



REVIEW PAPER

Monitoring of infliximab treatment in inflammatory bowel diseases – basic knowledge and current data based on clinical trials in a population of Polish patients

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ABSTRACT

Introduction and aim. Infliximab is the oldest biological drug belonging to the group of tumor necrosis factor antagonists. Despite the availability of many new biological therapies, this drug still plays an important role in the treatment of inflammatory bowel diseases. However, a significant problem related to pharmacotherapy is the high inter-individual variability of the response.

Material and methods. This study presents results of the research on the treatment with infliximab in the inflammatory bowel disease (IBD) patients including our own experience in Polish IBD patients.

Analysis of the literature. Therapeutic failure while using infliximab can be attributed partly to inadequate serum concentrations of the drug and the development of anti-drug antibodies. Many studies have attempted to find a relationship between the specific level of infliximab and the achieved healing effect. These analyses show that the optimal level of the drug differs depending on the type of disease, its phenotype, and therapeutic goal and that the optimization of infliximab therapy remains an open topic. Two studies involving the population of Polish IBD patients examined the level of infliximab during and after induction, as well as the frequency of anti-drug antibodies. Two studies involving a population of Polish IBD patients examined the level of infliximab during and after induction, as well as the frequency of anti-drug antibodies. These studies demonstrated the need for monitoring infliximab treatment at weeks 6 and 14.

Conclusion. Reactive monitoring is believed to enable the most rational treatment decisions; however, experts also recommend that proactive monitoring should measure infliximab concentrations at the end of induction and at least once during maintenance treatment.

Keywords. infliximab, Crohn's disease, therapeutic drug monitoring, ulcerative colitis

Introduction

The term inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC). These are chronic disorders of the gastrointestinal tract, and their incidence and prevalence is increasing worldwide. Obtaining disease remission is still a major challenge since no causal therapy is currently available.¹ The pathogenesis of IBD is complex and mul-

tifactorial. Disturbance of the immune system and an abnormal response to the intestinal microbiota are the main contributors to pathogenesis, in addition to the influence of environmental factors in a genetically susceptible host. Dysregulation of the immune system leads to epithelial damage and increased inflammation, which is sustained by intestinal bacteria and activated inflammatory cells.²

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Received: 26.05.2022 / Accepted: 22.06.2022 / Published: 30.09.2022

Pękala A. *Monitoring of infliximab treatment in inflammatory bowel diseases – basic knowledge and current data based on clinical trials in a population of Polish patients.* Eur J Clin Exp Med. 2022;20(3):251–259. doi: 10.15584/ejcem.2022.3.1.



Conventional therapies for IBD include agents which affect many elements of the inflammatory cascade within the intestines. These include corticosteroids, immunosuppressants such as thiopurines - [azathioprine (AZA), 6-mercaptopurine (6-MP)] and methotrexate (MTX), and 5-aminosalicylic acid (5-ASA). However, only some patients receiving this treatment are responsive to treatment and achieve remission. A breakthrough in the treatment of inflammatory bowel disease appeared after the introduction of biological drugs having a strong immunomodulatory effect. These are monoclonal antibodies which selectively suppress some cytokines of the inflammatory pathway such as tumor necrosis factor α (TNF- α), some adhesion molecules, or interleukins.³

The oldest biological drug is infliximab (IFX), which has been in use for two decades, and is a monoclonal antibody directed against the cytokine TNF- α . Tumor necrosis factor- α is one of the most investigated proinflammatory mediators involved in the pathogenesis of IBD.⁴ This cytokine stimulates the acute phase response, cachexia, cytotoxicity, influences the production of interleukins, increases the expression of adhesive molecules, and stimulates the fibroblast proliferation.⁵ Studies have shown that levels of TNF are increased in blood, stool, and intestinal mucosa samples of IBD patients and that these levels depend on the clinical disease activity. Anti-TNF monoclonal antibodies induce IBD remission in some patients. Furthermore, Anti-TNF blockade can promote apoptosis of activated T cells, and restore the proper functioning of the intestinal barrier by protecting epithelial cells from apoptosis and tight junction compromise in the gastrointestinal epithelium.⁶

Infliximab and other TNF- α antagonists are safe and highly effective for the induction and maintenance of remission for both UC and CD; however, for most of these drugs, a high inter-individual variability in response is observed.⁷ Up to approximately one-third of patients receiving IFX do not respond to induction therapy, while in primary responders, up to approximately 50% lose response to the drug over time and require dose intensification or treatment discontinuation.⁸ This severe limitation of TNF antagonist therapy has led to attempts to overcome treatment resistance through Therapeutic Drug Monitoring (TDM), which allows individualization of therapy. Measurement of drug concentrations and optimization of the dosing regimen increases the chance of treatment response. Moreover, it also allows us to avoid unnecessary interventions when the drug concentration is optimal.

