02

PERSPECTIVES ON TDM: POINT OF CARE TESTS (POCT)

ISSUE 2

INTRODUCTION

In this issue of Perspectives on TDM: POCT, Dr. Gionata Fiorino, and Dr. Giulia Roda, from Humanitas Research Hospital (Rozzano, Italy), and Dr. Edoardo Savarino and Dr. Sonia Facchin from the Gastroenterology Unit, Department of Surgery, Oncology and Gastroenterology, University of Padua (Italy), describe the scientific evidences about the benefits of TDM in IBD patients treated with biologic therapies and the clinical experience of using POC devices for TDM, respectively.

In their review article Dr. Fiorino and Dr. Roda introduce the concept of TDM as a useful tool for the optimization of therapies and for providing a personalized medicine. The authors review some of the key studies such as: CLASSIC II, ACCENT I, SONIC and meta-analysis that have provided evidence on the clinical and economic benefits of therapeutic drug monitoring of biological drugs. Authors highlight the importance of defining therapeutic cut offs for each drug and for each phase of treatment (induction and maintenance) in the treatment of patients with IBD. Regarding the roles of reactive versus proactive TDM, authors revise the AGA guidelines supporting reactive TDM and some of the published evidence on the role of proactive TDM (e.g. TAXIT and TAILORIX prospective trials and long term outcomes retrospective studies published in last years).

Overall, the data reviewed by Dr. Fiorino and Dr. Roda reflect a profound change in therapeutic strategies in IBD patients during the last years. From a clinically based approach to a treat to target strategy based on TDM as a cornerstone of IBD therapies with biological drugs.

Dr. Fiorino and Dr. Roda explain the benefits performing TDM with new point-of-care test (POCT) devices in order to facilitate decision-making at the point of care instead of depending long awaited results reports.

In the second article of this issue, Dr. Savarino and Dr. Facchin revise the major factors of primary failure in the induction phase of therapy and secondary failure after an initial response to treatment. Authors revise published literature showing that drug exposure is probably one of the major factors affecting treatment outcomes and it has been observed that there is a positive correlation between infliximab serum levels and clinical and endoscopic outcomes. Among other factors, authors also describe that immunogenicity of the drug and the

formation of ADAs (anti-drug antibodies) is associated with low drug exposure. Thus TDM may be a useful support tool for therapeutic decision-making in case of active disease or in situations with supratherapeutic drug concentrations.

To exemplify the utility of a point of care test for TDM, Dr. Savarino and Dr. Facchin describe two real world case reports of IBD patients being treated with infliximab and monitored for the presence of ADAs with a POCT (Promonitor Quick) designed for the detection of anti-infliximab antibodies (ATIs).

Articles

IMPACT OF POC DEVICES FOR TDM IN THE MANAGEMENT OF PATIENTS TREATED WITH BIOLOGIC DRUGS

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INTRODUCTION

Therapeutic Drug Monitoring (TDM) measures the drug trough concentration and the presence of antibodies against a specific drug. TDM is an important tool to optimize individual therapies to patients treated with biological drugs. Inflammatory Bowel Disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are progressive inflammatory disorders often treated with immunomodulators and/or biologics (i.e. anti-TNFs, antiinterleukins, antiintegrins, etc.). The trough concentrations of these drugs may vary due to different factors, such as disease severity, phenotype, inflammatory state, immunomodulatory usage, patient gender, and body mass index (BMI) as well as variability in drug clearance through immune- and nonimmune-mediated mechanisms and mechanistic failure[1].

Thus, TDM represents an important tool to decide which patients will be discontinued from anti-TNFs therapy and whether and when an increase of dosage is needed. The CLASSIC II study showed that trough level of anti-TNFs drugs (adalimumab, infliximab and certolizumab pegol) are variable between patients as mentioned above and between drugs with a half-life of 2 weeks for adalimumab and 14 days for certolizumab pegol and infliximab. These differences should be taken into account in clinical practice[2, 3].

