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Letter: infliximab concentrations during induction therapy - one size doesn't fit all.

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Infliximab, a chimeric anti-TNF antibody, has revolutionized the treatment of the inflammatory bowel diseases (IBD) namely Crohn's disease (CD) and ulcerative colitis (UC). Nevertheless, up to 30% of patients have a primary non-response (PNR), and most notably, up to 80% do not achieve clinical remission following induction therapy.[1] Preliminary data from therapeutic drug monitoring (TDM) studies suggest that these undesired clinical outcomes can be attributed either to low drug concentrations with or without antidrug antibodies or a mechanistic failure.[2, 3]

In a recent issue of Alimentary Pharmacology and Therapeutics, Bar-Yoseph et al.[4], in one of the largest cohorts, evaluated the association of early induction infliximab concentrations and antibodies to infliximab (ATI) with PNR. PNR was defined as the lack of clinical improvement by the end of induction period (week 14), which necessitated cessation of infliximab therapy. They found that both week 2 and week 6 infliximab concentrations were significantly lower among patients with PNR compared to responders. Additionally, ATI positivity at weeks 2 and 6 was also associated with PRN. Most importantly they identified a week 2 infliximab concentration <6.8 μg/mL and ATI titer >4.3 μg/mL-eq predictive of PNR.[4] This finding is of great value as the therapeutic drug window to target for infliximab induction therapy is largely unknown. Nevertheless, we think that these infliximab concentrations, although adequate to prevent clinically defined PNR, are probably too low for achieving more stringent therapeutic outcomes, such as early mucosal healing or at least early clinical remission.[5–10] The same group using the same in-house developed assay has previously shown that infliximab concentrations >9.2 μg/mL at week 2 were associated with fistula response at week 14.[3] However, a large retrospective study from Leuven demonstrated that higher week 2 infliximab concentrations >28.3 μg/mL were associated with early mucosal healing (week 10–14) in UC[9]. Furthermore, a recent pharmacokinetic (PK) analysis of the prospective randomized controlled trial (RCT) investigating tailored treatment with infliximab for active Crohn's disease (TAILORIX) showed that infliximab concentrations >23.1 μg/mL at week 2 were related with endoscopic remission at week 12 in

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CD using the Leuven's in-house developed enzyme-linked immunosorbent assay.[6] This discrepancy, as described also by the authors, may arise from differences in evaluated therapeutic outcomes, the TDM assay used and the IBD phenotype (Table 1). This, along with the fact that induction infliximab concentrations can fluctuate more than maintenance treatment due to PK issues, makes it hard to define clinically relevant infliximab induction concentration thresholds.

In conclusion, this study suggests that PNR of infliximab in IBD can be better explained by PK problems and immunogenicity rather than a mechanistic failure and that unfortunately anti-TNF are underdosed in many individuals. As new tools are soon to be available, such as point of care devices for measuring infliximab concentrations and PK models for accurately calculating infliximab dosing, early utilization of TDM to optimize anti-TNF therapy is not far away. Nevertheless, before a TDM-based therapeutic strategy during induction therapy can be widely applied data from RCTs is certainly warranted.

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Table 1.

Serum infliximab concentration thresholds during induction therapy associated with early therapeutic outcomes in inflammatory bowel disease.

Time point	IBD type	Therapeutic outcome of interest	Threshold (μg/mL)[a]	TDM assay	Assay type	Ref.
w2	CD	Clinical response (w14)	>16.9[b]	ELISA	Theradiag	[7]
w2	CD	Clinical remission (w14)	>20.4[b]	ELISA	Theradiag	[7]
w2	CD	Endoscopic remission (w12)	>23.1	ELISA	In house Leuven	[6]
w2	CD	Fistula response (w14)	>9.2	ELISA	AHLC	[3]
w2	UC	Clinical response (w14)	>11.5[b]	ELISA	Theradiag	[7]
w2	UC	Mucosal healing (w10–14)	≥28.3	ELISA	In house Leuven	[9]
w2	UC	Clinical remission (w14)	>15.3[b]	ELISA	Theradiag	[7]
w2	UC	Clinical remission (w30)	>14.5[b]	ELISA	Theradiag	[7]
w2	UC	Clinical remission (w14)	>21.3	ELISA	Mitsubishi Tanabe Pharma Corp	[8]
w2	CD/UC	Clinical response (w14)	>6.8	ELISA	AHLC	[4]
w6	CD	Endoscopic remission (w12)	>10	ELISA	In house Leuven	[6]
w6	CD	Fistula response (w14)	>7.2	ELISA	AHLC	[3]
w6	UC	Clinical response (w8)	>22	ELISA	Janssen Biotech Inc	[5]
w6	UC	Mucosal healing (w10–14)	≥15	ELISA	In house Leuven	[9]
w6	UC	Endoscopic response (w8)	>6.6	ELISA	Sanquin Diagnostics	[2]
w6	CD/UC	Clinical response (w14)	>3.5	ELISA	AHLC	[4]
w6	CD/UC	ATI formation	<13	HMSA	Prometheus	[10]

[a] Based on receiver operating characteristic analysis;

[b] Infliximab biosimilar CT-P13.

ELISA: enzyme-linked immunosorbent assay; HMSA: homogeneous mobility shift assay; AHLC: antihuman lambda chain antibody; CD: Crohn's disease; UC: ulcerative colitis; TDM: therapeutic drug monitoring; ATI: antibodies to infliximab; w: week; Ref: reference.