Digestive Diseases and Sciences (2021) 66:2744–2749
https://doi.org/10.1007/s10620-020-06567-x

ORIGINAL ARTICLE

No Difference of Adalimumab Pharmacokinetics When Dosed at 40 mg Every Week or 80 mg Every Other Week in IBD Patients in Clinical Remission After Adalimumab Dose Intensification

Stephane Paul[1,2] · Nicolas Williet[3] · Stéphane Nancey[4,5,6] · Pauline Veyrard[3] · Gilles Boschetti[4,5,6] · Jean-Marc Phelip[3] · Bernard Flourie[4,5,6] · Xavier Roblin[2,3,4]

Received: 14 May 2020 / Accepted: 19 August 2020 / Published online: 16 September 2020

Abstract

Introduction The pharmacokinetic equivalence of dose intensification with adalimumab (ADA) 80 mg every other week (EOW) compared to weekly 40 mg has only been supported by modeling systems.

Aim of the Study To compare the trough levels of ADA (TLA) and the occurrence of anti-ADA antibodies (AAA) between these two treatment regimens.

Patients and Methods This was a prospective study including all consecutive patients with inflammatory bowel disease (IBD) who had reached a longstanding and deep remission under treatment with ADA 40 mg once a week. In these patients, the ADA regimen was changed from 40 mg/week to 80 mg EOW. TLA and AAA levels using a drug-tolerant assay were monitored before and ten weeks after from the change in the ADA regimen and the results compared by a Wilcoxon paired test.

Results Sixty-two patients (60% CD, mean age 35 years) were included. Before and ten weeks after the changes of ADA regimen, the median TLA were (6.9 µg/mL versus 7.0 µg/mL, respectively; $P=0.34$) and the AAA levels (3.4 µg/ml-eq versus 3.0 µg/ml-eq, respectively; $P=0.25$.) were quite similar. Likewise, quartiles of TLA (Kendall test $r=0.91$; $P<0.001$) and AAA ($r=0.78$; $P<0.001$) did not differ before and after ADA regimen. When stratifying all the patients into 4 groups based on drug/antibody levels (immunogenic, subtherapeutic, therapeutic, or supratherapeutic), no patient needed for returning to the previous weekly regimen. In terms of acceptability, more than 60% of patients preferred an injection EOW compared once a week.

Conclusions In IBD patients who achieved a deep clinical remission under ADA 40 mg once a week, the pharmacokinetic of ADA was similar when ADA regimen was changed to 80 mg EOW. Given the patient's preference for the latter regimen, a modification of injection regimen should be systematically proposed.

Keywords Adalimumab · Anti-adalimumab antibodies · Pharmacokinetics · Switch

Abbreviations

ADA	adalimumab
TLA	trough levels of adalimumab
AAA	antibodies against adalimumab
CD	Crohn's disease
UC	Ulcerative colitis

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10620-020-06567-x) contains supplementary material, which is available to authorized users.

✉ Xavier Roblin
xavier.roblin@chu-st-etienne.fr

[1] Faculty of Medicine of Saint-Etienne, Immunology Unit University hospital of saint Etienne, CIC INSERM 1408, Saint-Etienne, France

[2] Groupe Immunité des muqueuses et Agents Pathogènes (GIMAP), INSERM U1111- International center for research in infectiology (CIRI), Saint-Etienne, France

[3] Department of Gastroenterology, Saint-Etienne University hospital, Saint-Etienne, France

[4] Department of Gastroenterology, Lyon-Sud University Hospital, Hospices Civils de Lyon, Pierre Bénite, France

[5] University Claude Bernard Lyon 1, Lyon, France

[6] INSERM U1111- International center for research in infectiology (CIRI), Lyon, France

TNF	Tumor necrosis factor
ELISA	Enzyme-linked immunosorbent assay
CRP	C-reactive protein
CDAI	Crohn's disease activity index

Introduction

Adalimumab has been shown to be effective in the induction and maintenance treatment of Crohn's disease (CD) and ulcerative colitis (UC) [1, 2]. Recent real-life-based data report that primary non-response to ADA therapy in CD is an issue that concerns around 27% of patients based on the large PANTS study [3]. In addition, loss of response over time is common and estimated at 20% per year [4] leading to therapeutic optimization able to recapture a clinical response in almost half IBD patients. [5–7]. In addition, therapeutic adherence to ADA remains modest since more than one-third of patients has insufficient compliance [8], contributing, at least in part to a secondary loss of response over time [9].