In the last decades, therapeutic strategies for IBD have changed from a clinically driven approach to a target-driven strategy and TDM is a crucial part of this process.

TDM IN CLINICAL PRACTICE

Numerous studies have demonstrated an association between anti-TNF drug concentration and IBD outcome. Higher drug levels are associated with better clinical outcomes, biological remission, and mucosal healing[4].

This association has been confirmed for both UC and CD for infliximab and adalimumab. In a meta-analysis including 22 studies and 3.483 IBD patients receiving infliximab, a trough level above 2 μg/mL was observed to be more likely associated with clinical remission

(P<0.001) and mucosal healing (P=0.004) compared to a lower drug concentration[5]. Another meta-analysis including 14 studies observed that patients with trough level over a predefined cutoff, which was different in each study, were more likely to achieve clinical remission than in presence of lower concentrations[6].

There is a lack of a single fixed cutoff since it depends on the variability between studies and between phase of intervention (induction or maintenance). In the ACCENT I trial, the optimal trough level threshold of infliximab at week 14 for a durable sustained response was greater than 3.5 μg/mL[7]. Additionally, similar studies have analyzed the relation of adalimumab trough level at induction phase and clinical outcome. Baert et al. showed that a drug concentration below 5 μg/mL of adalimumab at week 4 was significantly associated with a risk of anti-adalimumab antibody formation, an increased CRP and loss of response[8].

Of note, in the SONIC trial post hoc analysis, the rate of steroid-free remission at week 26 according to infliximab through levels in patients treated with infliximab alone or in combination with azathioprine (AZA) were similar for each drug quartile[9, 10]. These results suggest that it is drug concentration, not combination therapy, that is associated with clinical outcomes.

TDM including the monitoring of drug levels and ADA (anti-drug antibodies) titers during treatment can improve care by dose and schedule optimization and clinical outcomes improvement. In addition, TDM can provide cost savings benefits to patients and healthcare systems. A cost reduction between 28 and 34% based on patient data or simulations was observed in the groups utilizing TDM in their clinical practice strategy[11, 12].

So far only low-quality evidence supports the role of reactive therapeutic drug monitoring to guide changes in anti–tumor necrosis factor (TNF) therapy in patients with active inflammatory bowel disease. Guidelines have been published by the American Gastroenterology Association (AGA) and consist in 5 recommendations for anti-TNFs drugs and thiopurine but not for vedolizumab and ustekinumab due to the lack of data. AGA conditionally recommend (quality of evidence: low evidence) the use of reactive TDM to guide treatment changes in patients with active IBD on maintenance therapy who are being treated with anti-TNF agents or thiopurines[9].

Proactive TDM, which consists of the measurement of trough levels in remission, is still a matter of debate. The role for proactive TDM of infliximab has been explored in the TAXIT and TAILORIX studies, but superiority over symptom-based dose optimization has not been demonstrated in short term prospective studies. The TAXIT study showed that at 1 year, patients in the no routine TDM group had higher rates of ADA and undetectable infliximab trough levels. This presumably may increase the risk of disease flares and drug failure. However, the role of proactive TDM has not been defined because of the limited duration of follow up in the TAXIT study[13, 14]. Though, more recent retrospective studies have revealed that performing proactive TDM of infliximab or adalimumab may be associated with better long-term outcomes at more than 1 year follow-up[15], lower risk of treatment failure, greater drug persistence and fewer IBD-related hospitalizations compared to standard of care or reactive testing alone.[15-18].

Insufficient data concerns TDM during vedolizumab therapy, however drug levels at week 6 of approximately >20 µg/ml have been shown to be associated with improved clinical outcomes, including subsequent mucosal healing rates during maintenance and avoiding the need of dose escalation due to lack of response[19].

