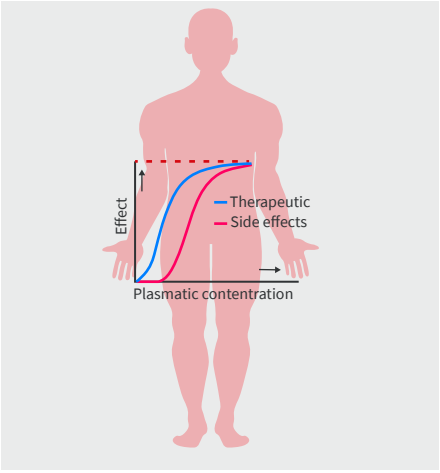
Mistakes in therapeutic drug monitoring of biologics in IBD and how to avoid them

Konstantinos Papamichail and Adam S. Cheifetz

Biological therapy has revolutionised the treatment of moderate to severe inflammatory bowel disease (IBD), namely Crohn's disease (CD) and ulcerative colitis (UC). However, up to one-third of patients with IBD are primary non-responders, and up to half can lose response over time.[1] These unwanted outcomes can be explained by either pharmacodynamic (mechanistic failure) or pharmacokinetic (PK) issues with or without the development of anti-drug antibodies (ADA), so-called immunogenicity.[1] Reactive therapeutic drug monitoring (TDM), defined as the measurement of drug concentrations and anti-drug antibody (ADA) levels in the setting of primary non-response (PNR) or secondary loss of response (SLR), can help to explain better and manage these unwanted outcomes. However, it would make sense to try to prevent PNR and SLR by routinely measuring drug concentrations and ADA to achieve and maintain a targeted therapeutic drug concentration, the so-called proactive TDM.

Here we discuss some common mistakes and significant errors to avoid when utilising TDM of biologics in patients with IBD. The discussion is based on evidence, whenever possible, and our clinical experience and perception of the field.



Mistake 1 Only doing empiric dose escalation and not performing reactive TDM in patients with a non-primary non-response or secondary loss of response to biological therapy

Reactive TDM has rationalised the management of PNR or SLR by identifying the underlying mechanisms of these unfavourable outcomes. Reactive TDM can help tailor and individualise treatment; for example, increasing the drug dose in patients with sub-therapeutic drug concentrations and undetectable or low-titer ADA. Testing for drug concentrations and ADA also would avoid giving more drugs to a patient with a mechanistic failure and adequate drug concentration. The latter would necessitate a switch in drug class.[2,3] Reactive TDM increases endoscopic remission rates and lessens hospitalisations compared to empiric treatment optimisation.[4] In addition, reactive TDM is more cost-effective than empiric drug optimisation based only on clinical symptoms.[5] Of note, the active disease should always be confirmed with objective measures of inflammation, including biomarkers, such as C-reactive protein (CRP) and faecal calprotectin, as well as endoscopy with histological evaluation.

Mistake 2 Failing to adequately optimise a previous biologic before changing to a new one

When utilising reactive TDM, a common mistake is abandoning treatment before optimising it. This is important as subsequent biologic therapies typically show less efficacy. It is most important when using anti-tumour necrosis factor (anti-TNF) therapy, specifically infliximab, as there are limited pharmacological options for some specific IBD phenotypes, such as perianal fistulising CD and acute severe ulcerative colitis. Of note, giving up on one anti-TNF due to adequate drug concentration suggests a mechanistic failure not just to that agent but all anti-TNFs. Thus, it is recommended that treatment discontinuation should not be considered until an infliximab or adalimumab concentration of at least 10-15 µg/ ml is achieved.[6] However, there may be occasions where these drug concentrations may not be attainable for various reasons, including very high drug clearance and insurance issues limiting dose intensification.

Mistake 3 Only doing reactive TDM and not utilising proactive TDM to optimise anti-TNF therapy

Cumulative evidence suggests that proactive TDM of anti-TNF therapy is associated with better outcomes than empiric treatment optimisation and/or reactive TDM. A recent meta-analysis, including retrospective studies and randomised controlled trials (RCTs), found that proactive TDM of anti-TNF therapy was associated with lower treatment failure rates than standard of care or reactive TDM. Moreover, proactive was associated with higher endoscopic remission rates than standard care.[7] A recent RCT regarding a biologic naïve paediatric population with CD who had responded to induction infliximab therapy showed that proactive TDM compared to clinically based dosing was superior regarding sustained corticosteroid-free clinical remission and endoscopic healing.[8] Other clinical scenarios that proactive TDM could efficiently guide clinical decisions are anti-TNF therapy de-escalation or even discontinuation and optimising infliximab monotherapy when combination therapy with an immunomodulator (IMM) is not an option due to patient preference or high risk of serious adverse

Cite this article as: Konstantinos Papamichail and Adam S. Cheifetz. Mistakes in therapeutic drug monitoring of biologics in IBD and how to avoid them. *UEG Education* 2023; 23: 12-18.
Konstantinos Papamichail is a Physician Scientist at the Center of Inflammatory Bowel Disease at Beth Israel Deaconess Medical Center and an Assistant Professor of Medicine at Harvard Medical School. **Adam S. Cheifetz** is the Director of the Center of Inflammatory Bowel Disease at Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215, US. and an Assistant Professor of Medicine at Harvard Medical School.
Illustrations: J. Shadwell
Correspondence to: kpapamic@bidmc.harvard.edu
Conflicts of interest: KP received lecture/speaker fees from Physicians Education Resource LLC and Grifols; scientific advisory board fees from ProciseDx Inc and Scipher Medicine Corporation; and serves as a consultant for Prometheus Laboratories Inc. **ASC** served as a consultant and or advisory board member for Janssen, Abbvie, Protagonist, Spherix, Artizan, Food is Good, Clario, Pfizer, Fresenius Kabi, Artugen, ProciseDx, Prometheus, Equillium, Samsung, Arena, Grifols, Bacainn, Bristol Myers Squibb, Takeda; unbranded speaker for BMS and Abbvie
Published online: 22 June, 2023.