Basically, increased frequency of injecting a drug has a negative impact on drug adherence. Thus, the greater interval between drug injections, especially in outpatients, should be taken into account to guide physician's decision in maintenance therapy for IBD patients and subsequently dose intensification of ADA therapy using the regimen 80 mg EOW should be preferred when it is possible compared with that of 40 mg once a week to achieve a better patient's compliance and acceptability. However, data on the pharmacokinetic consequences of changing the injection regimen (from 40 mg once a week to 80 mg EOW) during maintenance ADA therapy in IBD patients in remission are lacking. We aimed to evaluate the pharmacokinetics of ADA, including trough levels of ADA (TLA) and the occurrence of anti-ADA antibodies (AAA) when changing the schedule of ADA injection from ADA 40 mg once a week to ADA 80 mg EOW in a cohort of IBD patients in clinical remission.

Patients and Methods

Study Population

This was a prospective study that included all consecutive patients with IBD followed in two referral sites. Eligible patients were patients in clinical remission for at least 6 months under ADA therapy at an intensified dose of 40 mg SC once a week. Patients should use the self-ADA injection with the dedicated pen into the abdomen or front thigh. It was systematically proposed to these patients to modify the schedule of ADA injection to 80 mg SC EOW. Patients were part of the CNIL cohort (Number: 1849323), and all were informed and accepted by a written consent to participate in the study.

When ADA was used in combotherapy with an immunosuppressant, the dosage of this latter was stable at least 3 months before changing the ADA regimen and was also maintained stable during the whole study period. Clinical remission was defined for CD by a CDAI score < 150 with a fecal calprotectin level < 250 µg/g and for UC by a total Mayo score ≤ 3 with a rectal bleeding subscore not > 1 and an endoscopic subscore of 0 or 1.

Blood and Fecal Sampling for Pharmacokinetic and Calprotectin Monitoring

TLA and AAA monitoring was performed 24 h before changing the injection of 80 mg and ten weeks after just before a new injection of ADA. Blood samples were collected for monitoring TLA and AAA levels which was measured using the Lisa-Tracker Premium Adalimumab ELISA kits (Theradiag, Marne La Vallée, France). The TLA data were fully blinded to clinical results. The used drug-sensitive assay has been developed to reduce low-affinity binding of immune complexes or interfering molecules such as rheumatoid factor. A very efficient capture of free molecules was allowed by using specific buffers for both binding and washing steps. In addition, detection of AAA was assessed by a drug-tolerant technique on all samples, according to the method previously reported by Ben Horin et al. using anti-human lambda chain for the detection of antidrug antibodies [10]. Fecal calprotectin concentrations were measured using the fCAL® turbo assay (Buhlmann, Basel, Switzerland) before and ten weeks after having changed the rhythm of ADA injections.

Patient's Acceptability Assessment

To assess patient's preference, a simple self-questionnaire was offered to all enrolled patients to rate their own experience of the ADA regimen modification as favorable, neutral, or negative. In the event of a favorable or a negative experience, an open explanation was requested. All patients accepted questionnaire assessment systematically performed at W10 after modification of device (80 mg EOW). Supplementary Table 1 reports this questionnaire.

Statistical Analysis

Regarding paired comparisons of pharmacokinetic parameters at the 2 time points considered (before and after the ADA regimen modification), a Wilcoxon paired test was used for continuous variables (TLA and AAA levels) and the Mann–Kendall test for the concordance rate between

Table 1 Patient characteristics

Age mean (SD) (years)	35 (15)
Sex ratio M/F	60%
IBD type	37 CD, 25 UC
Phenotype ($n=$) (according to Montreal classification)	CD A2: 37 L1: 20 L2: 9 L3: 8 B1: 23 B2: 6 B3: 8 p: 6 UC E1: 4 E2: 12 E3: 9
Duration of disease mean (SD) (years)	4.5 (2.1)
Prior IFX (N, %)	15 (24%)
Concomitant azathioprine (N, %)	6 (10%)
Active smoking (N, %)	25 (40%)
CDAI/Clinical Mayo score at inclusion mean (SD)	CDAI: 85 (39) Clinical Mayo score: 2 (1)
Fecal calprotectin (µg/g stool) mean (SD)	120 (80)

quartiles. Regarding comparisons of two or more independent (sub)groups into the present cohort, Chi or Fisher tests were appropriately used for qualitative variables. Correlation between ADA levels and AAA was reported using Pearson correlation coefficient. The statistical significance was reached for a p value < 0.05. All statistical analyses were performed using R, version 3.2.2 (R project, Auckland, New Zealand).