Few evidences have been reported for ustekinumab (UST) as well showing that drug concentrations from 3.2 to 3.9 µg/mL had numerically increased rates of remission at 8 weeks after induction, but this was not significant. A clear association among clinical remission, CRP normalization, and endoscopic response with UST concentration was found in the maintenance UST study[20].

Loss of response, immunogenic reactions and the rising cost of treatments are driving the need for more personalized and cost-effective approaches to IBD management[11, 20, 22].

Loss of response to immunosuppressants or biologics occurs as non-immune mediated or immune-mediated mechanism. Non-immune-mediated pharmacokinetic failure correlated with subtherapeutic trough concentrations in the absence of ADA. Typically the cause is a rapid drug clearance in presence of an inflammatory state. Immune-mediated pharmacokinetic failure occurs in patients who have low or undetectable trough concentrations in the presence of ADA. Neutralizing ADA are causative of this kind of failure[1].

Currently, there are many commercial assays available to test trough concentrations and ADA but none is universally used in clinical practice. Different methods to measure trough concentrations are relatively comparable in terms of specificity, accuracy, and reproducibility while variability exists for assays assessing ADA.

UTILITY OF POC DEVICES FOR TDM IN CLINICAL PRACTICE

The majority of assays utilized for TDM are time-consuming and don't offer real time results that could help managing therapies during clinical assessment. Moreover they require repeated patient appointments and the collection of a determinate number of samples from different patients before a batch can be processed in the laboratory, delaying several days until clinicians are reported and thus, the decision-making[23].

Therefore, the availability of a point of care test (POCT) for TDM is of importance in clinical practice. The main features of a POCT for TDM in clinical practice should be:

- Fast results (20-30 minutes)
- Used at the point of care[22]
- Fully decentralized (if possible)[24]
- Drug levels: Quantitative
- ADA: Qualitative could be acceptable

Point of care devices may be a helpful tool for the early follow up of patients in the induction phase and also during the maintenance phase allowing physicians to optimize the therapies before the next dose. An optimal POCT should measure not only drug levels but also ADA titers and in the next future might be associated to biomarker detection.

CONCLUSION

TDM is useful for guiding the treatment of IBD patients with anti-TNFs drugs. Reactive TDM is currently recommended by AGA to guide decision making of therapy changes in patients with active IBD on maintenance therapy, while proactive TDM is still under debate. Several studies have demonstrated that it is during the induction phase when TDM is more important.

POC devices for TDM can be clinically useful and beneficial in the clinical practice because they allow for immediate appropriate management of IBD patients in the induction and maintenance therapy. POCT serve as a tool in clinical practice to make decisions in real time that could facilitate proactive TDM. Furthermore, the use of POCT in clinical practice might help decision-making such as increasing or decreasing drug dosage, switch out of class and also stopping immunomodulator in patients on combination therapy.

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References

1. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, and Singh S; on behalf of American Gastroenterological Association Institute Clinical Guidelines Committee, American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology 2017;153:827–834.
2. Sandborn WJ, Hanauer SB, Rutgeerts PJ, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II Trial. Gut 2007;56:1232–9.
3. Allez M, Karmiris K, Louis E, et al. Report of the ECCO pathogenesis workshop on anti-TNF therapy failures in inflammatory bowel diseases: definitions, frequency and pharmacological aspects. J Crohns Colitis. 2010 Oct;4(4):355-66.
4. Papamichael K, Cheifetz AS. Use of anti-TNF drug levels to optimise patient management. Frontline Gastroenterol. 2016 Oct;7(4):289-300.
5. Moore C, Corbett G, Moss AC. Systematic review and meta-analysis: serum infliximab levels during maintenance therapy and outcomes in inflammatory bowel disease. J Crohns Colitis. 2016;10:619–625.
6. Paul S, Moreau AC, Del Tedesco E et al. Pharmacokinetics of adalimumab in inflammatory bowel diseases: a systematic review and meta-analysis. Inflamm Bowel Dis. 2014 Jul;20(7):1288-95.
7. Cornillie F, Hanauer SB, Diamond RH, et al. Post induction 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. 2014;63:1721–1727.
8. Baert F, Kondragunta V, Lockton S, et al. Antibodies to adalimumab are associated with future inflammation in Crohn's patients receiving maintenance adalimumab therapy: a post hoc analysis of the Karmiris Trial. Gut. 2016;65:1126–1131.
9. Vande Casteele N, Herfarth H, J. K, Katz J, et al. American Gastroenterological Association Technical Review on the Role of Therapeutic Drug Monitoring in the Management of Inflammatory Bowel Diseases. Gastroenterology. 2017 Sep;153(3):835-857.e6.