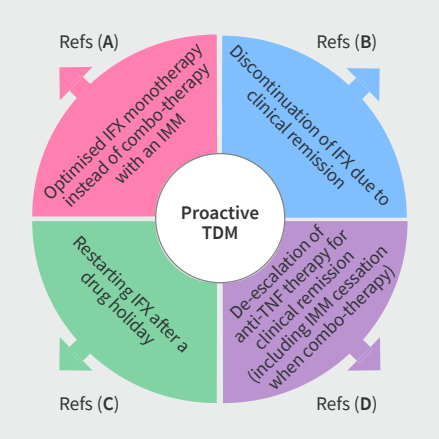


Figure 1 | Other potential applications of proactive therapeutic drug monitoring in clinical practice. TDM: therapeutic drug monitoring; IFX: infliximab; TNF: tumor necrosis factor; IMM: immunomodulators. Refs (**A**) 31,56 and 60-62,Refs (**B**) 63-67, Refs (**C**) 68-71 and Refs (**D**) 72-79.

events. Proactive TDM is also recommended after starting infliximab following a drug holiday (Figure 1).

Mistake 4 Using the same biologic drug concentration threshold for all patients

Optimal biologic drug concentrations to target can vary based on treatment phase, IBD phenotype, TDM assay used, targeted therapeutic outcome and route of drug administration (Figure 2). Most studies suggest that higher drug concentrations are needed to achieve more stringent therapeutic outcomes, including endoscopic and histologic healing. Recent data suggest that subcutaneous, compared to intravenous, administration of infliximab and vedolizumab produce multiple-fold higher serum drug concentrations due to PK differences.[9,10] Additionally, there may be discrepancies when measuring biologic drug concentrations among various assays, such as the enzyme-linked immunosorbent assay (ELISA), the homogenous mobility shift assay (HMSA) and point-of-care assays.[11-14] Importantly, higher drug concentrations are needed during the induction phase compared to the maintenance phase. Finally, higher drug concentrations are probably needed for patients with a more complicated phenotype, such as perianal fistulising CD.[15] Consequently, applying the "one-size-fits-all" concept when performing TDM for optimising biologics is a mistake. A more personalised approach is needed.

Mistake 5 Failing to attempt to overcome immunogenicity due to misinterpretation of anti-drug antibody titers

Misinterpretation of ADA titers is a common mistake, mainly as titers are often described in different units across various assays, and these results cannot be directly compared (Table 1). A study assessing three commercially available ELISAs for the measurement of ATI showed that a clinically relevant cut-off titer of 200 ng/mL, previously associated with lack of response to treatment optimisation,[16] when evaluated with the LISA-TRACKER assay (Theradiag) was equivalent to approximately 60 ng/mL on the RIDASCREEN assay (r-biopharm) and between 22.9 and 41 AU/mL on the Promonitor assay (Grifols).[17] To make it even more complicated, these ADA titers have to be evaluated in the setting of a drug-tolerant versus a drug-sensitive assay, the latter of which can only measure ADA when drug concentrations are undetectable. As a result, physicians may wrongly interpret a result of being a high ADA titer and switch medications. If interpreted correctly, an attempt to overcome immunogenicity by dose optimisation and/or adding an IMM should be considered. It is critical to understand what high-level ADA are for each assay a provider may utilise. An association of antibody to infliximab titers evaluated with different assays with therapeutic outcomes in IBD is described in Table 1.

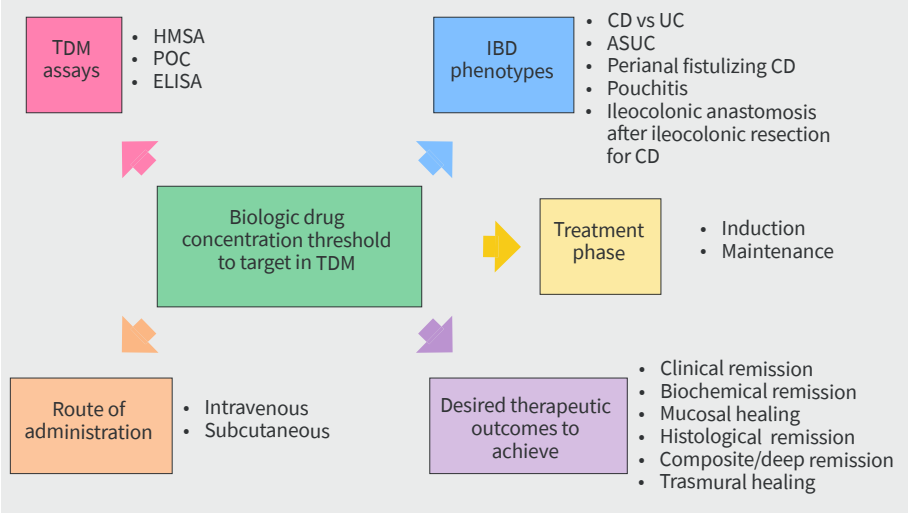


Figure 2 | Factors associated with biologic drug concentrations threshold to target in therapeutic drug monitoring. TDM: therapeutic drug monitoring; HMSA: homogenous mobility shift assay; POC: point-of-care; ELISA: enzyme-linked immunosorbent assay; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis, ASUC: acute severe ulcerative colitis.

Mistake 6 Neglecting to use proactive TDM when de-escalation of anti-TNF therapy is considered due to clinical remission

Growing data suggest that proactive TDM can efficiently guide clinical decisions when anti-TNF therapy de-escalation is considered in patients with IBD due to clinical remission, including lengthening the dosing intervals, decreasing the dose, and stopping the IMM in case of combination therapy. The TAXIT RCT showed that dose reduction in patients with IBD and infliximab trough concentrations higher than 7 µg/mL was safe (no flares or increase of inflammatory markers) and cost-effective.[18] A France study demonstrated that TDM-based infliximab de-escalation (drug concentrations higher than 7 µg/ml) in patients with IBD and clinical remission was associated with less relapse compared to empiric dose de-escalation based only on symptoms.[19] The same group showed that proactive TDM is important after infliximab de-escalation to maintain an adequate trough concentration.[20] A study from Drobne and colleagues found that infliximab concentrations ≥5 µg/ml at the time of IMM withdrawal are related to long-term response in patients with CD after discontinuation of IMMs.[21] Regarding adalimumab, concentrations higher than 12.2 µg/mL were associated with successful de-escalation in patients with IBD.[22] We would like to point out that the 'one-size-fits-all' also should not apply when proactive TDM is used for treatment de-escalation. Higher drug concentration thresholds may be required for patients with a more complicated IBD phenotype, such as perianal fistulising CD. In the PRECISION RCT, three patients had a recurrence of an old perianal fistula after dosing de-escalation of infliximab based on proactive TDM using a PK dashboard for supposing supra-therapeutic drug concentrations of >3 µg/ml. As previously shown, supra-therapeutic infliximab concentrations are probably higher than 15-20 µg/ml for this IBD population.[15] Furthermore, individual patients may require different drug concentration thresholds.