Results

Study Population

Sixty-two IBD patients, including 60% with CD, were included in this study (Table 1). The average age was 35 years, and 90% of them were treated with ADA monotherapy. During the whole follow-up (median FU: 10 weeks) after changing ADA regimen from 40 mg once a week to 80 mg EOW, no patient experienced a loss of response under ADA therapy.

ADA Pharmacokinetics

The median TLA levels did not differ before and ten weeks after having changed ADA regimen to 80 mg EOW (6.9 µg/mL versus 7.0 µg/mL, respectively; $P=0.34$) and were comparable for each patient (Wilcoxon paired test: 0.34) (Fig. 1a). The AAA levels were found similar before and after having changed ADA regimen (3.4 µg/ml-eq vs, 3.0 µg/ml-eq, respectively; $P=0.25$) and were also comparable for each patient (Wilcoxon paired test: 0.25) (Fig. 1b) (Table 2).

The quartiles of ADA as well as those of AAA were found closely similar before and 2 months after having changed ADA regimen (Kendall test: 0.91 and 0.78, respectively; $P<0.001$ for both) (Table 3). Finally, when stratifying into four groups based on drug/antibody levels (immunogenic with undetectable TLA and positive AAA ($n=4$), subtherapeutic TLA (<4.9 µg/ml)($n=16$), therapeutic TLA (between 4.9 and 12 µg/ml) ($n=26$), and supratherapeutic TLA (>12 µg/mL) ($n=16$), the patients prior modifying ADA regimen, all of them stayed in the same group at 2 months after changing to 80 mg EOW.

There was an inverse and linear correlation between TLA and AAA under therapy with ADA 40 mg once a week (Rho $=-0.84$; $P<0.001$). This correlation stayed quite similar 2 months after changing ADA regimen into 80 mg EOW (Rho $=-0.87$; $P<0.001$) (Supplementary Fig. 1).

Evolution of Clinical, Endoscopic, and Biomarker Scores Before and After Modification of ADA Schedule of Administration

The clinical activity score according to CDAI score for CD or Mayo clinical scores was similar before and ten weeks after the modification of regimen (median CDAI score: 70 (45–110) and 60 (30–95) before and ten weeks after modification of regimen, respectively; $P=0.65$; median clinical Mayo score: 1 (0–1) and 1 (0–1.5) before and ten weeks after the modification of regimen; $P=0.95$). Median fecal calprotectin and CRP levels were not changed after modification of ADA regimen ($P=0.40$ and 0.90, respectively) (Fig. 2). Moreover, in UC patients, Mayo clinic endoscopic score was reported on pre- and post-change in ADA frequency (week 10). Median clinical endoscopic score was similar between the two times: endoscopic subscore before (0 (0–1)) versus after modification of regimen (0 (0–1)); $P=0.95$ (Fig. 2).

