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Short Title: Adalimumab Clearance and therapeutic outcome

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ABSTRACT

Objective: We postulated that Adalimumab (ADA) drug clearance (CL) may be a more critical determinant of therapeutic outcome than ADA concentration. This was tested in Crohn's disease (CD) patients undergoing ADA maintenance treatment.

Methods: CD patients from 4 cohorts received ADA induction and started maintenance. Therapeutic outcomes consisted of endoscopic remission (ER), sustained C-reactive protein (CRP) based clinical remission (defined as CRP levels below 3 mg/L in the absence of symptoms) and fecal calprotectin (FC) levels below 100µg/g. Serum Albumin, ADA concentrations and anti-drug antibody status were determined using immunochemistry and homogenous mobility shift assay, respectively. CL was determined using nonlinear mixed effect model with Bayesian priors. Statistical analysis consisted of Mann-Whitney test, logistic regression with calculation of odds ratio. Repeated event analysis was conducted using nonlinear mixed effect model.

Results: In 219 patients enrolled (median age 40 years, 45% females), median CL was lower in ER as compared to active endoscopic disease status (median 0.247 L/day vs 0.326 L/day, respectively) (p=0.004). There was no significant difference in ADA concentrations between patients in endoscopic remission compared to recurrence (median 9.3 µg/mL vs 11.7 µg/mL respectively) (p=0.201). Sustained CRP-based clinical remission and FC levels below 100µg/g were generally associated with lower CL and higher ADA concentrations. Repeated event analysis confirmed those findings with better performances of CL than concentrations in associating with ER and other outcomes.

Conclusion: Lower ADA Clearance is associated with an improved clinical outcome for patients with Crohn's disease and may be a superior pharmacokinetic measure than concentrations.

Key words: Crohn's disease; Adalimumab, pharmacokinetics, Clearance

INTRODUCTION

Therapeutic drug monitoring (TDM) is now routine for many patients with CD receiving anti-tumor necrosis factor-α (TNF-α) therapies and helps direct and improve drug management[1]. The measurement of adalimumab (ADA, a monoclonal antibody targeting TNF-α) blood concentration can inform clinicians of the potential need for dose escalation to achieve exposure commensurate with disease control and provide reassurance regarding the absence of immune tolerance and formation of antibodies to adalimumab (ATA).

In order to maximize the clinical yield associated with ADA and availability to neutralize the inflammatory burden present, gastroenterologists have endorsed the TDM of ADA, reactively, in the face of inadequate disease control,[2, 3] or proactively with maintenance of ADA concentration above a minimal effective concentration, associated with enhanced drug tolerance and sustained disease control[4, 5]. Reactive or proactive; the decision to increase or decrease the dose intensity requires careful implementation to maintain exposure above the desired concentration. To that end, model informed precision guided dosing (MIPD) tools that employ clinical PK coupled with machine learning have recently demonstrated their value in assisting with the achievement of desired exposure[6], with the potential to also fine tune the therapeutic window between minimal effective concentration and potential overexposure where side effects may occur[7].

These MIPD tools are now implemented in clinical practice[8] and have demonstrated value in anti-TNF treatment.[9] Both retrospective and prospective clinical utility studies support the value of this approach to improve outcomes[6, 10]. Machine learning based tools now allow the determination of CL, a key predictive factor of pharmacokinetic (PK) origin that accelerates in the presence of immunization against the drug[11] and increasing inflammatory burden[12]. As such, this PK outcome measure which represents the monoclonal antibody containing volume available in the central compartment for pharmacological effect may perform equally well or better than ADA concentration in associating with outcome. This hypothesis was tested in this report.

METHODS

In this retrospective analysis, CD patients from 4 different cohorts started subcutaneous ADA treatment with standard induction schedule (160 mg followed by 80 mg and 40 mg every other week) followed by 40 mg every two weeks during maintenance (Cohort 1 through Cohort 3)[13 14, 15] or on an intensive induction schedule (160 mg weekly for 4 consecutive doses followed by 40 mg every other week) with the potential to increase the dose or frequency based on the presence of inflammation[16] (STRIDENT study). The first cohort (BOLOGNA cohort) was performed in the context of a one-year prospective observational clinical trial aimed at identifying biomarkers, and predictors of a failure response to commonly used biological therapy in patients with Crohn's Disease[13]. The second cohort (PredictCrohn) was a prospective multicenter cohort study in patients naïve to biologics and active luminal disease and followed for 14 weeks[14]. The third cohort (the POCER[15] study) examined a cohort of patients with ileo-colonic CD following intestinal resection of all macroscopic disease, with ADA used post-operatively to prevent recurrence. The fourth cohort (STRIDENT cohort) was from an open-label, single-centre, randomized controlled trial evaluating Intensive drug therapy versus standard drug therapy for symptomatic intestinal Crohn's disease strictures[16]. Patients from each cohort were followed longitudinally at each visit during their maintenance treatment. Blood specimens were collected periodically during maintenance, serum was isolated and stored until analysis. Serum ADA concentrations and antibodies to ADA (ATA) were determined using drug tolerant homogenous mobility shift assay in a clinical laboratory (Prometheus Laboratories, San Diego, CA)[17]. Lower and upper limit of quantification of the drug assay was 1.6 μg/mL and 50 μg/mL, respectively. Cutoff associated with ATA status was 1.7 U/mL. Serum Albumin and C-reactive protein (CRP) were determined using immunochemistry. Fecal calprotectin (FC) was determined using immunoassays with cut off below 100 μg/g consistent with endoscopic remission [18].