Mistake 7 Assuming that TDM of biologics is not useful during induction therapy

TDM during induction may be even more critical than during the maintenance phase as patients typically have the active disease (with low albumin

TDM assay	ATI units	Assay type	ATI titer	Therapeutic outcome	Refs
ELISA	ng/ml	RIDASCREEN (r-biopharm)	<282	Higher success rate of treatment optimization	40
			>222	Unable to overcome immunogenicity	41
		LISA-TRACKER (Theradiag)	>200	Lack of response to treatment optimization	42
	U/ml	IDKMonitor (Immundiagnostik)	<10	Recapture clinical remission	43
			>30	Non-response to dose intensification	44
	µg/ml	Prometheus Laboratories	>8	Shorter clinical response	45
		Janssen (in house)	>4.9	SLR	46
		Anti-human lambda chain antibody (in house)	≥4	Treatment discontinuation	47
			>9	Longer duration of response when anti-TNF agents are switched than when dosage is increased for SLR	48
			>4.3[a]	PNR at week 14	49
			>2.5[b]		
HMSA	U/ml	Anser IFX (Prometheus Laboratories)	<3.1	Biochemical remission (CRP≤5 mg/L)	50
			≥10	Immunogenicity to adalimumab	51
			<8.8	Drug retention	52
			>9.1	Failure of dose intensification after SLR	53
			>12	Higher risk for surgery	54
			<3.3	Post-adjustment endoscopic remission	55
			>9.1	Drug discontinuation / infusion reactions	56
			≤8.5	Drug concertation ≥5µg/mL and no ATI	57
			>10	Not able to overcome	58
ECLIA	ng/ml	DoseASSURE IFX (Esoterix-Labcorp)	<197	ATI reversal	59
			>23	Increased drug clearance	

[a]at week 2; [b]at week 6. TDM: therapeutic drug monitoring; ATI: antibodies to infliximab; ELISA: enzyme-linked immunosorbent assay; HMSA: homogeneous mobility shift assay; IMM: immunomodulator; CRP: C-reactive protein; SLR: secondary loss of response; PNR: primary non-response.

Table 1 | Association of antibody to infliximab titers evaluated with different assays with therapeutic outcomes in patients with IBD.

and high CRP levels) and increased drug clearance when an anti-TNF is initiated.

High drug clearance puts patients at higher risk of early ADA formation.[23] A prospective study in UC showed that ATI could be developed as early as day 18 during induction therapy leading to treatment failure in patients with moderate to severe UC.[24] Numerous studies have found that higher biological drug concentrations during and early after induction therapy are associated with higher rates of favourable therapeutic outcomes.[25] A prospective study using a PK dashboard to guide infliximab dosing early during induction therapy proactively recognised the need for early accelerated infliximab dosing in 80% of patients who started on 5 mg/kg and 60% of patients who started on a 10 mg/kg dose.[26] Of note, adherence to the forecasts of the PK dashboard for the third, mainly the fourth, infliximab infusion was associated with higher treatment durability and decreased formation of ADAs.[26] A recent study showed that early treatment optimisation based on proactive TDM compared to standard induction infliximab therapy was associated with higher combined corticosteroid-free clinical and biomarker remission (CRP < 5 mg/L) at week 52 (83% vs 40%, respectively, p<0.001) in a paediatric population with IBD.[27]

Mistake 8 Failing to apply therapeutic strategies to prevent immunogenicity in patients prone to develop anti-drug antibodies

Identifying patients prone to develop ADA (Figure 3) is vital, as immunogenicity has been associated with treatment failure and drug discontinuation.[28] In this case, there is a need to use therapeutic strategies to prevent immunogenicity, such as combination therapy with an IMM or proactive TDM (especially in cases when combination therapy with IMM is not an option).[29,30] A recent meta-analysis showed that HLADQA1*05 variants were associated with increased risk of immunogenicity and SLR in patients with immune-mediated inflammatory disorders treated with anti-TNF therapy.[30] However, it seems that when proactive TDM is performed, the risk of immunogenicity and SLR is mitigated.[31-33] Proactive TDM could also be a valid therapeutic strategy to prevent ADA formation in paediatric patients with IBD and in patients with more severe diseases who typically have an increased drug clearance and a greater risk of inadequate drug exposure and immunogenicity including those with low albumin and high CRP levels.

Mistake 9 Not using pharmacokinetic dashboards, if available, when performing TDM

Cumulative evidence suggests that PK dashboards incorporating factors such as type of IBD, type of drug, sex, CRP, albumin, weight, concomitant IMM use, previous drug concentrations, and anti-drug antibodies to individualise dosing can improve therapeutic outcomes.[34] The PRECISION trial showed that proactive TDM using a PK dashboard led to a higher rate of sustained clinical remission after one year of follow-up than conventional dosing (88% vs 64%, respectively, p=0.017).[35] In addition, patients in the proactive TDM group had lower faecal calprotectin levels compared to the control group (47 mg/g vs 144 mg/g, respectively, p=0.031).[35] In a study by Juncosa et al., the clinical remission rate increased from 65.7% to 80.4% after implementing PK dashboard-guided dose adjustments in patients with IBD treated with infliximab.[36] In another real-world cohort, Dubinsky et al. demonstrated that nonadherence to PK-driven infliximab dosing recommendations was a risk factor for immunogenicity and treatment discontinuation.[26]