10. Colombel JF, Adedokun OJ, Gasink C et al. Higher levels of infliximab may alleviate the need of azathioprine comedication in the treatment of patients with CD: a sonic post HOC analysis. DDW 2017. Chicago. Gastroenterology . 2017;S37–S38.)

11. Martelli L, Olivera P, Roblin X, et al. Cost-effectiveness of drug monitoring of anti-TNF therapy in inflammatory bowel disease and rheumatoid arthritis: A systematic review. J Gastroenterol. 2017 Jan;52(1):19-25.

12. Kopylov et al. (2014). Therapeutic drug monitoring in inflammatory bowel disease. Ann Gastroenterol. 2014;27(4):304-312.

13. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology 2015;148:1320-1329.

14. D'Haens GR, Vermeire S, Lambrecht G, et al. 692 Drug-level based dosing versus symptom-based dose adaptation in patients with Crohn's disease: a prospective, randomized multicenter study (TAILORIX). Gastroenterology. 2016;150(4), Supplement_1, Page S143.

15. Vaughn BP, Martinez-Vazquez M, Patwardhan VR, et al. Proactive therapeutic concentration monitoring of infliximab may improve outcomes for patients with inflammatory bowel disease: results from a pilot observational study. Inflamm Bowel Dis. 2014 Nov;20(11):1996-2003.

16. Papamichael K, Vajravelu RK, Vaughn BP, et al. Proactive Infliximab Monitoring Following Reactive Testing is Associated With Better Clinical Outcomes Than Reactive Testing Alone in Patients With Inflammatory Bowel Disease. J Crohns Colitis. 2018 Jun 28;12(7):804-810.

17. Papamichael K, Juncadella A, Wong D, et al. Proactive therapeutic drug monitoring of adalimumab is associated with better long-term outcomes compared to standard of care in patients with inflammatory bowel disease. J Crohns Colitis. 2019 Aug 14;13(8):976-981.

18. Burgess CJ, Reilly C, Steward-Harrison L, Balouch F, Lewindon PJ. Utility of proactive infliximab levels in paediatric Crohn's disease. Arch Dis Child. 2018 Jun 27. pii: archdischild-2018-315100.

19. Mark G. Ward, Miles P. Sparrow and Xavier Roblin. Therapeutic drug monitoring of vedolizumab in inflammatory bowel disease: current data and future directions. Ther Adv Gastroenterol 2018, Vol. 11: 1–10

20. Adedokun OJ, Xu Z, Gasink C, et al. Pharmacokinetics and exposure response relationships of ustekinumab in patients with Crohn's disease. Gastroenterology. 2018. pii:S0016-5085(18)30111–2.

21. Melmed GY, Irving PM, Jones J, et al. Appropriateness of Testing for Anti–Tumor Necrosis Factor Agent and Antibody Concentrations, and Interpretation of Results. Clin Gastroenterol Hepatol. 2016 Sep;14(9):1302-9.

22. Cheifetz.A. Overview of Therapeutic Drug Monitoring of Biologic Agents in Patients With Inflammatory Bowel Disease. Gastroenterol Hepatol (N Y). 2017 Sep;13(9):556–559.