The population PK parameters were estimated from the first cohort[13] and nonlinear mixed effect modeling,

(one compartment with linear elimination), with random effects on apparent CL (referred as CL thereafter) with albumin levels and ATA status as covariates. Apparent volume of distribution was fixed. These estimates were applied as Bayesian priors to calculate CL in all specimens available. The outcomes consisted of CRPbased clinical remission status corresponding to CRP levels below 3 mg/L in the absence of symptoms (Crohn's Disease Activity Index < 150 points) determined at each study visit, and sustained CRP-based clinical remission throughout maintenance (corresponding to CRP based clinical remission status achieved at all evaluable time points for a given patient). Endoscopic remission (ER) corresponded to the Simple Endoscopic Score for CD (SES-CD<3 points) available during treatment in Cohorts 1, 3 and 4 . Statistical analysis consisted of univariate and multivariate logistic regression with odds ratio (OR, with 95% confidence interval and pseudo R^2 calculated and reflective of the proportion of variance explained). Mann-Whitney test for group comparisons was used in this analysis. Results were expressed as median with interquartile ranges (IQR), as appropriate. The impact of PK parameters (ADA trough concentrations and CL estimates) on outcomes was estimated using longitudinal repeated event analysis using non-linear mixed effects modeling via Monolix (Lixoft, 2021R2). For each model tested the change in objective function value (ΔOFV, as assessed using -2 log likelihood [-2LL] by importance sampling) calculated with 5% level of significance to assess the value of the additional predictor where lower -2LL indicated better fit and performances in association with outcome.

RESULTS

The patient characteristics (n=219, with a total of 818 study visits and 211 endoscopic assessments during maintenance) are presented in **Table I,** the parameter estimates for the PK model is presented in **Table S1**. Population CL determined from Cohort 1 was 0.317 L/day with 8.9 L in the central compartment with albumin and immunization impacting CL and used as covariate for the calculation of the individual parameter estimates.

Less than half of the patients were in ER (46%). Sustained clinical remission, defined by CRP or FC below

100 ug/g, was achieved in 31% and 53%, respectively. Overall, the prevalence of ATA was seen in 10% (81/818) of the specimens. ATA positive status was associated with lower ADA concentrations than ATA negative status (<1.6 μg/mL [IQR: <1.6-<1.6] vs 11.2 μg/mL [IQR: <7.8-<14.8], respectively) (p<0.001) and higher CL (1.264 L/day [IQR: 0.660-1.580] vs 0.263 L/day [IQR: 0.197-0.373], respectively) (p<0.001). ATA status was associated with a 33.8-fold (95%CI: 18.7 - 61.0) higher likelihood to have ADA concentration below 5 μg/mL.

As presented in **Table II**, lower CL was associated with ER in two of three cohorts tested (all cohorts: 0.247 L/day [IQR: 0.195-0.340 L/day] vs 0.326 L/day [IQR: 0.203-0.730 L/day] in the presence and absence of ER, respectively) (p=0.004). There was a non-significant higher ADA concentration in the presence of ER (median 9.3 μg/mL [IQR:3.8-14.8 μg/mL] vs 11.7 μg/mL IQR: 7.9-14.1 μg/mL] in the presence and absence of ER, respectively) (p=0.201), and was statistically significant in cohort 1 (p=0.037). Sustained CRP based clinical remission status and FC below 100μg/g were generally associated with higher ADA concentration and lower CL in all cohort tested (except that concentration was not associated with FC levels in cohort 1).

Odds ratio analysis with low (≤5μg/mL), intermediate (>5μg/mL), and high (>10 μg/mL) ADA levels or CL (<0.318 L/day and <0.8 L/day) for each of the outcomes tested confirmed these findings (**Supplementary Tables S2 through S9**). The proportion of CD who achieved ER by ADA concentration (>5 μg/mL and >10 μg/mL) and CL (<0.8 L/day and <0.318 L/day) is presented in **Figure 1**. The proportions of those who achieved sustained CRP-based clinical remission and FC below 100μg/g are presented in **Figure 2** and **Figure 3**, respectively. Higher concentrations and lower CL yielded better disease control.

Multivariate analysis with ADA concentrations and CL revealed that ER was associated with CL (each unit

change in CL: adjusted OR=0.12 95%CI: 0,02; 0.79; p=0.028) while no association was detectable with ADA concentrations (p=0.152; **Table 3**). A total of 14.2% (pseudo R^2=0.142) of the variance in ER could be explained by CL and concentrations. Similar results were observed with sustained CRP-based clinical remission and FC below 100µg/g outcome measures with no significance of concentrations after adjusting for CL and where 41.0% and 12.6% of the variance in these therapeutic outcomes could be explained with these PK parameters, respectively.

Repeated analysis of the probability of ER over the maintenance period was tested using time, concentration, and CL as regressors, either on their own or in combination. As presented in **Table 4**, higher concentrations were not associated with ER (estimate: +0.050, relative standard error [RSE]: 68%) while higher CL (estimate -2.75; RSE=29%] resulted in lower probability of ER, this finding remaining significant after adjusting for time on treatment. Lower -2LL were achieved with CL than with concentrations with themselves as regressors (265.5 vs 276.3, ΔOFV = -10.8; $p<0.01$) and these findings remained significant after adjusting for time on treatment (260.5 vs 273.0, ΔOFV =-12.5; $p<0.05$). Repeated event analysis with CRP-based remission and FC below 100µg/g revealed that higher concentration and lower CL also associated better probability of having these improved outcomes (Supplementary Table S13 and S14). The probability of having the therapeutic outcome calculated from those estimates are summarized in **Figure 4**.

DISCUSSION

ADA drug CL is a recognised PK parameter, reflective of the volume containing ADA eliminated from the central compartment as a function of time (expressed as L/day). It is well established that immunization to ADA and other monoclonal antibodies results in high CL[11] with the consequence of having lesser ADA available, a condition that worsens with inflammation[19]; and potentially preventable with the concomitant immunosuppressant[20] or proactive achievement of exposure that promotes tolerance to the antigen fraction

itself (CDR3 of the fragment antigen binding domain of the IgG1)[21, 22]. In this report we describe the associations and performance characteristics of CL alone as well as ADA concentration in four cohorts of patients starting ADA treatment. All outcomes were collected during maintenance treatment. Endoscopic assessment (SES-CD score) was routinely performed with data available longitudinally.