Mistake 10 Using different assays when performing TDM in the same patient

Preliminary data suggest that there may be quantitative and qualitative inconsistencies among different assays when evaluating drug concentrations, as previously shown between the

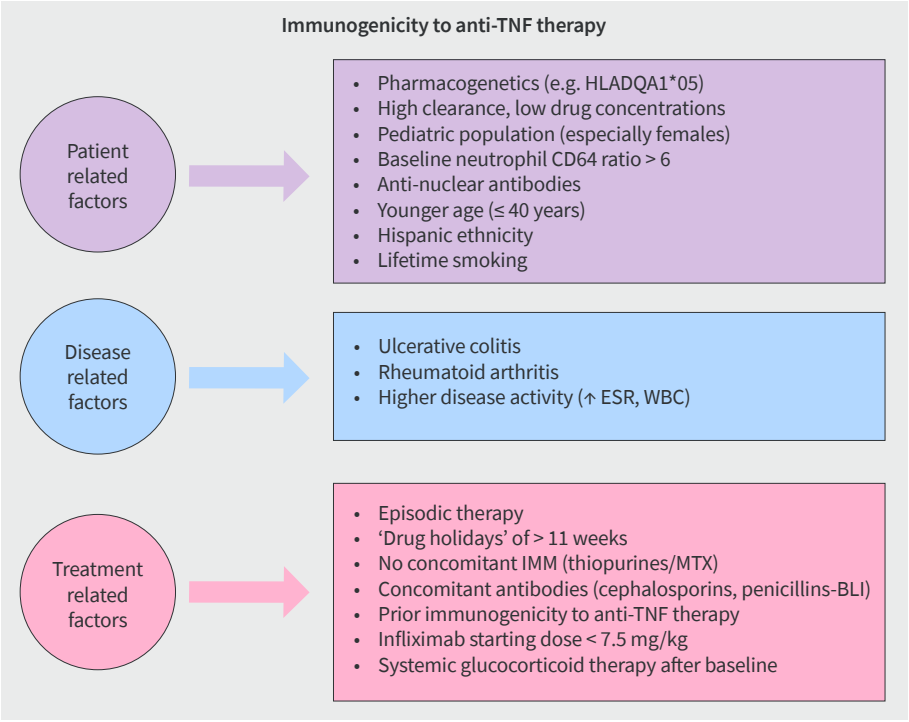


Figure 3 | Factors contributing to immunogenicity of anti-TNF therapy in IBD and other immune mediated inflammatory disorders. BLI: β-lactamase inhibitors; TNF: tumor necrosis factor; ADA: anti-drug antibodies; ESR: erythrocyte sedimentation rate; IMM: immunomodulators; WBC: white blood count; MTX: methotrexate. Refs 28, 31, 33, 47 and 80-94.

ELISA and the HMSA for infliximab, adalimumab and ustekinumab[12, 13] as well as the ELISA and point-of-care assays for adalimumab.[14] This may also be the case for different commercial kits using the same quantification method. For example, significant differences were found among different ELISA commercial kits for both infliximab[37] and golimumab.[11] Even most importantly, ADAs are not easy to correctly interpret as titers are often expressed in different units across different assays, such as the ELISA, the HMSA and the electrochemiluminescence immunoassay (ECLIA) (Table 1). A study from Leuven showed that an infliximab ADA titer cut-off of 8 µg/ml evaluated with a first-generation ELISA had a similar impact as the cut-off of 374 ng/ml measured with the second-generation ELISA and a cut-off of 119 ng/ml in the ready-to-use ELISA kit.[38] Consequently, ADA levels cannot be directly compared among assays and thresholds for low and high titers cannot be adequately defined. Discrepancies among assays could lead to inappropriate clinical decisions as these often rely on drug concentration thresholds to target and ADA titer cut-offs that can be overcome. It would make sense to use the same assay for each patient, at least until harmonisation of assays and units of measurement is feasible.[39] We recommend that physicians be very comfortable interpreting ADA in their chosen assay.