Aim

Reactive TDM is recommended in all cases of loss of response (LOR), whereas the role of proactive monitoring is still under investigation. At the same time, more

studies have demonstrated its usefulness. This article provides a review of infliximab treatment monitoring information, which is important in clinical practice. Data has been derived from recommendations of gastroenterological societies and from many clinical studies, including studies conducted on Polish IBD patients.

Material and methods

The study analyses numerous articles describing clinical trials and review papers on monitoring infliximab treatment in inflammatory bowel diseases. Two original studies on a group of Polish IBD patients were also included. The study included 84 and 65 patients with IBD treated with the biosimilar infliximab CT-P13 (Remsima) in the 3rd degree IBD center in south-eastern Poland (the city of Rzeszów) between the year 2016 and 2019.

Analysis of the literature

Pharmacokinetics of infliximab

Infliximab is a chimeric human-mouse monoclonal antibody that binds with high affinity to both the soluble and transmembrane forms of human TNF- α . A single intravenous infusion of infliximab produces a dose-proportional increase in the maximum serum concentration (C_{max}).

In most patients, IFX is detectable in the serum within 8 to 12 weeks after a single dose. The mean half-life is 8 to 9.5 days. There are many factors which can affect the concentration of a drug by either increasing or decreasing its clearance. Increased clearance leading to decreased infliximab concentrations may be associated with anti-drug antibodies (ADA), increased inflammatory activity of the disease, increased fecal excretion, low serum albumin concentration, and reduced body mass. Decreased clearance of the drug may occur with concomitant immunosuppression.⁹

Dosage of infliximab and drug therapeutic window

Infliximab is administered at a fixed dose and intervals derived from previous dose-finding studies for IFX.^{10,11} According to the summary of product characteristics for IFX and biosimilars, the dosage of IFX is 5 mg/kg of body mass during induction therapy at 0, 2, and 6 weeks followed by 5 mg/kg of body mass every 8 weeks for maintenance therapy. In Crohn's disease, dose escalation up to 10 mg/kg has been shown to restore treatment response. These data are based on the ACCENT I and II studies, which determined the dosing of IFX for Crohn's disease, and the ACT-1 and ACT-2 studies, which analyzed a population of UC patients treated with the original IFX.^{12,13} Simultaneously, in a post-hoc analysis of the ACT data from UC patients, the mean serum concentration of IFX in both induction and maintenance therapy was significantly greater in patients with clinical response and mucosal healing than in other

patients. Additionally, subsequent and current studies have shown that increased exposure to IFX is associated with better outcomes in UC.¹⁴

A recent analysis of numerous studies examining the need for IFX dose escalation in IBD showed that patients with UC more often required dose escalation than patients with Crohn's disease.¹⁵ However, attempts to alter the dosing regimen and accelerate the induction strategy in severe UC have produced inconclusive results. A small retrospective analysis of 50 patients with severe UC showed that the accelerated induction strategy of IFX reduces the need for an early colectomy.¹⁶ In contrast, a retrospective study and meta-analysis found no association between accelerated IFX induction therapy and lower rates of colectomy in patients with acute severe ulcerative colitis (ASUC) when compared to standard induction therapy.¹⁷ Similarly, it was recently shown that the use of high-dose IFX therapy did not increase 3-month colectomy-free survival in this cohort.¹⁸