Overall, our data support the expert opinion that ADA concentrations have value[1], based on their association with outcomes in patients with CD. However, the portion of the clinical picture explained by the concentrations themselves was modest (with pseudo R^2 consistently below 20% for each of the three outcomes tested). ADA concentrations above 5 and 10 μg/mL yield several fold higher likelihood of better outcome than levels < 5 μg/mL. The measurement of concentration is therefore likely to assist with clinical decision making with respect to treatment and monitoring.

The volume containing ADA present in the central compartment and eliminated as function of time, is the CL. In this study it performed better than concentration alone. Lower CL and better retention of ADA yielded better endoscopic outcome (median: 0.246 L/day vs 0.320 L/day vs, in the presence and absence of ER, respectively; **Table 2**), sustained clinical disease control and lower inflammation. Also, for each of the outcomes tested, multivariate analysis of CL and concentration as independent predictors revealed higher likelihood of ER, sustained CRP based remission and FC levels below 100 μg/g were all a function of lower CL, with contribution of concentrations after adjusting with CL. Nonlinear mixed effect modelling of the longitudinal data also confirmed these findings with lower -2log likelihood for CL than concentration for each of the outcome tested.

Our data suggests that CL is a predictive PK factor that may assist with optimization of ADA treatment and potentially other monoclonal antibodies, particularly the anti-TNF agents. The clinician may decide to dose intensify in the presence of higher CL and lower concentration, or reduce dose intensity in the presence of

remission, high concentrations and lower CL. Indeed, in each of the cohorts tested we systematically observed that in the presence of both lower CL and higher drug concentration disease control was superior (data not shown).

In this work we cannot address the causality of the association with outcomes, but it is tempting to suggest that two key characteristics converge toward lower CL. Firstly absence of immunization and efficient PK (reflected by adequate albumin levels) and secondly achievement of sufficient supply of anti-cytokine drug as a reservoir available for the neutralization of inflammatory burden present. We acknowledge that this analysis is retrospective and that these findings could be significant by chance, or due to type one error, and confirmation will be required. However, these data suggest that CL is PK predictive factor in its own right, potentially outperforming drug concentration.

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TABLES

Table 1: Patient Characteristics

	Cohort 1 (BOLOGNA) Italy	Cohort 2 (PredictCrohn) Spain	Cohort 3 (POCER) Australia	Cohort 4 (STRIDENT) Australia	All cohorts
Number of patients	53	60	32	74	219
Age	35 (25-44)	40 (30-49)	39 (29-47)	44 (20-51)	40 (29-48)
Gender (female)	34%	46%	47%	52%	45%
Number of cycles	182	313	115	208	818
Dose per two weeks	40 (40-40)	40 (40-40)	40 (40-40)	40 (40-40)	40 (40-40)
Weight (Kg)	70 (62-70)	72 (60-80)	75 (62-70)	78 (66-87)	73 (62-82)
Albumin (g/dL)	4.0 (3.8-4.3)	4.0 (3.6-4.5)	4.1 (3.8-4.3)	3.9 (3.6-4.2)	4.0 (3.7-4.3)
ADA Concentration (µg/mL)	10.0 (5.2-12.8)	10.0 (7.1-14.0)	9.1 (4.7-14.1)	13.2 (8.2-17.7)	10.5 (6.8-14.4)
ADA concentration >5 µg/mL	76% (139/182)	86% (268/313)	72% (83/115)	88% (184/208)	82% (674/818)
ADA >10 µg/mL	49% (90/182)	50% (156/313)	43% (50/115)	65% (135/208)	53% (431/818)
ATA positive (>1.7 U/mL)	15% (28/182)	6% (18/313)	12% (14/115)	10% (21208)	10% (81/818)
Clearance (L/day)	0.280 (0.220-0.539)	0.279 (0.196-0.420)	0.301 (0.204-0.520)	0.242 (0.174-0.377)	0.273 (0.194-0.434)
SES-CD below 3 points	57% (51/90)	NA	41% (27/66)	36% (20/55)	46% (98/211)
CRP based clinical remission	47% (84/178)	51% (120/236)	54% (43/80)	50% (104/207)	50% (351.701)
Sustained CRP based clinical remission	26% (14/53)	22% (13/60)	41% (13/32)	38% (27/74)	31% (67/219)
Fecal calprotectin below 100 µg/g	38% (45/119)	NA	46% (39/85)	66% (134/204)	53% (218/408)

Results are expressed as median (IQR) as appropriate.

Table 2: PK variables and Outcomes

Median ADA concentration and CL are provided (with IQR) for each outcome variable and cohort with p value. Top estimate corresponds to the median and IQR in the absence of the outcome. Bottom estimate corresponds to the median and IQR in the presence of the outcome.