References

1. Fine S, Papamichael K, Cheifetz AS, et al. Etiology and management of lack or loss of response to anti-tumor necrosis factor therapy in patients with inflammatory bowel disease. *Gastroenterol Hepatol* (N Y) 2019; 15: 656-665.
2. Roblin X, Rinaudo M, Tedesco E, et al. Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases. *Am J Gastroenterol* 2014; 109: 1250-1256.
3. Yanai H, Lichtenstein L, Assa A, 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* 2015; 13: 522-530.
4. Kelly OB, Donnell SO, Stempak JM, et al. 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* 2017; 23: 1202–1209.
5. Marquez-Megias S, Nalda-Molina R, Sanz-Valero J, et al. Cost-effectiveness of therapeutic drug monitoring of anti-tnf therapy in inflammatory bowel disease: a systematic review. *Pharmaceutics* 2022; 14: 1009.
6. Cheifetz AS, Abreu MT, Afif W, et al. A Comprehensive Literature Review and Expert Consensus Statement on Therapeutic Drug Monitoring of Biologics in Inflammatory Bowel Disease. *Am J Gastroenterol* 2021; 116: 2014-2025.
7. Sethi S, Dias S, Kumar A, et al. Meta-analysis: the efficacy of therapeutic drug monitoring of anti-TNF-therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2022. Online ahead of print. http://doi.org/10.1111/apt.17313.
8. Kang B, J S Moon, Y J Lee, et al. Proactive dosing is superior to clinically based dosing in terms of endoscopic healing in paediatric patients with Crohn's disease receiving maintenance infliximab: A randomized controlled trial. *J Crohn's Colitis* 2023; 17(Supplement_1): i159.
9. Bergqvist V, Holmgren J, Klintman D, Marsal J. Real-world data on switching from intravenous to subcutaneous vedolizumab treatment in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2022;55:1389–1401.
10. Little RD, Ward MG, Wright E, et al. Therapeutic drug monitoring of subcutaneous infliximab in inflammatory bowel disease-understanding pharmacokinetics and exposure response relationships in a new era of subcutaneous biologics. *J Clin Med* 2022;11:6173.
11. Berger AE, Duru G, de Vries A, et al. Comparison of immunoassays for measuring serum levels of golimumab and antibodies against golimumab in ulcerative colitis: a retrospective observational Study. *Ther Drug Monit* 2019; 41: 459–66.
12. Papamichael K, Clarke WT, Vande Casteele N, et al. Comparison of assays for therapeutic monitoring of infliximab and adalimumab in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2021; 19: 839–841.
13. Verdon C, Vande Casteele N, Heron V, Germain P, Afif W. Comparison of serum concentrations of ustekinumab obtained by three commercial assays in patients with Crohn's disease. *J Can Assoc Gastroenterol* 2020; 4: 73–77.
14. Cherry M, Dutzer D, Nasser Y, et al. Point-of-care assays could be useful for therapeutic drug monitoring of IBD patients in a proactive strategy with adalimumab. *J Clin Med* 2020; 9: 2739
15. Yarur AJ, Kanagala V, Stein DJ, et al. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. *Aliment Pharmacol Ther* 2017; 45: 933-940.
16. Paul S, Tedesco E, Marotte H, et al. Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: a prospective study. *Inflamm Bowel Dis* 2013; 19: 2568-76.
17. West TA, Sam M, Toong C. Comparison of three commercially available ELISA assays for anti-infliximab antibodies. *Pathology* 2021; 53: 508-514.
18. 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: 1320-9.
19. Lucidarme C, Petitcollin A, Brochard C, et al. Predictors of relapse following infliximab de-escalation in patients with inflammatory bowel disease: The value of a strategy based on therapeutic drug monitoring. *Aliment Pharmacol Ther* 2019; 49: 147–54.
20. Petitcollin A, Brochard C, Siproudhis L, et al. Pharmacokinetic parameters of infliximab influence the rate of relapse after de-escalation in adults with inflammatory bowel diseases. *Clin Pharmacol Ther* 2019; 106: 605–15.
21. Drobne D, Bossuyt P, Breynaert C, et al. Withdrawal of immunomodulators after co-treatment does not reduce trough level of infliximab in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2015; 13: 514–521.
22. Aguas Peris M, Bosó V, Navarro B, et al. Serum Adalimumab Levels Predict Successful Remission and Safe Deintensification in Inflammatory Bowel Disease Patients in Clinical Practice. *Inflamm Bowel Dis* 2017; 23: 1454-1460.
23. Brandse JF, Mould D, Smeekes O, et al. A real-life population pharmacokinetic study reveals factors associated with clearance and immunogenicity of infliximab in inflammatory bowel disease. *Inflamm Bowel Dis* 2017; 23: 650–60.
24. Brandse JF, Mathot RA, van der Kleij D, et al. Pharmacokinetic features and presence of anti-drug antibodies associate with response to infliximab induction therapy in patients with moderate to severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2016; 14: 251–8.
25. Sparrow MP, Papamichael K, Ward MG, et al. Therapeutic drug monitoring of biologics during induction to prevent primary non-response. *J Crohns Colitis* 2020; 14: 542-556.
26. Dubinsky MC, Mendiolaza ML, Phan BL, et al. Dashboard-driven accelerated infliximab induction dosing increases infliximab durability and reduces immunogenicity. *Inflamm Bowel Dis* 2022; 28: 1375-1385.
27. Lawrence S, Faytrouni F, Harris RE, et al. Optimized Infliximab Induction Predicts Better Long-Term Clinical and Biomarker Outcomes Compared to Standard Induction Dosing. *J Pediatr Gastroenterol Nutr* 2022; 75: 601-607.