Generally, the therapeutic level of IFX is 3–7 µg/ml, an IFX level < 3 µg/ml is considered sub-therapeutic, while an IFX level > 7 µg/ml is supratherapeutic.¹⁹ In contrast, American guidelines recognize IFX concentrations ≥ 5 µg/ml as target trough levels.²⁰ However, some patients may require greater levels of the drug. The target level of IFX to achieve endoscopic and clinical remission may range from 8–12 µg/ml. Even greater drug levels have been reported for fistula healing in Crohn's disease, ranging from 18–20 µg/ml.^{21,22} Many studies have attempted to associate IFX concentration with a response or clinical, endoscopic, or histological remission. For example, one retrospective study of patients with CD showed that IFX concentrations > 9.8 µg/ml were associated with endoscopic and histological remission.²³ Another study of UC patients showed that greater drug levels were required to achieve histological remission. In that study, histological remission was achieved at a concentration > 10.5 µg/ml and endoscopic remission with an IFX concentration > 7.5 µg/ml.²¹

In a study involving a Polish population, the concentration of biosimilar IFX associated with clinical response and the absence of LOR during a year of treatment was 4.6 µg/ml for CD and 3.1 µg/ml for UC at 14 weeks.²⁴ For comparison, other studies in CD patients demonstrated a sustained clinical response with an IFX level of at least 3.5 µg/ml or at least 7 µg/ml at week 14.^{25,26} In patients with UC, mucosal healing was associated with an IFX concentration of ≥ 5.1 µg/ml at week 14 and ≥ 2.3 µg/ml at week 30. Endoscopic remission was observed at IFX concentrations ≥ 6.7 µg/ml at week 14 and ≥ 3.8 µg/ml at week 30.²⁷ These differences seem to suggest that optimal IFX levels for response or remission may differ between patients.

During induction therapy, levels of IFX are significantly greater, but a therapeutic window has not yet

been established. Large differences in target drug levels are reported depending on the type of disease, its phenotype, and the analyzed therapeutic targets.²⁸ For CD at week 2, a level of IFX above 16.9 µg/ml may be sufficient to achieve a clinical response and above 20.4 µg/ml for clinical remission at week 14. In contrast, UC patients demonstrated a clinical response to an IFX level > 11.5 µg/ml at 2 weeks and clinical remission at 14 weeks at a level > 15.3 µg/ml.²⁹

Investigating the concentration of infliximab and anti-drug antibodies

Various methods exist to measure IFX levels, with the three most commonly used being enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and homogenous mobility shift assay (HMSA). The most common assay for quantifying biopharmaceuticals is ELISA, in which the drug is captured on a plate and detected using a secondary antibody.³⁰

For the most reliable assessment of IFX concentrations, minimal measurements are taken, which are measurements occurring just before the next infusion of the drug. A single measurement of IFX concentration may not be sufficient in an individual patient, and it may be necessary to measure sequential trough levels and interpret them in relation to therapeutic response. At the same time, it is necessary to continuously take into account factors which may have influenced the variability of drug exposure, such as changes in the dosing schedule and changes in drug clearance.³¹

For measuring levels of anti-drug antibodies (ADA), different assay types are used, in which the ADA are detected using the labeled biopharmaceutical itself. Usually, IFX concentration is measured in the first stage. If the drug concentration is undetectable or sub-therapeutic, ADA testing is indicated in the second step.

Presence and significance of anti-drug antibodies

ADA may already be detected 2–4 weeks after the first administration of the drug. Two types of ADA can be distinguished: binding antibodies – BAb, which decrease the drug level by increasing drug clearance via immune complex formation and neutralizing antibodies – NAb, which block the pharmacologically active site of the drug. In practice, the distinction between binding and neutralizing antibodies does not matter, since almost all ADA are neutralizing and the available tests do not differentiate their type.³² For the proper interpretation of the antibody measurement, information on the type of assay used for ADA measurement is needed, which may be a drug-sensitive or non-drug-sensitive assay. Usually, the most available test is ELISA, which is a drug-sensitive test. This test can only quantify the unbound excess of ADA and/or drug; however, it does not detect them when they are bound with each other.³³ In contrast to

ELISA, drug-tolerant assays will provide a more accurate assessment and detect drug-associated ADA, regardless of IFX level. Because not all ADA lead to decreased drug levels, and clinical efficacy is primarily related to an adequate IFX level, the drug-sensitive ELISA appears to be sufficient in daily practice, although its limitations should be taken into consideration. The test usually gives a positive ADA result only when the drug level is low or undetectable, which in practice means that the drug has not reached a clinically effective threshold. However, obtaining a double-negative result of the drug and antibodies may be a false result, and only the use of a drug-insensitive test allows us to detect ADA.³²