	PK estimate	SES-CD remission (<3 points)	Sustained CRP based clinical remission	FC below 100 µg/g
Cohort 1	Concentration (µg/mL)	6.7 (<1.6-12.8) 11.0 (8.3-12.8) p=0.037	8.5 (3.6-12.5) 12.0 (10.1-14.0) p=0.009	8.5 (3.0-13.4) 10.8 (7.4-12.2) p=0.710
	CL (L/day)	0.490 (0.211-1.240) 0.247 (0.216-0.324) p=0.002	0.325 (0.226-0.699) 0.239 (0.194-0.277) p=0.002	0.339 (0.207-0.829) 0.264 (0.235-0.380) p=0.005
Cohort 2	Concentration (µg/mL)	Not available	9.5 (6.4-13.4) 12.3 (9.4-15.7) p=0.008	Not available
	CL (L/day)	Not available	0.290 (0.206-0.442) 0.231 (0.164-0.303) p<0.001	Not available
Cohort 3	Concentration (µg/mL)	8.6 (4.5-12.6) 10. (5.9-14.2) p=0.735	7.1 (3.1-12.1) 10.6 (8.5-15.0) p=0.003	7.5 (3.7-10.0) 11.5 (5.3-15.0) p=0.017
	CL (L/day)	0.312 (0.241-0.491) 0.256 (0.184-0.435) p=0.190	0.370 (0.223-0.761) 0.255 (0.173-0.319) p<0.001	0.348 (0.265-0.610) 0.252 (0.175-0.470) p=0.033
Cohort 4	Concentration (µg/mL)	13.2 (7.5-17.6) 14.8 (11.2-23.3) p=0.273	10.8 (5.9-15.5) 14.5 (12.1-20.6) p<0.001	9.9 (5.8-15.5) 13.8 (10.0-18.6) p=0.005
	CL (L/day)	0.320 (0.191-0.678) 0.213 (0.171-0.289) p=0.047	0.314 (0.205-0.524) 0.187 (0.143-0.235) p<0.001	0.361 (0.248-0.619) 0.197 (0.154-0.279) p<0.001
All Cohorts	Concentration (µg/mL)	9.3 (3.8-14.8) 11.7 (7.9-14.1) p=0.201	9.4 (5.4-13.6) 12.6 (9.8-15.8) p<0.001	8.6 (4.1-13.5) 12.3 (8.6-15.8) p<0.001
	CL (L/day)	0.326 (0.203-0.730) 0.247 (0.195-0.340) p=0.004	0.311 (0.213-0.552) 0.220 (0.168-0.281) p<0.001	0.353 (0.238-0.670) 0.230 (0.172-0.331) p<0.001

Table 3: **Multivariate logistic regression for outcomes with ADA concentration and CL**

Results are presented for all 4 cohorts combined. **Table S11-S13** provide results by cohort.

	PK estimate	Adjusted OR per unit change	P value	Pseudo R^2
ER	Concentration (µg/mL)	0.96 (0.92,1.01)	0.152	0.142
	CL (L/day)	0.12 (0.02,0.79)	0.028	
Sustained CRP based remission	Concentration (µg/mL)	0.98 (0.95,1.01)	0.238	0.410
	CL (L/day)	0.02 (0,0.07)	<0.001	
FC below 100µg/g	Concentration (µg/mL)	1.02 (0.98,1.05)	0.333	0.126
	CL (L/day)	0.24 (0.11,0.52)	<0.001	

Table 4: **Repeated event analysis with ER**

Estimates are provided with relative standard error (<50% indicates significant association).

	Time only	Conc. only	CL only	Time and concentrations	Time and CL
Population	0.88 (62%)	-1.05 (49%)	0.81 (52%)	1.19 (53%)	2.84 (22%)
Time regressor (wks)	-0.024 (40%)†	NA	NA	-0.037 (28%)†	-0.037 (30%)†
PK regressor	NA	+0.050 (68%)	-2.75 (29%)†	+0.033 (106%)	-2.81 (34%)†
-2LL	273.1	276.3	265.5	273.0	260.5

†<50% is significant regressor; NA: not applicable. -2LL: -2 log likelihood.

FIGURES

Figure 1: **ADA concentration and CL in association with ER**

ER was defined as SES-CD score below 3 points.
Top panel: Overall, ADA concentration >5 µg/mL, and >10 µg/mL associated with 2.6-fold (95%CI: 1.3-5.2) (p=0.007; pseudo R^2=0.047) and 2.1-fold (95%CI: 1.2-3.7) (p=0.008; pseudo R^2=0.040) higher likelihood of ER respectively (**Table S2**).
Bottom panel: Overall, CL <0.318 L/day, and <0.8 L/day associated with 2.5-fold (95%CI: 1.4-4.4) (p=0.002; pseudo R^2=0.058) and 3.0-fold (95%CI: 1.3-6.7) (p=0.008; pseudo R^2=0.047) higher likelihood of ER, respectively (**Table S3**).

Figure 2 ADA PK parameter and sustained CRP based remission.

Top panel: Overall, ADA concentration >5 µg/mL, and >10 µg/mL associated with 9.7-fold (95%CI: 2.3-41.7) (p<0.001; pseudo R^2=0.181) and 4.5-fold (95%CI: 2.3-8.9) (p<0.001; pseudo R^2=0.146) higher likelihood of sustained CRP based clinical remission, respectively (**Table S4**).
Bottom panel: Overall, CL <0.318 L/day, and <0.318 L/day associated with 6.5-fold (95%CI: 2.9-14.4) (p<0.001; pseudo R^2=0.197) and 10.6-fold (95%CI: 1.4-80.4) (p<0.001; pseudo R^2=0.133) higher likelihood of sustained CRP based clinical remission (**Table S5**).

Figure 3 ADA concentration and CL in association with FC below 100µg/g

Top panel: Overall, ADA concentration >5 µg/mL, and >10 µg/mL associated with 3.3-fold (95%CI: 2.0-5.7) (p<0.001; pseudo R^2=0.064) and 3.2-fold (95%CI: 2.2-4.9) (p<0.001; pseudo R^2=0.094) higher likelihood of FC below 100µg/g, respectively (**Table S6**).
Bottom panel: Overall, CL <0.318 L/day, and <0.318 L/day associated with 3.2-fold (95%CI: 2.1-4.9) (p<0.001; pseudo R^2=0.093) and 4.1-fold (95%CI: 2.1-7.9) (p<0.001; pseudo R^2=0.062) higher likelihood of FC below 100µg/g, respectively (**Table S7**).