23. Facchin S, Buda A, Cardin R, et al. P475 Rapid point-of-care anti-drug antibodies measurement correlates with standardised T tests and facilitate a proactive therapeutic drug monitoring approach in IBD patients on anti-TNF-α maintenance therapy. Journal of Crohn's and Colitis, Volume 13, Issue Supplement_1, March 2019, Pages S349–S350, https://doi.org/10.1093/ecco-jcc/jjy222.599

24. Ametzazurra A, Rivera N, Hernández A.M, et al. P503 Rapid point-of-care monitoring of

anti-infliximab antibodies in patients with inflammatory bowel disease treated with the reference infliximab or CT-P13 in routine clinical practice, Journal of Crohn's and Colitis, Volume 11, Issue suppl_1, 1 February 2017, Pages S335–S336, https://doi.org/10.1093/ecco-jcc/jjx002.627.

Articles

UTILITY OF POC DEVICE FOR THE ASSESSMENT OF ANTI-DRUG ANTIBODIES IN CLINICAL PRACTICE FOR IBD PATIENTS TREATED WITH BIOLOGICS

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INTRODUCTION

The introduction of monoclonal antibodies (mAbs) for the treatment of inflammatory bowel disease (IBD) resulted in a better management of patients with IBD.[1] Indeed, they were demonstrated to be superior to conventional therapies, including steroids and thiopurines, in terms of safety and effectiveness.[2-4] However, a large number of patients either fail to respond initially (i.e. primary non-failure) or lose response to therapy (i.e. secondary failure) during the maintenance period of treatment. In particular, several studies showed that 10-30% of the patients do not respond to Infliximab (IFX) induction, whereas an annual rate of 10-20% of the initial IFX responders tend to stop due to loss of response.[5]

Among the several factors associated with poor treatment outcomes, low mAb exposure has been advocated to play a major role[6-12]. Indeed, it has been clearly established in the medical literature that patients with IFX primary failure have significantly lower serum trough levels of the drug compared to patients who achieve clinical response or remission. Moreover, it has been observed a clear positive correlation between IFX serum levels and rates of endoscopic improvement and remission, whereas undetectable IFX levels place patients at an increased risk of hospitalization and surgery. The interindividual variation in mAbs serum levels in IBD patients has been associated to various potential factors: body mass index, albumin serum concentration, gender, smoking and disease phenotype/activity are known to impact the pharmacokinetics and pharmacodynamics of mAbs, therefore, influencing the drug availability on the patients' serum; moreover, the immunogenicity of the drug and the consequent formation of antibodies able to neutral-

ize mAbs has been clearly correlated with low drug serum concentrations[7-13].Consequently, gastroenterologists have begun to use the monitoring of serum mAbs concentrations and the formation of anti-drug antibodies during therapy (Therapeutic Drug Monitoring, TDM) for the therapeutic decision-making process in the case of loss or suboptimal response to medical treatment[14, 15]. Moreover, TDM may also support mAbs de-escalation in case of supratherapeutic serum concentrations, enhancing the cost-effectiveness of the therapeutic process and avoiding unnecessary side effects[16].

Several methods for TDM have been developed, validated and made commercially available for their use in hospitals and laboratories. Some of them are able to measure both mAbs and antibodies to mAbs, whereas others are specific for one of these quantifications. Most of the available methods rely on an Enzyme-Linked Immunosorbent Assay (ELISA) technique[17]. Thus, they are time-consuming, require the collection of a determinate number of blood samples before a batch can be processed in the laboratory and do not provide real time results for the management of the patients during clinical assessment. In this context, the availability of a point of care test for TDM (POCT) represented an important step forward for improving the management of IBD patients in clinical practice[18]. In particular, POCs can be pivotal in the early follow up of patients in the induction phase and also during the maintenance phase because clinicians can make changes in the therapies before the next dose. We report here two cases that clearly illustrate the benefit from a POCT-driven management according to our experience with TDM.

