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Editorial

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Higher Adalimumab Drug Levels Are Associated with Mucosal Healing in Patients with Crohn's Disease

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Anti-tumour necrosis factor [TNF] therapy has revolutionised the treatment of patients with inflammatory bowel disease [IBD], both Crohn's disease [CD] and ulcerative colitis [UC]. In addition to steroid-free clinical remission, objective therapeutic outcomes, such as mucosal healing, are emerging as goals of care in IBD, **leading to the concept of a treat-to-target therapeutic approach.**[1] Mucosal healing is associated with favourable therapeutic outcomes in IBD including lower relapse, hospitalisation and surgery rates.[2]

Exposure-response studies of anti-TNF therapy, based on therapeutic drug monitoring [TDM], show that favourable therapeutic outcomes, such as mucosal healing, are associated with high serum drug concentrations and undetectable anti-drug antibodies.[3,4,5,6,7,8,9] However, the majority of these studies, as well as two recently published meta-analyses, refer mainly to infliximab.[3,4,5,6,7,8,9,10,11]. Only limited data are available regarding the relationship of adalimumab concentrations, and antibodies to adalimumab [ATA], with favourable clinical outcomes and specifically with mucosal healing.[4,5,6,7] Based on these preliminary data, higher adalimumab levels and absence of ATA during maintenance therapy are associated with mucosal healing in IBD [Tables 1 and 2].

In this issue of the *Journal of Crohn's and Colitis*, Zittan and co-workers using a large, homogeneous CD cohort demonstrate that patients with mucosal healing [defined as absence of any ulceration in all ileocolonic segments] during maintenance therapy have higher median adalimumab concentrations compared with those without mucosal healing [14.7 vs 3.4 μg/ml, respectively, $p < 0.001$].[4] Higher adalimumab concentrations were also identified in patients with combined clinical remission (defined as Harvey Bradshaw Index [HBI] < 5) and mucosal healing compared with those patients not in deep remission [13 vs 4.8 μg/ml, respectively, $p = 0.005$].[4] In a multivariate logistic regression model, higher adalimumab concentrations (odds ratio [OR]: 1.2; 95% confidence interval [CI]: 1.07–1.34), and lower HBI scores [OR: 4.2; 95% CI: 1.5–12.5] were identified as the only variables independently associated with mucosal healing.[4]

Based on receiver operating characteristic [ROC] curve analysis, a cut-off of an adalimumab concentration of 8.14 μg/ml best discriminated subjects with mucosal healing from those without (sensitivity [SN]: 91.4%; specificity [SP]: 76%; positive predictive value [PPV]: 84.2%; negative predictive value [NPV]: 86.4%) achieving combined accuracy of 85%. This compares with SN and SP of 97.1% and 60%, respectively, [PPV: 77.3%; NPV: 93.8%] with a combined accuracy of 81.7% when based on the previously described cut-off of 4.9 μg/ml.[4,7] This, along with data from other recent studies, suggests that a threshold of 4.9 μg/ml may not be sufficient to achieve mucosal healing or deep remission.[5,6,7] Nevertheless, adalimumab thresholds associated with mucosal healing in IBD may vary depending on when and how drug concentrations are measured, the definition of mucosal healing, and the study population [CD vs UC], as described in detail in Table 1.

Furthermore, Zittan *et al.* also demonstrated an inverse association of ATA, measured with the drug-tolerant homogeneous mobility shift assay [HMSA], with mucosal healing. This finding of ATA being associated with ongoing endoscopic disease is in agreement with a previous study.[5] Nevertheless, in two other studies ATA positivity was not associated with non-healing, although this could be probably due to a small sample size as well as the different assay used for evaluating ATA [Table 2].[6,7]

Limitations of the study by Zittan and colleagues are its retrospective design and the fact that adalimumab concentrations were evaluated in serum samples taken at various time points between injections described in the footnote of Table 1. This, however, likely reflects better real-life clinical practice, as patients are not likely to have their blood drawn just before their injections [trough concentration]. Additionally, preliminary pharmacokinetic data suggest that subcutaneously administered drugs [such as adalimumab] have a relatively flat drug concentration curve between injections as compared with intravenous medications.[5,12] Another limitation of the study is a potential sample bias, as serum was mainly available from clinically stable patients during maintenance and not from those on relapse indicating a secondary loss of response. This could have resulted in higher serum adalimumab concentrations in patients with mucosal healing, as these patients, in contrast to those

Table 1. Adalimumab concentration thresholds during maintenance therapy associated with endoscopic outcomes in inflammatory bowel disease.