Figure 4 Probability of achieving outcome by ADA concentration and CL

All estimates are provided in **Table 4** (ER) and **supplementary Table 13 and 14** (CRP based clinical remission and FC below 100µg/g, respectively). Estimates from the nonlinear mixed effect model of the outcome in relation to the PK parameter is provided with relative standard error expressed as % (<50% indicates significance); -2 log likelihood (-2LL) is also reported.

Panel A: probability of SESC-CD below 3 points and CL (estimate=-2.75 [RSE: 29%]; -2LL: 265.5); *Panel B*: probability of CRP based clinical remission and CL (estimate=-5.04 [RSE: 24%];); *Panel C*: probability of FC below 100 ug/g and CL (estimate=-1.57 [RSE: 52%]; -2LL: 193.2); *Panel D*: probability of SESC-CD below 3 points and concentration estimate=0.050 [RSE: 68%]; -2LL: 276.3); *Panel E*: probability of CRP based clinical remission and concentration (estimate=0.10 [RSE: 38%]; -2LL: 237.9); *Panel F*: probability of FC below 100 ug/g and concentration (estimate=0.210 [RSE:32%]; -2LL: 193.2).

SUPPLEMENTARY MATERIALS

Table S1 Parameter Estimates nonlinear mixed effect model and Bayesian prior.

Parameter	Estimate	Definition
CL/F_pop (L/day)	0.317	Population apparent CL
V/F_pop (L)	8.9	Population apparent V1
Ka (day^{-1})	0.2	Absorption constant
Omega CL	0.501	Inter-patient variability on CL (SD)
beta_Cl_ATA_1	0.806	Covariate estimate ATA status on Cl
beta_Cl_logtALB	-2.2	Covariate estimate ALB on C
a	1	additive error model

Table S2 OR for ER and ADA concentration above cutoffs.

	Cutoff	OR	P value	Pseudo R2
Cohort 1	>5 µg/mL	3.74 (1.39,10.05)	0.007	0.095
	>10 µg/mL	3.27 (1.37,7.82)	0.006	0.097
Cohort 3	>5 µg/mL	1.56 (0.5,4.83)	0.445	0.012
	>10 µg/mL	1.92 (0.71,5.22)	0.197	0.031
Cohort 4	>5 µg/mL	Infinite	--	--
	>10 µg/mL	1.83 (0.5,6.78)	0.364	0.022
All	>5 µg/mL	2.58 (1.29,5.17)	0.007	0.047
	>10 µg/mL	2.11 (1.21,3.68)	0.008	0.040

Table S3 OR for ER and CL below cutoffs.

	Cutoff	OR	P value	Pseudo R2
Cohort 1	<0.318 L/day	3.78 (1.55,9.24)	0.003	0.114
	<0.8 L/day	3.33 (1.12,9.91)	0.030	0.066
Cohort 3	<0.318 L/day	1.02 (0.38,2.73)	0.964	<0.01
	<0.8 L/day	2.73 (0.52,1.85)	0.234	0.036
Cohort 4	<0.318 L/day	4.24 (1.18,14.33)	0.027	0.134
	<0.8 L/day	4.75 (0.54,41.8)	0.160	0.085
All	<0.318 L/day	2.48 (1.41,4.36)	0.002	0.058
	<0.8 L/day	2.96 (1,31,6.67)	0.006	0.047

Table S4 OR for sustained CRP based clinical remission and ADA above cutoffs.

	Cutoff	OR	P value	Pseudo R2
Cohort 1	>5 µg/mL	5.78 (0.68,49.33)	0.054	0.150
	>10 µg/mL	7.33 (1.74,30.94)	0.003	0.233
Cohort 2	>5 µg/mL	Infinite	--	--
	>10 µg/mL	4.07 (0.81,20.45)	0.058	0.124
Cohort 3	>5 µg/mL	13.33 (1.43,123.94)	0.005	0.322
	>10 µg/mL	4.48 (0.99,20.35)	0.052	0.145
Cohort 4	>5 µg/mL	Infinite	--	--
	>10 µg/mL	5.51 (1.65,18.4)	0.006	0.172
All	>5 µg/mL	9.72 (2.27,41.73)	0.002	0.181
	>10 µg/mL	4.55 (2.33,8.9)	<0.001	0.146

Table S5 OR for sustained CRP based clinical remission and CL below cutoffs.

	Cutoff	OR	P value	Pseudo R2
Cohort 1	<0.318 L/day	4.75 (1.14,19.73)	0.032	0.158
	<0.8 L/day	3.90 (0.45,34.02)	0.218	0.081
Cohort2	<0.318 L/day	6.80 (0.81,56.93)	0.077	0.192
	<0.8 L/day		--	--
Cohort 3	<0.318 L/day	7.22 (1.44,36.22)	0.016	0.235
	<0.8 L/day	Infinite	--	--
Cohort 4	<0.318 L/day	17.64 (2.2,141.28)	<0.001	0.334
	<0.8 L/day	Infinite	NA	NA
All	<0.318 L/day	6.46 (2.89,14.45)	<0.001	0.197
	<0.8 L/day	10.58 (1.39,80.36)	0.023	0.133

Table S6 OR for FC below 100 ug/g and ADA concentration above cutoffs.

	Cutoff	OR	P value	Pseudo R2
Cohort 1	>5 µg/mL	4.92 (1.58,15.33)	0.002	0.123
	>10 µg/mL	1.9 (0.9,4.02)	0.092	0.030
Cohort 3	>5 µg/mL	1.55 (0.6,3.96)	0.363	0.012
	>10 µg/mL	4.57 (1.8,11.6)	<0.001	0.146
Cohort 4	>5 µg/mL	3.47 (1.42,8.5)	0.006	0.045
	>10 µg/mL	3.11 (1.69,5.73)	<0.001	0.081
All	>5 µg/mL	3.37 (1.97,5.75)	<0.001	0.064
	>10 µg/mL	3.24 (2.16,4.87)	<0.001	0.094

Table S7 OR for FC below 100 ug/g and CL below cutoffs.