In a Polish study where the presence of the ADA was assessed via ELISA during induction and maintenance therapy, ADA were present in 20.4% of patients with non-therapeutic CT-P13 levels and 50% of patients with undetectable CT-P13 concentrations, with up to 100% of patients having undetectable drug levels at week 6 of treatment. Only one patient with detectable drug levels had antibodies simultaneously.³⁴ Reports of the prevalence of ADA against IFX are inconsistent due to the various assay formats used to monitor immunogenicity and the period of treatment in the clinical trial. In general, the reported detection rate for ADA covers a wide range (from 20 to 71.8%).³⁵ In our study of a Polish population, a total of 84 patients with IBD received CT-P13 and were followed-up for an average of 7 months. Overall, 20.4% of patients with non-therapeutic levels of IFX had concomitant antibodies. The percentage of patients with ADA detected during induction treatment was 11.3% compared to 9.6% during maintenance therapy; however, undetectable levels of IFX were a significant risk factor for antibody development and non-response at week 6 of therapy.³⁴

Another important element in the assessment of IFX immunogenicity is the estimation of ADA titers. For 1st generation ELISA, a cut-off of 8 µg/ml was established, above which the titer is considered high. This corresponds to 374 ng/ml in 2nd generation ELISA and a cut-off of 119 ng/ml in ready-to-use ELISA kits.³⁶ A high titer was also defined for RIDASCREEN (R-Biofarm, Germany) and InformTx/Lisa Tracker (Theradiag, France), having a cut-off value of 200 ng/ml, and an antibody assay range of 10-200 ng/ml. For other tests, there are insufficient data to establish an appropriate cut-off value for high titers of anti-IFX antibodies.³⁷ A high antibody titer is of greater significance; however, some patients can generate an enduring high titer ADA response, while in some patients this response is only temporary. Studies have shown that ADA titers can decrease over time and that detection of ADA may be transient in IBD patients treated with IFX.³⁸

ADA may reduce the efficacy of IFX therapy by neutralizing the drug, preventing it from binding to TNF,

and by enhancing the clearance rate due to formation of complexes. The presence of ADA against IFX is also associated with a higher risk of infusion reactions. Infusion-related reactions after administration of IFX are the most common adverse effects of the drug and the reported incidence rate varies between 4–15%.³⁹

A factor which appears to contribute to adverse events is the formation of very large TNFi-ADA complexes, which tend to be formed only at high ADA concentrations. Although the frequency of antibody production is relatively high, there have been relatively few cases of serious infusion-related reactions. This can be explained by the fact that the majority of TNFi-ADA complexes are small non-immune activating complexes.⁴⁰ The low frequency of antibody-related adverse events has also been confirmed by a Polish study. No allergic infusion-related reactions were observed in 9 patients who had antibodies over a broad range of 2.3 to 30 AU/ml and had received another infusion due to delayed antibody response.³⁴

Risk factors and prevention of ADA

Infliximab has been shown to be the most immunogenic of all biologic drugs. For comparison, a large meta-analysis showed that of the patients using IFX, 25.3% developed ADAC compared to 14.1% using adalimumab, 6.9% using certolizumab, 3.8% using golimumab and 1.2% using etanercept.^{41,42} Factors which increase the risk of formation of antibodies against IFX are a longer disease duration, a higher baseline activity, and not being TNF treatment-naïve.⁴² The frequency of antibody and titer detection can vary depending on the IFX dosing regimen and the usage of other medication. Anti-drug antibody formation is also affected by the serum concentration of TNFi. In clinical practice, attempts to overcome immunogenicity led to higher trough levels of IFX. Sufficiently high drug levels have been shown to suppress the immune response toward TNFi, especially in the first three months of treatment.⁴³ It was demonstrated that upon dose intensification, low concentration ADAs (not detectable using a drug-sensitive assay) disappear in more than half of the patients and are not clinically relevant. Greater ADA concentrations require greater drug doses to maintain the therapeutic effect.⁴⁴ At the same time, it has been shown that with appropriately high antibody titers, optimization of the dosage is ineffective. In the absence of detectable IFX, high titers of ADA necessitate a change in therapy.³⁷

Many studies have shown that concomitant use of immunosuppressive agents (methotrexate, 6-mercaptopurine, azathioprine, and others) during biological therapy reduced the probability of ADA formation and among biological drugs, this is especially true of IFX.⁴⁵ The pharmacokinetic benefits of combination therapy, which lead to greater anti-TNF drug levels and less