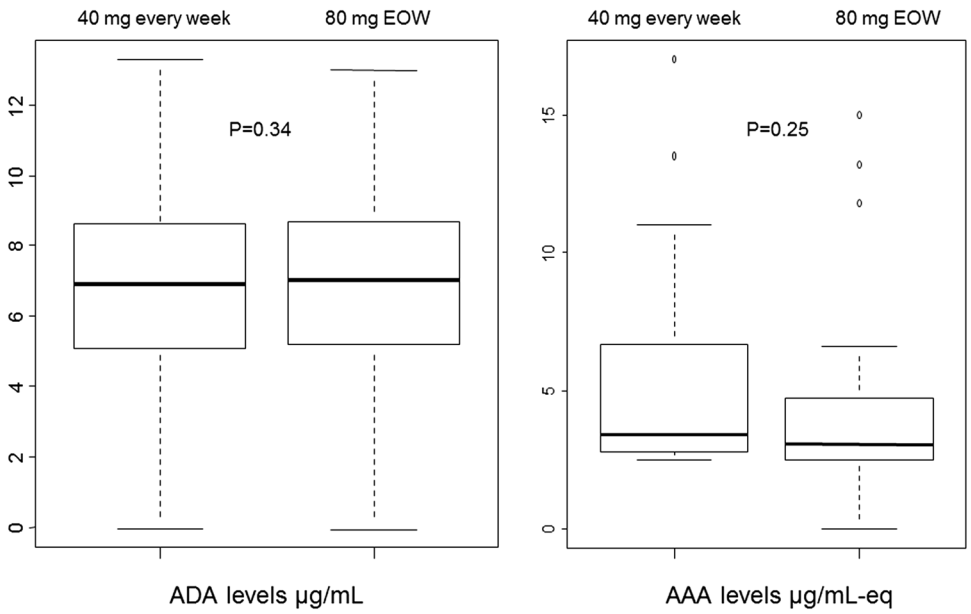

Fig. 1 **a** Comparison of median TLA levels before and ten weeks after having changed ADA regimen to 80 mg EOW (6.9 µg/mL versus 7.0 µg/mL, respectively; $P=0.34$). **b** Comparison of median AAA levels before and after having changed ADA regimen (3.4 µg/ml-eq vs. 3.0 µg/ml-eq, respectively; $P=0.25$)

Table 2 Pharmacokinetics of ADA (AAA: anti-ADA antibody)

Median variability [IQR]	Before changing ADA dose regimen	After changing ADA dose regimen	*P* value (Wilcoxon paired test)
TLA (µg/mL)	6.9 [5.1–8.6]	7.0 [5.2–8.7]	0.34
AAA (µg/mL-eq)	3.40 [2.82–6.70]	3.05 [2.52–4.70]	0.25

Table 3 ADA quartiles before and after changing ADA dose regimen from ADA 40 mg once a week to 80 mg EOW (AAA: anti-ADA antibody)

Quartiles TLA	[0,5.1] [5.1,6.9] [6.9,8.6] [8.6,13.3]
ADA: 40 mg once a W	"18 (30 1%)" "13 (21 1%)" "15 (25 1%)" "15 (25 1%)"
ADA: 80 mg EOW	"15 (25 1%)" "15 (25 1%)" "15 (25 1%)" "16 (26 1%)"
	Kendall test: 0.91
Quartiles AAA anti-ADA antibody	[2.5,2.8] [2.8,3.4] [3.4,6.7] [6.7,17)
ADA: 40 mg once a W	"6 (29 1%)" "6 (29 1%)" "6 (29 1%)" "3 (14 1%)"
ADA 80 mg EOW	"4 (21 1%)" "6 (32 1%)" "6 (32 1%)" "3 (16 1%)"
	Kendall test: 0.78

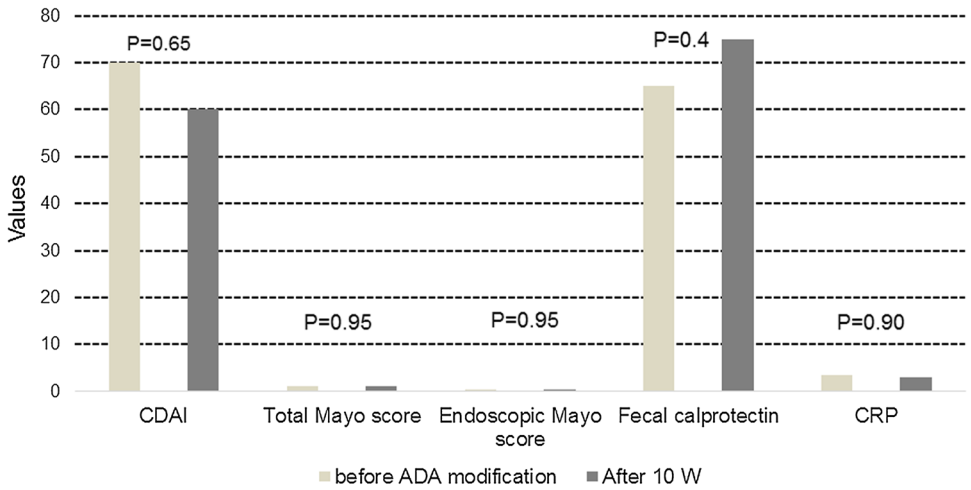

Fig. 2 Changes in Mayo clinic score, Mayo clinic endoscopic score, CDAI, fecal calprotectin levels (µg/g stools), CRP levels (mg/L) before and after modification of ADA regimen (ADA 80 mg/sc EOW)

Fecal Calprotectin Monitoring

Median fecal calprotectin levels did not differ before and after having modified ADA regimen in IBD patients (120 µg/g stool versus 110 µg/g stool, respectively; $P=0.40$). There was no difference in terms of ADA pharmacokinetics and fecal calprotectin levels in CD and UC patients.