	Cutoff	OR	P value	Pseudo R2
Cohort 1	<0.318 L/day	2.35 (1.09,5.08)	0.027	0.053
	<0.8 L/day	4.84 (1.34,17.43)	0.006	0.103
Cohort 3	<0.318 L/day	1.68 (0.71,3.98)	0.234	0.020
	<0.8 L/day	5.14 (1.05,25.1)	0.022	0.091
Cohort 4	<0.318 L/day	4.83 (2.58,9.04)	<0.001	0.145
	<0.8 L/day	2.62 (0.99,6.99)	0.053	0.223
All	<0.318 L/day	3.25 (2.15,4.9)	<0.001	0.093
	<0.8 L/day	4.07 (2.10,7.90)	<0.001	0.062

Table S8 OR for CRP based clinical remission and ADA concentration above cutoffs.

	Cutoff	OR	P value	Pseudo R2
Cohort 1	>5 µg/mL	8.44 (3.34,21.34)	<0.01	0.203
	>10 µg/mL	3.02 (1.64,5.56)	<0.01	0.085
Cohort2	>5 µg/mL	2.15 (1.03,4.46)	0.036	0.023
	>10 µg/mL	1.98 (1.18,3.33)	0.009	0.034
Cohort 3	>5 µg/mL	5.43 (1.93,15.28)	0.001	0.162
	>10 µg/mL	3.80 (1.42,10.17)	0.006	0.114
Cohort 4	>5 µg/mL	6.02 (1.98,18.32)	0.002	0.092
	>10 µg/mL	3.32 (1.82,6.07)	<0.001	0.091
All	>5 µg/mL	4.28 (2.76,6.65)	<0.001	0.089
	>10 µg/mL	2.62 (1.93,3.55)	<0.001	0.066

Table S9 OR for CRP based clinical remission and CL below cutoffs.

	Cutoff	OR	P value	Pseudo R2
Cohort 1	<0.318 L/day	3.43 (1.83,6.43)	<0.001	0.102
	<0.8 L/day	9.37 (3.15,27.99)	<0.001	0.191
Cohort 2	<0.318 L/day	1.75 (1.03,2.96)	0.039	0.022
	<0.8 L/day	3.68 (1.30,10.4)	0.008	0.040
Cohort 3	<0.318 L/day	4.56 (1.76,11.82)	0.001	0.150
	<0.8 L/day	28.64 (3.55,231.27)	<0.001	0.357
Cohort 4	<0.318 L/day	5.86 (3.07,11.21)	<0.001	0.178
	<0.8 L/day	5.74 (1.61,20.58)	0.002	0.069
All	<0.318 L/day	3.13 (2.28,4.29)	<0.001	0.087
	<0.8 L/day	7.21 (3.92,13.26)	<0.001	0.116

Table S10 Multivariate analysis for ER with ADA concentration and CL

	PK estimate	Adjusted OR per unit change	P value	Pseudo R^2
Cohort 1	ADA concentration (µg/mL)	0.95 (0.84,1.09)	0.468	0.138
	Clearance (L/day)	0.12 (0.02,0.79)	0.028	
Cohort 3	ADA concentration (µg/mL)	0.93 (0.8,1.07)	0.314	0.100
	Clearance (L/day)	0.13 (0.01,2.22)	0.158	
Cohort 4	ADA concentration (µg/mL)	0.99 (0.92,1.06)	0.885	0.431
	Clearance (L/day)	0 (0,0.02)	0.018	

Table S11 Multivariate analysis for FC below 100µg/g with ADA concentration and CL

	PK estimate	Adjusted OR per unit change	P value	Pseudo R^2
Cohort 1	ADA concentration (µg/mL)	0.89 (0.77,1.03)	0.118	0.280
	Clearance (L/day)	0.06 (0.01,0.52)	0.012	
Cohort 3	ADA concentration (µg/mL)	1.07 (0.95,1.2)	0.254	0.091
	Clearance (L/day)	0.54 (0.07,4.16)	0.558	
Cohort 4	ADA concentration (µg/mL)	1.02 (0.97,1.07)	0.378	0.109
	Clearance (L/day)	0.27 (0.09,0.82)	0.020	
	Clearance (L/day)	**0.24 (0.11,0.52)**	**<0.001**	

Table S12 Multivariate analysis for sustained CRP remission with ADA concentration and CL

	PK estimate	Adjusted OR per unit change	P value	Pseudo R^2
Cohort 1	ADA concentration (µg/mL)	0.98 (0.92,1.05)	0.579	0.169
	Clearance (L/day)	0.14 (0.03,0.66)	0.112	
Cohort 2	ADA concentration (µg/mL)	0.93 (0.85,1.03)	0.162	0.446
	Clearance (L/day)	0.03 (0,0.25)	0.006	
Cohort 3	ADA concentration (µg/mL)	0.81 (0.68,0.97)	0.034	0.787
	Clearance (L/day)	0 (0.01,0.02)	0.001	
Cohort 4	ADA concentration (µg/mL)	0.97 (0.92,1.02)	0.277	0.807
	Clearance (L/day)	0 (0,0.02)	<0.001	
	Clearance (L/day)	**0.02 (0.01,0.07)**	**<0.001**	

Table S13: **Repeated event analysis with CRP based clinical remission status**.
Estimates are provided with relative standard error (<50% indicates significant association).