28. Bots SJ, Parker CE, Brandse JF, et al. Anti-drug antibody formation against biologic agents in inflammatory bowel disease: a systematic review and meta-analysis. *BioDrugs* 2021; 35: 715-733.
29. Fousekis FS, Papamichael K, Kourtis G, et al. The efficacy of immunomodulators in the prevention and suppression of anti-drug antibodies to anti-tumor necrosis factor therapy in inflammatory bowel disease. *Ann Gastroenterol* 2022; 35: 1-7.
30. Solitano V, Facciorusso A, McGovern DPB, et al. HLA-DQA1*05 genotype and immunogenicity to tumor necrosis factor-α antagonists: a systematic review and meta-analysis. *Clin Gastroenterol Hepato*l 2023 Apr 13:S1542-3565 (23) 00270-7. http://doi.org/10.1016/j.cgh.2023.03.044. Online ahead of print.
31. Spencer EA, Dubinsky MC, Dervieux T, et al. Failure to achieve target drug concentrations during induction and not HLA-DQA105 carriage is associated with anti-drug antibody formation in patients with inflammatory bowel disease. *Gastroenterology* 2022 May;162 (6): 1746-1748.e3. http://doi.org/10.1053/j.gastro.2022.01.009.
32. Fuentes-Valenzuela E, García-Alonso FJ, Maroto-Martín C, et al. Influence of HLADQA1*05 genotype in adults with inflammatory bowel disease and anti-TNF treatment with proactive therapeutic drug monitoring: a retrospective cohort study. *Inflamm Bowel Dis* 2023 Jan 7;izac259. http://doi.org/10.1093/ibd/izac259. Online ahead of print.
33. Colman RJ, Xiong Y, Mizuno T, et al. Antibodies-to-infliximab accelerate clearance while dose intensification reverses immunogenicity and recaptures clinical response in paediatric Crohn's disease. *Aliment Pharmacol Ther* 2022; 55: 593-603.
34. Papamichael K, Cheifetz AS. Optimizing therapeutic drug monitoring in inflammatory bowel disease: a focus on therapeutic monoclonal antibodies. *Expert Opin Drug Metab Toxicol* 2021; 17: 1423-1431.
35. Strik AS, Löwenberg M, Mould DR, et al. Efficacy of dashboard driven dosing of infliximab in inflammatory bowel disease patients; a randomized controlled trial. *Scand J Gastroenterol* 2021; 56:145-154.
36. Santacana Juncosa E, Rodríguez-Alonso L, Padullés Zamora A, et al. Bayes-based dosing of infliximab in inflammatory bowel diseases: Short-term efficacy. *Br J Clin Pharmacol* 2021; 87: 494-505.
37. Schmitz EMH, van de Kerkhof D, Hamann D, et al. Therapeutic drug monitoring of infliximab: performance evaluation of three commercial ELISA kits. *Clin Chem Lab Med* 2016;54: 1211-9.
38. Imbrechts M, Van Stappen T, Compernolle G, Tops S, Gils A. Anti-infliximab antibodies: how to compare old and new data? *J Pharm Biomed Anal* 2020; 177: 112842.
39. Papamichael K, Afif W, Drobne D, et al. Therapeutic drug monitoring of biologics in inflammatory bowel disease: unmet needs and future perspectives. *Lancet Gastroenterol Hepato*l 2022; 7: 171-185.
40. Dreesen E, Van Stappen T, Ballet V, et al. Anti-infliximab antibody concentrations can guide treatment intensification in patients with Crohn's disease who lose clinical response. *Aliment Pharmacol Ther* 2018; 47(3): 346–355. https://doi.org/10.1111/apt.14452
41. Van Stappen T., Vande Casteele N., Van Assche G., et al. Clinical relevance of detecting anti-infliximab antibodies with a drug-tolerant assay: post hoc analysis of the TAXIT trial. *Gut* 2018; 67(5): 818–826. https://doi.org/10.1136/gutjnl-2016-313071
42. Paul S, Del Tedesco E, Marotte H, et al. Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: a prospective study. *Inflamm Bowel Dis* 2013; 19(12): 2568–2576. https://doi.org/10.1097/MIB.0b013e3182a77b41
43. Tun GSZ, Robinson K, Marshall L, et al. The effect of infliximab dose escalation in inflammatory bowel disease patients with antibodies to infliximab. *Eur J Gastroenterol Hepatol* 2022; 34(3), 295–301. https://doi.org/10.1097/MEG.0000000000002289
44. Kim ES, Kwon Y, Choe YH, Kim MJ. Free antibodies-to-infliximab are biomarker for predicting the effect of dose intensification in pediatric Crohn's disease patients with secondary loss of response. *Therap Adv Gastroenterol* 2023;16. https://doi.org/10.1177/17562848231170948
45. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003; 348(7), 601–608. https://doi.org/10.1056/NEJMoa020888
46. Koga A, Matsui T, Takatsu N, et al. Trough level of infliximab is useful for assessing mucosal healing in Crohn's disease: a prospective cohort study. *Intest Res* 2018; 16 (2), 223. https://doi.org/10.5217/ir.2018.16.2.223
47. Tournier Q, Paul S, Williet N, et al. Early detection of anti-drug antibodies during initiation of anti-tumour necrosis factor therapy predicts treatment discontinuation in inflammatory bowel disease. *Aliment Pharmacol Ther* 2021; 53 (11), 1190–1200. https://doi.org/10.1111/apt.16333
48. Yanai H, Lichtenstein L, Assa A, et L. Levels of drug and antidrug antibodies are associated with outcome of interventions after loss of response to infliximab or adalimumab. *Clin Gastroenterol Hepatol* 2015; 13(3), 522–530.e2. https://doi.org/10.1016/j.cgh.2014.07.029
49. Bar-Yoseph H, Levhar N, Selinger L, et al. Early drug and anti-infliximab antibody levels for prediction of primary nonresponse to infliximab therapy. *Aliment Pharmacol Ther* 2018; 47: 212– 218. https://doi.org/10.1111/apt.14410
50. Vande Casteele N, 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. https://doi.org/10.1136/gutjnl-2014-307883
51. Vande Casteele N, Sandborn WJ, Feagan, BG, et al. Real-world multicentre observational study including population pharmacokinetic modelling to evaluate the exposure–response relationship of vedolizumab in inflammatory bowel disease: ERELATE Study. *Aliment Pharmacol Ther* 2022; 56: 463–476. https://doi.org/10.1111/apt.16937
52. Papamichael K, Vajravelu RK, Osterman MT, and Cheifetz, AS. Long-Term Outcome of Infliximab Optimization for Overcoming Immunogenicity in Patients with Inflammatory Bowel Disease. *Digest Dis Sci* 2018; 63 (3), 761–767. https://doi.org/10.1007/s10620-018-4917-7
53. Vande Casteele N, Gils A, Singh S, et al. Antibody response to infliximab and its impact on pharmacokinetics can be transient. *Am J Gastroenterol* 2013; 108(6), 962–971. https://doi.org/10.1038/ajg.2013.12
54. Zitomersky NL, Atkinson BJ, Fournier K, et al. Antibodies to infliximab are associated with lower infliximab levels and increased likelihood of surgery in pediatric IBD. *Inflamm Bowel Dis* 2015; 21 (2):307-314. https://doi.org/10.1097/MIB.0000000000000284
55. Kelly OB, Donnell SO, Stempak JM, et al. 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* 2017; 23 (7), 1202–1209. https://doi.org/10.1097/MIB.0000000000001126
56. Lega S, Phan BL, Rosenthal CJ, et al. Proactively Optimized Infliximab Monotherapy Is as Effective as Combination Therapy in IBD. *Inflamm Bowel Dis* 2019; 25 (1), 134–141. https://doi.org/10.1093/ibd/izy203
57. Battat R, Lukin D, Scherl EJ, et al. Immunogenicity of Tumor Necrosis Factor Antagonists and Effect of Dose Escalation on Anti-Drug Antibodies and Serum Drug Concentrations in Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2021; 27(9), 1443–1451. https://doi.org/10.1093/ibd/izaa313
58. Cohen RZ, Schoen BT, Kugathasan S, and Sauer CG. Management of Anti-drug Antibodies to Biologic Medications in Children With Inflammatory Bowel Disease. *J Ped Gastroenterol Nutr* 2019; 69 (5), 551–556. https://doi.org/10.1097/MPG.0000000000002440
59. Colman RJ, Mizuno T, Fukushima K, et al. Real world population pharmacokinetic study in children and young adults with inflammatory bowel disease discovers novel blood and stool microbial predictors of vedolizumab clearance. *Aliment Pharmacol Ther* 2023; 57: 524–539. https://doi.org/10.1111/apt.17277
60. Drobne D, Kurent T, Golob S, et al. Optimised infliximab monotherapy is as effective as optimised combination therapy, but is associated with higher drug consumption in inflammatory bowel disease. *Aliment Pharmacol Ther* 2019;49 (7):880–889.
61 Colombel J-F, Adedokun OJ, Gasink C, et al. Combination Therapy With Infliximab and Azathioprine Improves Infliximab Pharmacokinetic Features and Efficacy: A Post Hoc Analysis. *Clin Gastroenterol Hepatol* 2019; 17: 1525–1532.
62 Solitano V, Facciorusso A, Dermot P B McGovern DPB, et al. HLA-DQA1-05 Genotype and Immunogenicity to Tumor Necrosis Factor-α Antagonists: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2023 Apr 13;S1542-3565 (23) 00270-7. doi: 10.1016/j.cgh.2023.03.044. Online ahead of print.
63 Louis E, Mary J-Y, Vernier-Massouille G, et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology* 2012; 142: 63-70.
64 Papamichael K, Casteele NV, Ann Gils A, et al. Long-term outcome of patients with Crohn's disease who discontinued infliximab therapy upon clinical remission *Clin Gastroenterol Hepatol* 2015; 13: 1103–1110.
65 Ben-horin S, Chowers SY, Ungar B, et al. Undetectable anti-TNF drug levels in patients with long-term remission predict successful drug withdrawal. *Aliment Pharmacol Ther* 2015; 42: 356–564.
66 Bots SJ, Kuin S, Ponsioen CY, et al. Relapse rates and predictors for relapse in a real-life cohort of IBD patients after discontinuation of anti-TNF therapy. *Scand J Gastroenterol* 2019; 54 281–288.
67 Kang B, Choi SY, Choi YO, et al. Subtherapeutic Infliximab Trough Levels and Complete Mucosal Healing Are Associated With Sustained Clinical Remission After Infliximab Cessation in Paediatric-onset Crohn's Disease Patients Treated With Combined Immunosuppressive Therapy. J *Crohns Colitis* 2018; 12: 644-652.
68 Baert F, Drobne D, Gils A, et al. Early trough levels and antibodies to infliximab predict safety and success of reinitiation of infliximab therapy. *Clin Gastroenterol Hepatol*. 2014; 12: 1474-81.
69 Boschetti G, Nachury M, Laharie D, et al. Efficacy and Safety of Infliximab Retreatment in Crohn's Disease: A Multicentre, Prospective, Observational Cohort (REGAIN) Study from the GETAID. *Am J Gastroenterol* 2022; 117: 1482–1490.
70 Normatov I, Fluxa D, Wang JD, et al. Real-World Experience With Proactive Therapeutic Drug Monitoring During Infliximab Reintroduction. *Crohns Colitis* 360 2021; 3 (3): otab048.
71 Noor NM, Sousa P, Bettenworth D, et al. ECCO Topical Review on Biological Treatment Cycles in Crohn's Disease .*J Crohns Colitis* 2023; Jan 10:jjad001. doi: 10.1093/ecco-jcc/jjad001. Online ahead of print.
72 Drobne D, Bossuyt P, Breynaert C, et al. Withdrawal of immunomodulators after co-treatment does not reduce trough level of infliximab in patients with Crohn's disease. *Clin Gastoenterol Hepatol* 2015; 13: 514–521.
73 Vande Casteele NV, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology* 2015; 148: 1320-1329.
74 Amiot A, Hulin A, Belhassan M, et al. Therapeutic drug monitoring is predictive of loss of response after de-escalation of infliximab therapy in patients with inflammatory bowel disease in clinical remission. *Clin Res Hepatol Gastoenterol* 2016; 40: 90-98.
75 Aguas Peris M, Bosó V, Navarro B, et al. Serum Adalimumab Levels Predict Successful Remission and Safe Deintensification in Inflammatory Bowel Disease Patients in Clinical Practice. *Inflamm Bowel Dis* 2017; 23: 1454-1460
76 Lucidarme C, Petitcollin A, Brochard C, et al. Predictors of relapse following infliximab de-escalation in patients with inflammatory bowel disease: the value of a strategy based on therapeutic