ADA production, are most important during the first 12 months of therapy; however, these benefits may also persist beyond this time. The benefits of adding an immunomodulator to anti-TNF therapy are also seen in patients who have previously failed immunomodulator treatment. Immunogenicity is reduced, which would lead to an increase in serum anti-TNF levels, and through concomitant therapy, may contribute to a reduction in disease activity.⁴⁶ Studies have shown that both thiopurines and MTX exert beneficial effects on the pharmacokinetics of anti-TNF agents when used in combination therapy with biological drugs.⁴⁷

Reactive monitoring of infliximab treatment

Reactive monitoring of IFX treatment involves measuring drug concentrations in cases of non-response or a decrease in response, usually in a patient who initially responds to treatment and involves maintenance treatment. Knowledge of the IFX level makes it possible to distinguish between patients with normal levels of the drug and patients with non-therapeutic IFX levels, who additionally require measurement for the presence and concentration of ADA. Infliximab treatment algorithms make the management dependent on low or normal drug and antibody levels. Patients having symptoms of active disease and low IFX levels with concomitant high concentrations of antibodies against IFX should switch to another TNF antagonist or another biological drug. Patients having symptoms of active disease, low concentrations of IFX, and absence of antibodies (or having them in low titers) should undergo dosage intensification.⁴⁸ Patients having a therapeutic concentration of the drug should be evaluated to confirm the presence of active disease using objective methods such as endoscopic or radiologic examinations. If active disease is confirmed, anti-TNF therapy should be discontinued and a surgical treatment option should be considered. Many studies have confirmed the significant benefits of reactive monitoring during IFX treatment.⁴⁹ An alternative to reactive monitoring is empirical dose escalation based on clinical symptoms alone and this has also been shown to be relatively beneficial.⁵⁰ However, reactive TDM of biologics is ultimately recommended as the new standard of care as it enables the most rational therapeutic decisions to be undertaken.³⁷

An important advantage of TDM is not only the possibility to determine the extent to which treatment should be escalated but also to identify patients who will not benefit from dosage increase due to normal drug levels or the presence of high antibody titers. In clinical practice, this also means a more rational choice for the next drug. Patients who have a secondary loss of IFX efficacy due to high antibody titers are most likely to respond well to another anti-TNF agent. Patients who have therapeutic levels of IFX are also likely to have suf-

ficient levels of the drug to saturate all of the TNF- α , and their disease is mediated by a different inflammatory pathway that should be the new target for therapy. It was also shown that in the case of IFX efficacy loss in the absence of ADA, the response to a second anti-TNF agent is likely to be weaker.^{51,52} However, in line with recommendations from the latest 2019 international gastroenterological consensus, IFX should not be discontinued in patients with active disease, unless drug levels exceed 10 $\mu\text{g/ml}$.³⁷

Proactive monitoring in maintenance therapy

Proactive therapeutic concentration monitoring is the measurement of a drug concentration at a determined time point followed by drug titration to a target dose. It involves aiming for a specific serum drug level as an independent treatment target, regardless of the patient's disease activity or response status. It is not part of standard practice, but its use is intended to predict and prevent treatment failure, mainly to prevent secondary loss of response. Studies examining the benefits of conducting proactive TDM have yielded mixed results. A role for proactive TDM of IFX was explored in the landmark studies, TAXIT and TAILORIX; however, superiority over symptom-based dose optimization was not demonstrated. The TAXIT study showed that the 3–7 mg/mL trough concentration after dose escalations results in an improved response in CD patients at a lower drug cost due to dose de-escalations in some patients.^{53,54} A prospective randomized trial of 122 biologic-naïve adult patients with active CD found that increasing the IFX dose based on a combination of symptoms, biomarkers, and serum drug concentrations did not lead to corticosteroid-free clinical remission in a larger proportion of patients than increasing the IFX dose based on clinical symptoms alone.⁵⁵ However, they observed that in IFX treatment, proactive TCM of IFX often identified patients with low or undetectable trough levels and increased the likelihood of maintaining treatment.^{56,57}