	Time only	Conc. only	CL only	Time and concentrations	Time and CL
Population	-0.32 (206%)	-0.95 (54%)	2.33 (24%)	-1.06 (62%)	2.77 (39%)
Time regressor (wks)	-0.010 (118%)	NA	NA	-0.002 (705%)	-0.003 (410%)
PK regressor	NA	0.10 (38%)†	-5.04 (24%)†	+0.1 (53%)	-5.64 (32%)†
-2LL	272.0	265.8	237.9	265.9	239.1

†<50% is significant regressor; NA: not applicable. -2LL: -2 log likelihood.

Table S14: **Repeated event analysis with FC levels below 100µg/g**.
Estimates are provided with relative standard error (<50% indicates significant association).

	Time only	Conc. only	CL only	Time and concentrations	Time and CL
Population	1.26 (59%)	-1.32 (91%)	1.20 (49%)	3.23 (50%)	10.74 (18%)
Time regressor (wks)	-0.017 (102%)	NA	NA	-0.082 (41%)†	-0.082 (31%)†
PK regressor	NA	+0.210 (32%)†	-1.57 (52%)	+0,18 (78%)	-7.2 (21%)†
-2LL	196.9	203.3	193.2	197.9	202.7

†<50% is significant regressor; NA: not applicable. -2LL: -2 log likelihood.

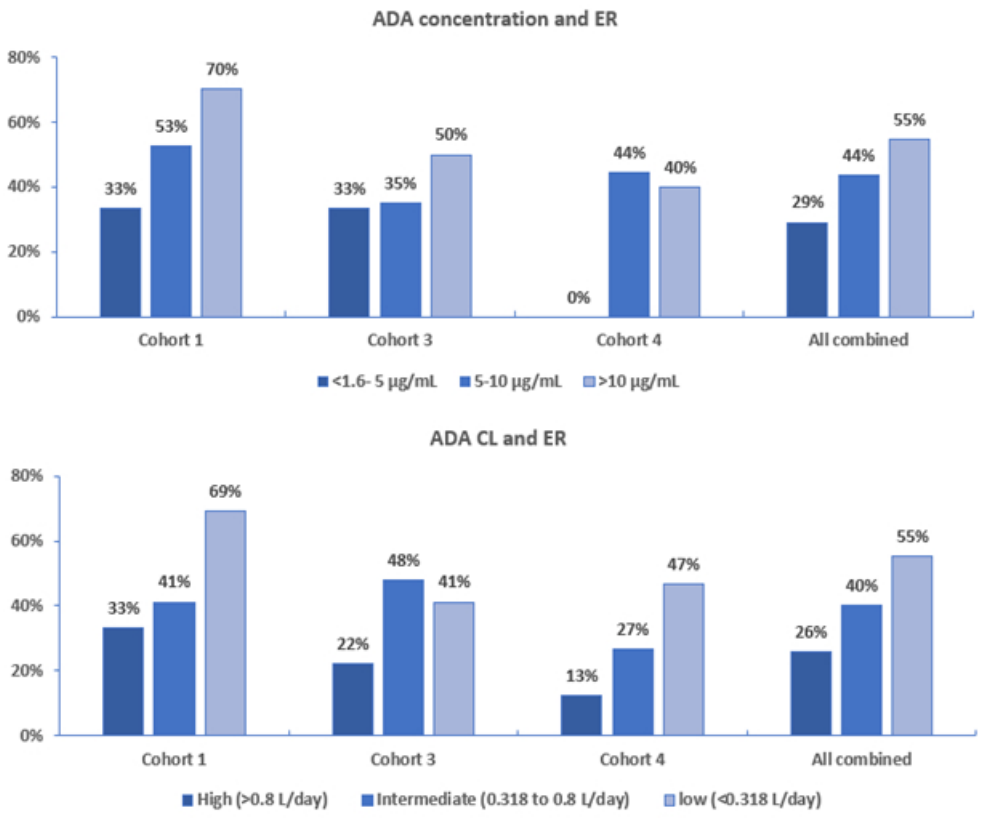

Figure 1

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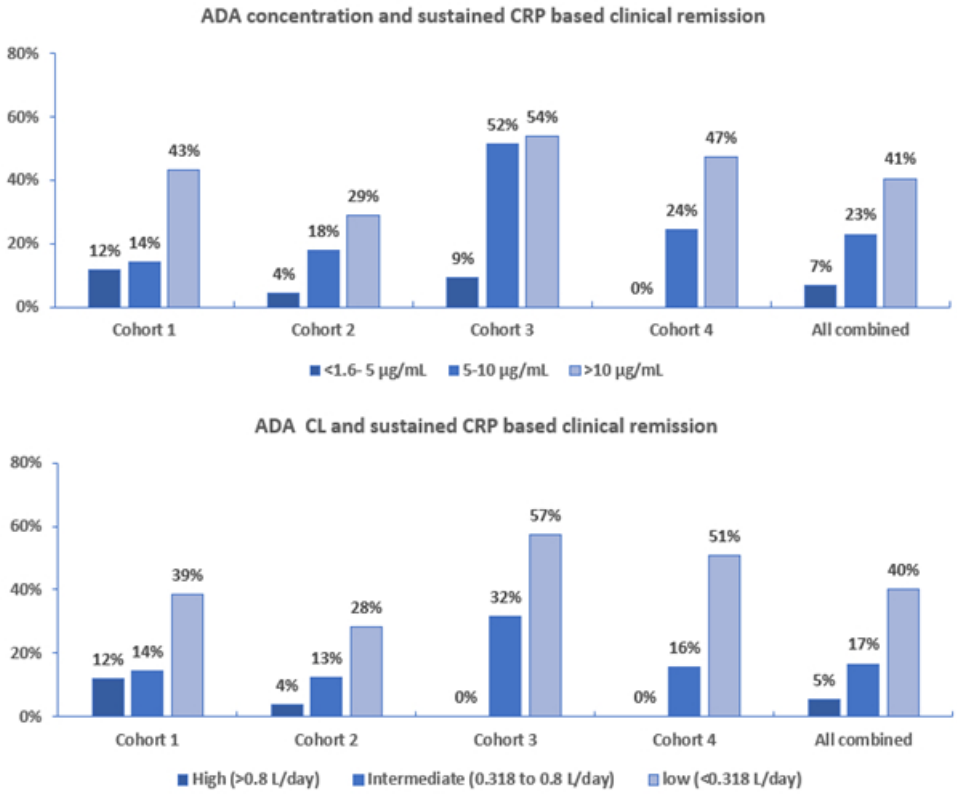