CASE REPORT 1

A 63-year old man, with a previous diagnosis of severe Ulcerative Colitis (UC), with distal localization (diagnostic colonoscopy performed in May 2017) and on therapy with mesalamine and azathioprine for steroid-dependent disease (since January 2018), was referred to our IBD Unit in February 2019. In his medical history, he had arterial hypertension on medical therapy. The patient reported disease recurrence with rectal bleeding, diarrhea (>20 bowel movements) and abdominal pain. A colonoscopy was performed, showing a severe ulcerative pancolitis (Mayo 3). The patient was hospitalised and treated with IV steroids with only partial response. Therefore, we opted to start IFX treatment at the dose of 5mg/kg, but the clinical response after the first two infusions was not adequate (partial Mayo score passed from 12 to 8). ADA (anti-drug antibodies) measured by using the POCT device had a negative result (<23 AU) and the trough levels (TL) were low (2,27µg/mL). Thus, we opted to accelerate the infusion protocol administrating the third IFX dose after two weeks from the second one and then continuing with 5mg/kg every 4 weeks. The patient was revaluated after the 4th infusion and he had a good clinical response (Mayo score 4) with fecal calprotectin levels that decreased from 2015 µg/g to 842 µg/g. Moreover, he repeated ADA and TL assessment which confirmed the absence of antibodies against IFX (<23 AU) and the presence of TL in the normal range (>7.05 µg/mL). A colonoscopy performed at 6 months after IFX initiation showed a clear and marked endoscopic response (Mayo 1). At the last follow-up visit, the patient was on IFX therapy at a standard dose dose (5mg/kg every 8 weeks) and on colectomy-free disease remission.

CASE REPORT 2

A 31-year old woman, with a previous diagnosis of ankylosing spondylitis and recurrent uveitis treated with Etanercept, was referred to our IBD Unit in September 2018 because of new onset of diarrhea and abdominal pain. Ileo-colonscopy and small bowel magnetic resonance imaging revealed a Crohn's disease with ileo-cecal and rectal involvement, without strictures or fistulas. The patient stopped Etanercept and started Infliximab therapy at the dose of 5 mg/kg every 8 weeks with clinical (Harvey bradshaw index decreased from 10 to 5) and biochemical response (reduction of CRP from 2.1 mg/100ml to 0.3 mg/100ml and fecal calprotectin from 1382 µg/g to 452 µg/g). After 8 months of treatment, according to current Organization for the Study of Inflammatory Bowel Diseases (IOIBD) suggestions[19], disease assessment was repeated by means of colonoscopy which showed persistence of disease activity at the rectum (i.e. deep ulcers), whereas the ileo-cecal involvement was markedly reduced. The PCR was within the normal values and fecal calprotectin was 295 µg/g. ADA measured by using the POCT device had a positive result (>23 AU) and the trough levels (TL) were low (1,87µg/mL). Therefore, we opted to increase IFX treatment at the dose of 10mg/kg every 8 weeks and to add Azathioprine at low dose (50mg/day) in order to neutralize the immunogenicity to the drug, and we repeated the colonoscopy after 6 months. The endoscopic examination showed a clear and marked endoscopic response, with complete disappearance of the ulcers and only the presence of mild erythema was found. Also, the ADA were measured by using the POCT device with a negative result (<23 AU) and the trough levels (TL) were normal (5,52µg/mL). At the last follow-up visit, the patient was on IFX therapy at high dose (10mg/kg every 8 weeks) and fecal calprotectin was 59 ug/g.

