeutic Drug monitoring in Inflammatory Bowel Disease, Gastroenterology 153 (2017) 827–834.

[27] N. Vande Casteele, H. Herfarth, J. Katz, Y. Falck-Ytter, S. Singh, American Gastroenterological Association Institute Technical Review on the Role of Therapeutic Drug Monitoring in the Management of Inflammatory Bowel Diseases, Gastroenterology 153 (2017) 835–857 (e6).

[28] K. Papamichael, N.V. Casteele, M. Ferrante, A. Gils, A.S. Cheifetz, Therapeutic Drug monitoring during Induction of Anti-Tumor Necrosis factor Therapy in Inflammatory Bowel Disease: defining a Therapeutic Drug Window, Inflamm. Bowel Dis. 23 (2017) 1510–1515.

[29] F.S. Velayos, J.G. Kahn, W.J. Sandborn, B.G. Feagan, A test-based strategy is more cost effective than empiric dose escalation for patients with Crohn's disease who lose responsiveness to infliximab, Clin. Gastroenterol. Hepatol. 11 (2013) 654–666.

[30] C.L. Krieckaert, S.C. Nair, M.T. Nurmohamed, C.J. van Dongen, W.F. Lems, F.P. Lafeber, et al., Personalised treatment using serum drug levels of adalimumab in patients with rheumatoid arthritis: an evaluation of costs and effects, Ann. Rheum. Dis. 74 (2015) 361–368.

[31] C. Steenholdt, J. Brynskov, O.Ø. Thomsen, L.K. Munck, J. Fallingborg, L.A. Christensen, et al., Individualized Therapy is a Long-Term Cost-Effective Method compared to Dose Intensification in Crohn's Disease patients Failing Infliximab, Dig. Dis. Sci. 60 (2015) 2762–2770.

[32] L. Martelli, P. Olivera, X. Roblin, A. Attar, L. Peyrin-Biroulet, Cost-effectiveness of drug monitoring of anti-TNF therapy in inflammatory bowel disease and rheumatoid arthritis: a systematic review, J. Gastroenterol. 52 (2017) 19–25.

[33] K. Karmiris, G. Paintaud, M. Noman, C. Magdelaine-Beuzelin, M. Ferrante, D. Degenne, et al., Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease, Gastroenterology 137

(2009) 1628–1640.
[34] Adedokun OJ, Sandborn WJ, Feagan BG, Rutgeerts P, Xu Z, Marano CW, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. Gastroenterology. 2014;147:1296–1307.e5.
[35] N.V. Casteele, R. Khanna, B.G. Levesque, L. Stitt, G.Y. Zou, S. Singh, et al., The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease, Gut. 64 (2015) 1539–1545 (/gutjnl; 2014:307883).
[36] W. Reinisch, B.G. Feagan, P.J. Rutgeerts, O.J. Adedokun, F.J. Cornillie, R. Diamond, et al., 566 Infliximab Concentration and Clinical Outcome in Patients With Ulcerative Colitis, Gastroenterology 142 (2012) (S-114).
[37] Y.L. Chiu, D.T. Rubin, S. Vermeire, E. Louis, A.M. Robinson, K.G. Lomax, et al., Serum adalimumab concentration and clinical remission in patients with Crohn's disease, Inflamm. Bowel Dis. 19 (2013) 1112–1122.
[38] X. Roblin, H. Marotte, M. Rinaudo, E. Del Tedesco, A. Moreau, J.M. Phelip, et al., Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases, Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 12 (2014) 80–84 (e2).
[39] W.J. Sandborn, B.G. Feagan, C. Marano, H. Zhang, R. Strauss, J. Johanns, et al., Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis, Gastroenterology 146 (2014) 85–95 quiz e14–15.
[40] J.F. Colombel, W.J. Sandborn, M. Allez, J.L. Dupas, O. Dewit, G. D'Haens, et al., Association between plasma concentrations of certolizumab pegol and endoscopic outcomes of patients with Crohn's disease, Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 12 (2014) 423–431 (e1).
[41] F. Cornillie, S.B. Hanauer, R.H. Diamond, J. Wang, K.L. Tang, Z. Xu, et al., Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial, Gut 63 (2014) 1721–1727.
[42] N. Vande Casteele, M. Ferrante, G. Van Assche, V. Ballet, G. Compernolle, K. Van Steen, et al., Trough Concentrations of Infliximab Guide Dosing for Patients with Inflammatory Bowel Disease, Gastroenterology 148 (2015) 1320–1329 e.3.
[43] S. Paul, E. Del Tedesco, H. Marotte, M. Rinaudo-Gaujous, A. Moreau, J.-M. Phelip, et al., Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: a prospective study, Inflamm. Bowel Dis. 19 (2013) 2568–2576.
[44] H. Yanai, L. Lichtenstein, A. Assa, Y. Mazor, B. Weiss, A. Levine, et al., Levels of drug and antidrug antibodies are associated with outcome of interventions after loss of response to infliximab or adalimumab, Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 13 (2015) 522–530 e2.
[45] A. Valido, J. Silva-Dinis, M.J. Saavedra, N. Bernardo, N. Fonseca, AB1231 Efficacy and cost analysis of a systematic switch from originator infliximab to biossimilar ct-p13 of all patients with inflammatory arthritis from a single Centre, Ann. Rheum. Dis. 77 (2018) 1712–1713.
[46] O.B. Kelly, S.O. Donnell, J.M. Stempak, A.H. Steinhart, M.S. Silverberg, Therapeutic Drug monitoring to Guide Infliximab Dose Adjustment is Associated with Better Endoscopic Outcomes than Clinical Decision making Alone in active Inflammatory Bowel Disease, Inflamm. Bowel Dis. 23 (7) (2017 Jul) 1202–1209.
[47] G. D'Haens, S. Vermeire, G. Lambrecht, F. Baert, P. Bossuyt, B. Pariente, et al., Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Concentrations Does Not Increase Clinical, Endoscopic, and Corticosteroid-Free Remission in Patients With Active Luminal Crohn's Disease, Gastroenterology 154 (5) (2018 Apr) 1343–1351 e1.
[48] R.A. Perinbasekar, S.A. Brown, N. Syed, S. Lonsako, R.K. Cross, Proactive Monitoring of Infliximab (IFX) and Adalimumab (ADA) Drug and Anti-Drug Antibody Concentration Utilizing the Labcorp Assay in Inflammatory Bowel Disease (IBD) Patients, Gastroenterology 152 (Suppl. 1) (April 2017) S392 Issue 5.