At the same time, many analyses were carried out which showed that obtaining a response and remission in IBD is associated with a higher concentration of IFX in the serum.⁵⁸ Several later studies have shown not only the benefits but also the advantage of a proactive approach to monitoring IFX concentration in comparison to reactive TDM. These analyses showed that proactive monitoring was associated with better clinical outcomes, which meant greater durability of the drug, less need for IBD-related surgery or hospitalization, and a lower risk of anti-IFX antibodies, and was more cost-effective.⁵⁹ In addition, it has been shown that maintaining the therapeutic concentration of IFX allows us to obtain comparable results, regardless of the concomitant use of immunosuppression.⁶⁰ This observation suggests that patients receiving IFX monotherapy with

contraindications to immunosuppression will benefit significantly from proactive treatment monitoring. Experts believe that the minimum trough concentration of IFX in patients in remission should be greater than 3 µg/ml and recommend at least one measurement of IFX concentration during maintenance treatment.³⁷

Proactive monitoring in infliximab induction therapy

Proactive monitoring in induction treatment involves measuring the concentration of IFX at weeks 2 and 6 before the second and third induction doses, and is indirectly related to the measurement of post-induction concentrations at 14 weeks of treatment. Large post-hoc analyses from ACT1 and 2 and TIALORIX showed that greater levels of IFX during induction therapy at weeks 2 and 6, in both UC and CD patients, are required to achieve endoscopic remission.^{61,62}

However, TDM during induction therapy is much less used than in maintenance therapy, both in practice and in clinical trials. Two of our studies conducted on a population of Polish patients related mainly to monitoring during this treatment period. Sixty-five patients (32 with CD and 33 with UC) were recruited for the study with regular measurements during and after the induction period. In addition to the minimum measurements at 6 and 14 weeks, we also assessed the usefulness of indirect measurements at 10 and 12 weeks. Our study showed that with the standard IFX dosage of 5 mg/kg, only 57.6% of UC patients and 68.8% of CD patients achieved the IFX treatment minimum of 3 µg/ml at week 14, although over 80% of both groups showed primary treatment response. In the course of our follow-up, more than half of the UC patients with non-therapeutic drug levels and all CD patients experienced loss of response to treatment or required a dosage increase. No additional benefit was demonstrated from taking indirect measurements at weeks 10 and 12. Our results clearly suggest that patients with non-therapeutic drug levels at week 14 require further monitoring and supervision as they are at high risk of losing response.²⁵

During induction, TDM is not currently considered the standard of care, although guidelines from gastroenterological societies indicate the advisability of measuring IFX levels at 14 weeks in all patients.³⁷

It is currently recommended to aim for a target of 7–10 µg/ml. In patients with a high initial inflammatory load [e.g. ASUC or CD with anal fistulas], it is also recommended to measure IFX levels earlier in induction and aim for higher target drug concentrations at these time points: week 2 [20–25 µg/ml] and week 6 [10–15 µg/ml].⁶³ The possibility of early antibody detection is an additional benefit of proactive monitoring of IFX treatment during induction.

In a study involving a population of Polish IBD patients treated with biosimilar IFX (CT-P13), the pres-

ence of ADA detected by ELISA was examined during induction and maintenance treatment. A total of 84 IBD patients received CT-P13 and were followed on average for 7 months. The percentage of people with antibodies detected during induction treatment was 11.3% compared to 9.6% during maintenance treatment. The study showed a statistically significant relationship between undetectable levels of CT-P13 and the presence of ADA at week 6 of therapy (ADA was detected in all patients with undetectable levels of CT-P13, $p=0.381$). Patients with IBD and undetectable levels of CT-P13 prior to the third induction dose were at high risk for the presence of ADA as well as primary non-response.³⁴

Conclusion

Use of therapeutic drug monitoring of biopharmaceuticals to personalize treatment is an important new standard having an impact on IBD therapy. Despite many studies on the determination of the therapeutic window for IFX, the optimal trough concentration of IFX remains unclear and falls within a very wide range, making effective monitoring-based therapy increasingly important. In everyday practice, a limitation may also be the availability of tests for measuring the level of IFX and antibodies, making it impossible to obtain a quick result. Recent developments in point-of-care testing are very promising, which determine the concentrations of IFX and ADA within minutes and will enable real-time TDM.

Declarations

Funding

This research received no external funding.

Author contributions

Conceptualization, A.P.; Writing – Original Draft Preparation, A.P.; Writing – Review & Editing, A.P.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

Data supporting the results of this study shall, upon appropriate request, be available from the corresponding author.

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