DISCUSSION:

Monoclonal antibodies against the tumour necrosis factor have an important role in the management of IBD. However, the response rate of patients to these therapies is far from perfect, probably due to many factors including the pharmacokinetics (PK) of the drugs. As understanding of PK of these agents improves, new therapeutic algorithms for their use will develop. It is now clear that the development of ADA and low serum drug concentrations are associated with worse clinical, biochemical and endoscopic outcomes. Moreover, since current therapeutic options in case of infliximab or adalimumab failures remain limited, particular attention should be paid to enhance the utility and improve the capability of these drugs to be effective. In this particular context, the POC devices for TDM can be clinically useful and beneficial in the clinical practice because they permit us to immediately modify our management approach during the induction and maintenance therapy for our patients, as our clinical cases clearly showed. POCT may serve as a tool in clinical practice to make decisions in real time, facilitating a proactive TDM and enhancing the effectiveness of current IBD treatments.

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References

1. Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: Practical insights. *Nat Rev Gastroenterol Hepatol*. 2015;12(9):537-545.
2. Mao EJ, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalisation and surgery in Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther*. 2017;45(1):3-13.
3. Cholapranee A, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. *Aliment Pharmacol Ther*. 2017;45(10):1291-1302.
4. Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis. *Aliment Pharmacol Ther*. 2018;47(2):162-175.
5. Schnitzler F, Fidder H, Ferrante M, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: Results from a single-centre cohort. *Gut*. 2009;58(4):492-500.
6. O.J. A, W.J. S, B.G. F, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. *Gastroenterology*. 2014;147(6):1296-1307.
7. Brandse JF, Mathôt RA, van der Kleij D, et al. Pharmacokinetic Features and Presence of Antidrug Antibodies Associate With Response to Infliximab Induction Therapy in Patients With Moderate to Severe Ulcerative Colitis. *Clin Gastroenterol Hepatol*. 2016;14(2):251-258.
8. Seow CH, Newman A, Irwin SP, Steinhart AH, Silverberg MS, Greenberg GR. Trough serum infliximab: A predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. *Gut*. 2010;59(1):49-54.
9. Casteele N Vande, Khanna R, Levesque BG, et al. The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease. *Gut*. 2015;64(10):1539-1545.
10. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology*. 2015;148(7):1320-1329.
11. Bodini G, Giannini EG, Savarino V, et al. Infliximab trough levels and persistent vs transient antibodies measured early after induction predict long-term clinical remission in patients with inflammatory bowel disease. *Dig Liver Dis*. 2018;50(5):452-456.
12. Bodini G, Giannini EG, De Maria C, et al. Anti-TNF therapy is able to stabilize bowel damage progression in patients with Crohn's disease. A study performed using the Lémann Index. *Dig Liver Dis*. 2017;49(2):175-180.
13. Fasanmade AA, Adedokun OJ, Ford J, et al. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. *Eur J Clin Pharmacol*. 2009;65(12):1211-1228.
14. Strik AS, Bots SJA, Dhaens G, Löwenberg M. Optimization of anti-TNF therapy in patients with Inflammatory Bowel Disease. *Expert Rev Clin Pharmacol*. 2016;9(3):429-439.
15. O'Toole A, Moss AC. Optimizing Biologic Agents in Ulcerative Colitis and Crohn's Disease. *Curr Gastroenterol Rep*. 2015;17(8).

16. Williet N, Paul S, Peyrin-Biroulet L, Roblin X. Pharmacokinetics of Infliximab and Reduction of Treatment for Inflammatory Bowel Diseases. *Dig Dis Sci*. 2016;61(4):990-995.
17. Vermeire S, Dreesen E, Papamichael K, Dubinsky MC. How, When, and For Whom Should We Perform Therapeutic Drug Monitoring? *Clin Gastroenterol Hepatol*. 2019.
18. Strik AS, Wang YMC, Ruff LE, Yashar W, Messmer BT, Mould DR. Individualized Dosing of Therapeutic Monoclonal Antibodies—a Changing Treatment Paradigm? *AAPS J*. 2018;20(6).
19. L. P-B, W. S, B.E. S, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. *Am J Gastroenterol*. 2015;110(9):1324-1338.