Figure 2

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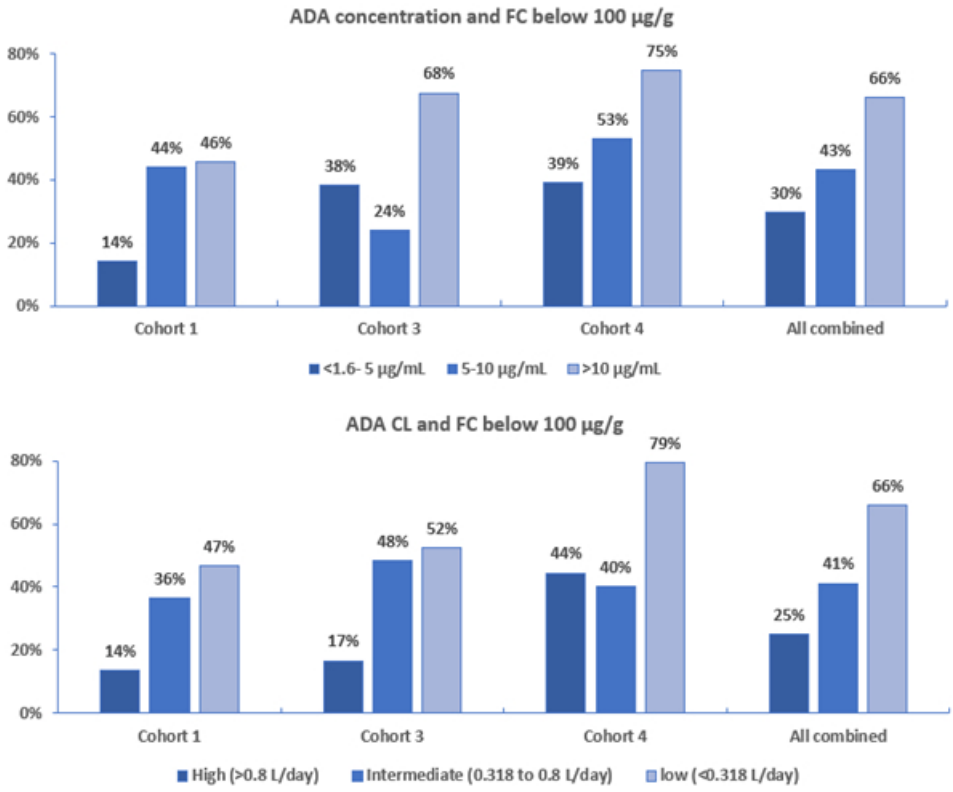

Figure 3

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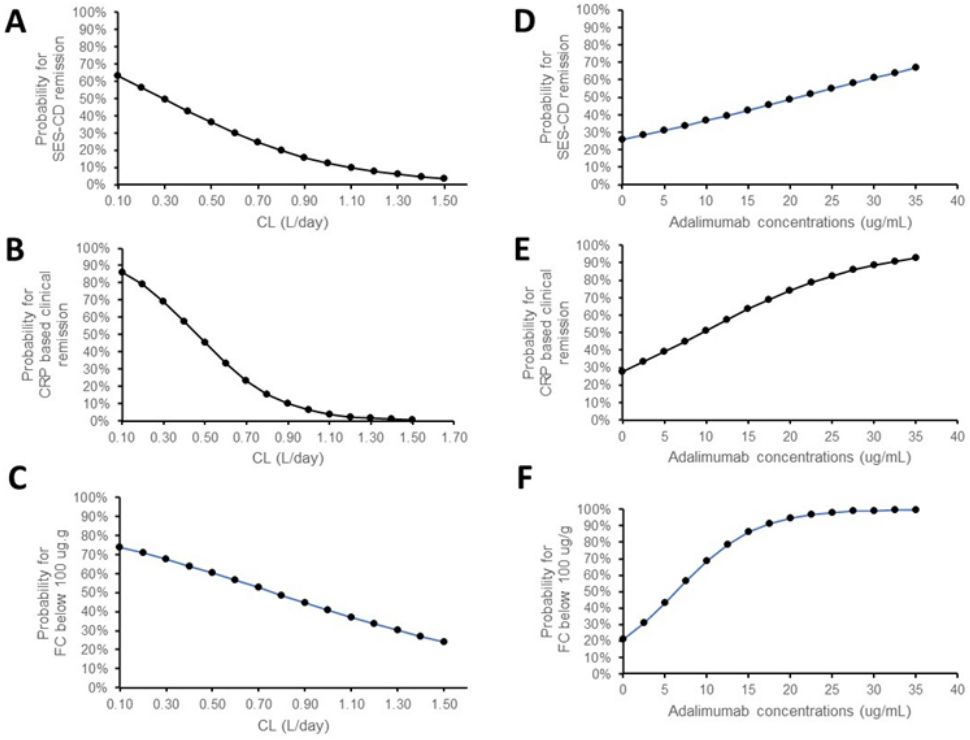

Figure 4

416x312mm (47 x 47 DPI)