drug monitoring. *Alimet Pharmacol Ther* 2019; 49: 147-154.
77 Petitcollin A, Brochard C, Siproudhis L, et al. Pharmacokinetic Parameters of Infliximab Influence the Rate of Relapse After De-Escalation in Adults With Inflammatory Bowel Diseases. *Clin Pharmacol Ther* 2019; 106: 605-615.
78 Allegretti JR, Canakis A, McClure E, et al. Infliximab De-escalation in Patients With Crohn's Disease in Clinical Remission Is Safe and Well-tolerated *Inflamm Bowel Dis* 2021; 27: 2031–2033.
79 Santacana Juncosa E, Rodríguez-Alonso L, Padullés Zamora A, et al. Bayes-based dosing of infliximab in inflammatory bowel diseases: Short-term efficacy. *Br J Clin Pharmacol* 2021; 87: 494–505
80 Kim, JY, Lee, Y, Choe, B-H, et al. Factors Associated with the Immunogenicity of Anti-Tumor Necrosis Factor Agents in Pediatric Patients with Inflammatory Bowel Disease. *Gut Liver* 2021; 15: 588–598.
81 Sazonovs A, Kennedy NA, Moutsianas L, et al. HLA-DQA1*05 Carriage Associated With Development of Anti-Drug Antibodies to Infliximab and Adalimumab in Patients With Crohn's Disease. *Gastroenterology* 2019; 158: 189–199.
82 Vermeire S, Noman M, Van Assche G, et al. Autoimmunity associated with anti-tumor necrosis factor alpha treatment in Crohn's disease: a prospective cohort study. *Gastroenterology* 2003; 125: 32–39.
83 Veisman I, Yablecovitch D, Kopylov U, et al. Predictors of Immunogenicity to Infliximab among Patients with Inflammatory Bowel Disease: Does Ethnicity Matter? *Isr Med Assoc J* 2021; 23: 788-793.
84 Trotta MC, Alfano R, Cuomo G, et al. Comparison of Timing to Develop Anti-Drug Antibodies to Infliximab and Adalimumab Between Adult and Pediatric Age Groups, Males and Females .*J Pediatr Pharmacol Ther* 2022; 27: 63–71.
85 Brun MK, Goll GL, Jørgensen KK, et al. Risk factors for anti-drug antibody formation to infliximab: Secondary analyses of a randomised controlled trial. *J Intern Med* 2022; 292: 477–491.
86 Kim ES, Kim SK, Park D-Il, et al. Comparison of the Pharmacokinetics of CT-P13 Between Crohn's Disease and Ulcerative Colitis. *J Clin Gastroenterol* 2022; Apr 26 http://doi.org/10.1097/MCG.0000000000001715 Online ahead of print.
87 Zhu K, Ding X, Chen Z, et al. Association between genetic variants and development of antibodies to infliximab: A cross-sectional study in Chinese patients with Crohn's disease. Front *Pharmacol* 2023; 14: 1096816
88 Vande Casteele N, Abreu MT, Flier S, et al. Patients With Low Drug Levels or Antibodies to a Prior Anti-Tumor Necrosis Factor Are More Likely to Develop Antibodies to a Subsequent Anti-Tumor Necrosis Factor. *Clin Gastroenterol Hepatol* 2022; 20: 465–467.
89 Brun MK, Bjørlykke H, Viken MK, et al. HLA-DQ2 is associated with anti-drug antibody formation to infliximab in patients with immune-mediated inflammatory diseases. *J Intern Med* 2023: 293: 648–655.
90 Hanauer SB, Wagner CL, Bala M, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. *Clin Gastroenterol Hepatol* 2004; 2: 542–553.
91 Ungar B, Chowers Y, Yavzori M, et al. The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. *Gut* 2014; 63: 1258–1264.
92 Gorelik Y, Freilich S, Gerassy-Vainberg S, et al. Antibiotic use differentially affects the risk of anti-drug antibody formation during anti-TNFα therapy in inflammatory bowel disease patients: a report from the epi-IIRN. *Gut* 2022; 71: 287–295.
93 Roblin X, Williet N, Boschetti G, et al. Addition of azathioprine to the switch of anti-TNF in patients with IBD in clinical relapse with undetectable anti-TNF trough levels and antidrug antibodies: a prospective randomised trial. *Gut* 2020; 69: 1206–1212.
94 Ungar B, Haj-Natour O, Kopylov U, et al. Ashkenazi Jewish Origin Protects Against Formation of Antibodies to Infliximab and Therapy Failure. *Medicine* (Baltimore) 2015; 94: e673.