IBD type	No.	Threshold [μg/ml]	Endoscopic outcome	Definition of mucosal healing	SN	SP	PPV	NPV	Assay	Ref.
CD	60	≥ 8.14[a]	Mucosal healing	Absence of any ulceration in all ileocolonic segments	91	76	84	86	HMSA	[4]
CD / UC	66 [CD: 59]	≥ 7.5[b]	Mucosal healing	Lack of any inflammation in the intestinal mucosa [erosions, ulcers, granularity, or friability]	62	83	NR	NR	HMSA	[5]
CD / UC	67 [CD: 58]	> 7.1	Mucosal healing	CD: SES-CD < 3 UC: endoscopic Mayo score < 2 or absence of any sign of inflammation both for CD and UC	32	85	51	72	ELISA[c]	[6]
CD / UC	40 [CD: 22]	< 4.9	Absence of mucosal healing	CD: disappearance of all ulcerations on all ileocolonic segments UC: endoscopic Mayo score < 2	66	85	88	51	ELISA[d]	[7]

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; No., number of patients; ELISA, enzyme-linked immunosorbent assay; HMSA, homogeneous mobility shift assay; SN, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; Ref., reference; NR, not reported; SES-CD, simple endoscopic score for CD.

[a]Based on serum samples collected at intervals of 1-6 days before drug administration date, for patients who received adalimumab every other week or up to 48 h before the drugs were administered, for patients who received adalimumab every week.

[b]Based on randomly collected serum samples [as opposed to trough serum samples].

[c]Anti-human lambda chain detection ELISA.

[d]Lisa-Tracker Premium ELISA kit [Theradiag, Marne la valée, France].

Table 2. Antibodies to adalimumab and mucosal healing in inflammatory bowel disease.

IBD type	No.	Previous anti-TNF, %	ATA titre cut-off	ATA [+], % MH vs no MH	*p*-Value	Assay	Ref.
CD	60	60	1 U/ml	2.9 vs 28	0.03	HMSA	[4]
CD / UC	66 [CD: 59]	64	0.55 U/ml	13.8 vs 37.8	0.03	HMSA	[5]
CD / UC	67 [CD: 58]	42	1.7 μg/ml	33.3 vs 56.4[a]	0.13	ELISA[b]	[6]
CD / UC	40 [CD: 22]	NR	10 ng/ml	6.2 vs 33.3	0.06	ELISA[c]	[7]

IBD, inflammatory bowel disease; No., number of patients; ELISA, enzyme-linked immunosorbent assay; CD, Crohn's disease; UC, ulcerative colitis; HMSA, homogeneous mobility shift assay; Ref., reference; NR, not reported; TNF, tumour necrosis factor; ATA, antibodies to adalimumab; U, units; MH, mucosal healing.

[a]With adequate drug concentrations [> 4.9 μg/ml].

[b]Anti-human lambda chain detection ELISA.

[c]Lisa-Tracker Premium ELISA kit [Theradiag, Marne la vallée, France].

with increased intestinal inflammation, may have higher serum drug concentrations due to lower drug clearance secondary to decreased tissue TNF burden and faecal loss from a leaky gut.[8,9]

In conclusion, this study and data from other studies suggest that higher anti-TNF concentrations are associated with mucosal healing in patients with IBD. These data combined with those regarding pre-emptive dose optimisation using TDM for anti-TNF therapy could be a first step towards proactive individual, personalised treatment and going beyond a treat-to-target to a treat-to trough therapeutic strategy.[13,14,15] Nevertheless, before this strategy can be implemented in clinical practice, robust drug concentration thresholds associated with favourable objective therapeutic outcomes, such as mucosal healing and normalisation of C-reactive protein [CRP] or faecal calprotectin, as well as the time [trough vs peak or intermediate levels] and the assay used for TDM, should be clearly defined by large, prospective clinical trials.[16,17]

Furthermore, looking at the other side of the coin, when aiming for higher anti-TNF drug concentrations to increase efficacy, safety concerns may arise. However, there are only limited data regarding the potential association of supra-therapeutic drug concentrations with increased toxicity or adverse events. Preliminary data suggest that high infliximab dosing [between 10 mg and 22.5 mg/kg every 4 to 7 weeks] may be associated with serious infections,[18] whereas higher anti-TNF concentrations [infliximab >5 μg/ml and adalimumab > 6.6 μg/ml] are associated with an impaired quality of life (based on the Inflammatory Bowel Disease Questionnaire [IBDQ]), particularly regarding systemic symptoms and emotional status.[19] Finally, another study showed that higher preoperative serum anti-TNF drug levels are associated with higher rates of adverse postoperative outcomes in CD, such as postoperative morbidity, infectious complications, or hospital re-admissions.[20]

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Author Contributions

Both authors drafted and critically revised the manuscript and approved the final version.

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