TRENDING TOPICS

COMPARISON STUDIES BETWEEN POC DEVICES AND ELISA ASSAYS FOR THE DETECCION OF ANTI-INFLIXIMAB ANTIBODIES

P605 RAPID DETECTION OF ANTI-INFLIXIMAB ANTIBODIES IN INFLAMMATORY BOWEL DISEASE PATIENTS TREATED WITH THE REFERENCE BIOLOGIC OR THE BIOSIMILAR CT-P13: PERFORMANCE COMPARISON WITH ELISA.

Fiorino G., Ametzazurra A., Nagore D., Hernández A.M., Torres N., Radice S., Gilardi D., Correale C., Allocca M., Furfaro F., Alfieri M., Pascual J., Recalde X., Martínez A., Danese S.
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https://doi.org/10.1093/ecco-jcc/jjx002.729

SA 1888 RAPID DETECTION OF ANTI-INFLIXIMAB ANTIBODIES IN INFLAMMATORY BOWEL DISEASE PATIENTS TREATED WITH THE REFERENCE BIOLOGIC OR THE BIOSIMILAR CT-P13: PERFORMANCE COMPARISON WITH ELISA

Fiorino G, Ametzazurra A, Nagore D, Hernández AM, Torres N, Radice S, Gilardi G, Correale C, Allocca M, Furfaro F, Alfieri MF, Pascual J, Recalde X, Martínez A, Danese S.
Gastroenterology, April 2017 Volume 152, Issue 5, S384.
https://www.gastrojournal.org/article/S0016-5085(17)31523-8/fulltext

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P554 POINT OF CARE DETECTION OF ANTI-INFLIXIMAB ANTIBODIES IN INFLAMMATORY BOWEL DISEASE PATIENTS TREATED WITH THE BIOSIMILAR SB2: PERFORMANCE COMPARISON WITH ELISA

R. Atreya, H. Schmitt, S. Fischer, M. F. Neurath, X. Rekalde, D. Nagore, A. Ametzazurra.
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PROACTIVE TDM OF ANTI-DRUG ANTIBODIES WITH POC DEVICES

P475 RAPID POINT-OF-CARE ANTI-DRUG ANTIBODIES MEASUREMENT CORRELATES WITH STANDARDIZED T TESTS AND FACILITATE A PROACTIVE THERAPEUTIC DRUG MONITORING APPROACH IN IBD PATIENTS ON ANTI-TNF-A MAINTENANCE THERAPY

S. Facchin*, A. Buda, R. Cardin, R. D'Incà, F. Zingone, N. Agbariah, E. Savarino.
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Journal of Crohn's and Colitis, Volume 11, Issue suppl_1, 1 February 2017, Pages S335–S336.
https://doi.org/10.1093/ecco-jcc/jjx002.627

SA 1912 RAPID POINT-OF-CARE MONITORING OF ANTI-INFLIXIMAB ANTIBODIES IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE TREATED WITH THE REFERENCE INFLIXIMAB OR CT-P13 IN ROUTINE CLINICAL PRACTICE.

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Gastroenterology, April 2017 Volume 152, Issue 5, S391.
https://www.gastrojournal.org/article/S0016-5085(17)31547-0/fulltext

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FRI0195 POINT-OF-CARE MONITORING OF ANTI-INFLIXIMAB ANTIBODIES IN PATIENTS TREATED WITH THE REFERENCE INFLIXIMAB OR CT-P13 IN ROUTINE CLINICAL PRACTICE.

Ametzazurra A, Rivera N, Balsa A, MP Arreba, E Ruiz, C Plasencia, J Ortiz, D Pascual-Salcedo, MC Muñoz, C De Aysa, MJ Allande, N Torres, AM Hernández, X Recalde, A Martínez, D Nagore.
Annals of the Rheumatic Diseases 2017;76:555.
https://ard.bmj.com/content/76/Suppl_2/555.2

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