Your therapeutic drug monitoring of biologics in IBD briefing

UEG week

- 'Mercaptopurine treatment using therapeutic drug monitoring is effective in Ulcerative Colitis: A placebo-controlled randomized trial' session at UEG Week 2022 [https://ueg.eu/library/mercaptopurine-treatment-using-therapeutic-drug-monitoring-is-effective-in-ulcerative-colitis-a-placebo-controlled-randomized-trial/8d4a3616-9363-11ed--8769-0242ac140004]
- 'Ultraproactive therapeutic drug monitoring based on point-of-care testing of infliximab is not superior to reactive drug monitoring in patients with inflammatory bowel disease: 1 year results of a pragmatic clinical trial' session at UEG Week virtual 2020 [https://ueg.eu/library/ultraproactive-therapeutic-drug-monitoring-based-on-point-of-care-testing-of-infliximab-is-not-superior-to-reactive-drug-monitoring-in-patients-with-inflammatory-bowel-disease-1-year-results-of-a-pragmatic-clinical-trial/1e4779e2-9361-11ed-a0ef-0242ac140004]
- 'Clinically adjusted versus therapeutic drug monitoring dosing regimens with adalimumab in patients with moderately to severely active Crohn's disease: results from the SERENE-CD maintenance study' session at UEG Week virtual 2020 [https://ueg.eu/library/clinically-adjusted-versus-therapeutic-drug-monitoring-dosing-regimens-with-adalimumab-in-patients-with-moderately-to-severely-active-crohns-disease-results-from-the-serene-cd-maintenance-study/199019cc-9361-11ed-a264-0242ac140004]
- 'Proactive therapeutic drug monitoring is superior to standard treatment during maintenance therapy with infliximab; the randomized nor-drum part B clinical trial' session at UEG Week virtual 2021 [https://ueg.eu/library/proactive-therapeutic-drug-monitoring-is-superior-to-standard-treatment-during-maintenance-therapy-with-infliximab-the-randomized-nor-drum-part-b-clinical-trial/7ff836ee-9362-11ed-8a3d-0242ac140004]

Standards and Guidelines

- van Rheenen PF, Aloi M, Assa A, et al. The Medical Management of Paediatric Crohn's Disease: an ECCO-ESPGHAN Guideline Update. *J Crohns Colitis* 2020 Oct 7;jjaa161. [https://doi.org/10.1093/ecco-jcc/jjaa161]. Online ahead of print.
- Torres J, Bonovas S, Doherty G, et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. *J Crohns Colitis*. 2020;14:4-22. [https://doi.org/10.1093/ecco-jcc/jjz180].
- Papamichael K, Cheifetz AS, Melmed GY, et al. Appropriate Therapeutic Drug Monitoring of Biologic Agents for Patients With Inflammatory Bowel Diseases. *Clin Gastroenterol Hepatol* 2019;17:1655-1668. [https://doi.org/10.1016/j.cgh.2019.03.037]
- Cheifetz AS, Abreu MT, Afif W, et al. A Comprehensive Literature Review and Expert Consensus Statement on Therapeutic Drug Monitoring of Biologics in Inflammatory Bowel Disease. *Am J Gastroenterol*. 2021;116:2014-2025. [https://doi.org/10.14309/ajg.0000000000001396]
- Raine T, Bonovas S, Burisch J, et al. ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment. *J Crohns Colitis* 2022;16:2-17. [https://doi.org/10.1093/ecco-jcc/jjab178].