Adverse Events

No adverse effect was reported during the follow-up period.

Patient's Preference

Based on the results of self-questionnaires, the majority of patients (60%) report that the ADA regimen with one SC injection EOW was more convenient when compared with the previous one once a week. Thirty percentage of them found no difference between the both regimens of ADA injection and indicate that ADA SC injections with the dedicated pen were simple and fully painless whatever the rhythm of drug injection. However, all of them decided to pursue ADA regimen at one injection 80 mg EOW. Only 10% of patients did not appreciate the modification of ADA regimen and had the feeling of a negative experience. These patients preferred a regular once a week-based injection considered as very easy and painful (with the habit of a particular day within the week) and feared to forget performing their ADA injection with the novel regimen one injection EOW. Thus, for this reason, all of these latter patients wished going back to the previous ADA regimen with one injection once a week.

Discussion

To our best knowledge, this is the first real-world open-label prospective study investigating the potential differences in terms of pharmacokinetics and patient's preferences between 2 optimized ADA dose regimens in IBD patients. Here, we report that pharmacokinetics of ADA (based on TLA and AAA using a drug-tolerant assay) did not differ when ADA regimen was changed from 40 mg once a week to 80 mg EOW in a cohort of consecutive IBD patients in longstanding clinical remission. In addition, most of the patients found more convenient the latter ADA regimen by preferring to minimize the frequency of drug injection. These daily practice-based results differ from those from modeling data reporting significantly lower median TLA when using the ADA 80 mg EOW regimen compared to that ADA 40 mg once a week. These discrepancies are likely due to intra- and inter-individual variabilities, which can probably not be fully captured in previous modeling studies. However, based on the present findings, one might speculate that the area under the curve could be larger under ADA 80 mg EOW than under ADA 40 mg once a week. By analyzing the quartiles of ADA before and after changing its regimen of injection, no difference was observed. Finally, when stratifying all the patients according to the TLA/AAA profile, none of them changed their status. In our cohort, only 6% of patients in clinical remission had undetectable TLA associated with AAA using drug-sensitive or drug-tolerant assay. These results are in accordance with those from 2 clinical trials, the pivotal CHARM trial and the SONIC study in which nearly 5% of patients and less than 10% of cases, respectively, experienced these particular pharmacokinetic profile [11, 12] and ADA discontinuation could be possibly considered in these patients [13]. Using a drug-tolerant assay in the present study, AAA were detected in 17% of patients and these results are in line with those from Ungar et al. [14] and from the recently published PANTS study [3]. The modification of ADA dose regimen from 40 mg once a week to 80 mg EOW was not associated with the occurrence and the levels of AAA within 2 months.

We acknowledge some limitations of our study since it was not a randomized study with a direct head-to-head comparison of the resulting pharmacokinetics from patients under one of the 2 dose regimens. In our prospective study, PK were compared longitudinally in all patients who met inclusion criteria prior and after changing dose regimens. We also excluded external parameters that could substantially impact the pharmacokinetics of ADA, in particular, in active disease at the time of inclusion or in case of recent introduction of thiopurines to ADA therapy. However, our study cannot determine the best issue between ADA 40 mg once a week and ADA 80 mg EOW when a loss of response to ADA 40 mg EOW occurred. Nevertheless, our results could indirectly suggest that the 80 mg EOW might be as effective as 40 mg once a week in terms of PK given the probably larger area under the curve during the ADA dose regimen once a week. However, dedicated studies are mandatory to address this issue.

In the present study, all patients had to use the ADA pens for SC injection. Previous multicenter studies previously confirm that TLA were similar between the pen and the prefilled syringe [13].

In conclusion, we demonstrated that TLA and occurrence and levels of AAA do not differ in patients with inactive IBD under maintenance therapy with dose-intensified ADA between ADA dose regimens 40 mg once a week and 80 mg EOW. In addition, the latter was preferred by most of the patients by reducing the frequency of SC injections. Altogether, these findings suggest that changing the dose regimen to 80 mg EOW instead of 40 mg once a week should be systematically proposed to our IBD patients in clinical practice.

Compliance with Ethical Standards

Conflict of interest All authors have declare that they have no conflict of interest.

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