TREATMENT WITH TOFACITINIB IN REFRACTORY PSORIATIC ARTHRITIS. NATIONAL MULTICENTER STUDY OF THE FIRST 87 PATIENTS OF CLINICAL PRACTICE

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ABSTRACT

Objectives: Tofacitinib (TOFA) is the first Janus kinase (JAK) inhibitor approved for Psoriatic Arthritis (PsA). It has shown efficacy in patients refractory to anti-TNFα in Randomized Clinical Trials (RCT). Our aim was to assess efficacy and safety of TOFA in clinical practice.

Methods: Observational, open-label multicenter study of PsA patients treated with TOFA due to inefficacy or adverse events of previous therapies. Outcome variables were efficacy, sparing corticosteroid-dose effect, retention rate and safety. Comparative study of clinical features between our cohort of patients and those from the OPAL BEYOND trial was performed.

Results: 87 patients (28 women/59 men), mean age of 52.8±11.4 years. All patients were refractory to b-DMARDs and/or to cs-DMARDs plus Apremilast. TOFA was started at 5mg twice daily after a mean follow-up of 12.3±9.3 years from PsA diagnosis. At first month, $DAS28_{ESR}$ decreased from 4.8 [4.1-5.4] to 3.7 [2.8-4.7] ($p < 0.01$), DAPSA from 28 [18.4-34.1] to 15.5 [10.1-25.7] ($p < 0.01$) and C-reactive protein from 1.9 [0.3-5.0] to 0.5 [0.1-2.2] mg/dL ($p < 0.01$). Also, TOFA led to a significant reduction of prednisone dose. Mild adverse effects were reported in 21 patients (24.13%), mainly gastrointestinal symptoms. TOFA retention rate at month 6 was 77% (CI 95%; 65.2-86.3 %). Patients of clinical practice were older with longer disease duration and received biologic agents more commonly than those in the OPAL BEYOND trial.

Conclusion: Data from clinical practice confirm that TOFA seems to be effective, rapid and relatively safe in refractory PsA despite clinical differences with patients in RCT.

Abbreviations:

ACR: American College of Rheumatology

b-DMARDs: biologic disease-modifying antirheumatic drugs

CI: confidence interval

CRP: C-reactive protein

cs-DMARDs: conventional synthetic disease-modifying antirheumatic drugs

DAPSA: disease activity in psoriatic arthritis score

DAS28-ESR: Disease Activity Score-28 with erythrocyte sedimentation rate

EMA: European Medicines Agency

HAQ-DI: Health Assessment Questionnaire–Disability Index

IL: interleukin

IQR: interquartile range

JAK: Janus kinase

LFN: leflunomide

MDA: minimal disease activity

MTX: methotrexate

NSAIDs: nonsteroidal anti-inflammatory drugs

OR: odds ratio

PASI: psoriasis area-and-severity index

PsA: psoriatic arthritis

RCT: randomized clinical trials

SD: standard deviation

SSZ: sulfasalazine

TNFα: tumor necrosis factor α

TOFA: tofacitinib

ts-DMARDs: targeted synthetic disease-modifying antirheumatic drugs

1. INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disorder comprising a wide spectrum of clinical domains, including skin and nail involvement, enthesitis, dactylitis as well as axial and peripheral arthritis (1). The recommended therapy depends on the clinical manifestations. It may include nonsteroidal anti-inflammatory drugs (NSAIDs); conventional synthetic disease-modifying antirheumatic drugs (cs-DMARDs), targeted synthetic (ts)-DMARDs, such as phosphodiesterase-4 inhibitors; and biologic (b)-DMARDs such as anti-tumor necrosis factor α (anti-TNFα), interleukin (IL)-12/23 and IL-17 inhibitors (2,3).

Anti-TNFα are the current standard of care for PsA patients with an inadequate response to conventional therapy (2,3). However, loss of efficacy is not uncommon in the clinical practice (4). In addition, the proportion of patients achieving Minimal Disease Activity (MDA) across Randomized Clinical Trials (RCT) with anti-TNFα is highly variable, ranging from 33% to 52% at 24 weeks (5–8). The proportion of patients fulfilling MDA criteria at 12 months in observational studies and open-label cohorts, ranged from 44% to 64% (9–12).

IL-17 inhibitors seem to be especially useful for skin and musculoskeletal manifestations of PsA (13). However, they are not useful or even harmful in patients with underlying inflammatory bowel disease. IL-12/23 inhibitor and Apremilast have shown modest and slow joint response, with an ACR 20 response of 43.7% and 40.7% at 24 weeks, respectively (14–17).

Tofacitinib (TOFA) is the first Janus kinase (JAK) inhibitor approved for the treatment of PsA by the European Medicines Agency (EMA) in June 2018. TOFA is a small-molecule inhibitor of JAK1, JAK3 and, to a lesser extent, JAK2 (18) which inhibits key immune triggers of both psoriasis and PsA (19). In the OPAL Beyond trial, TOFA showed to be more effective than placebo in active PsA patients with an inadequate response to anti-TNFα (20).

Randomized clinical trials (RCT) are the best tool to assess the efficacy of therapeutic agents (21). They are conducted under highly standardized design and strict inclusion criteria to ensure the reliability of results (22,23). However, it is known that the demographic and clinical features of patients included in RCT may differ from those of clinical practice. These differences may have an influence on the clinical outcomes when applied to patients seen in daily clinical practice (24–30). In this regard, it is very important to carry out observational studies in order to obtain real-world evidence, which is needed to improve health care decision making and to assess the feasibility of evidence from RCTs (24,25,30–32).

Taking all these considerations into account, our aim was to assess the efficacy and safety of TOFA in PsA patients from a real clinical setting with inadequate response and/or with unacceptable side effects to conventional therapy. In addition, we aimed to compare the clinical profile of patients from our cohort with those patients included in the OPAL BEYOND trial (20).

2. PATIENTS and METHODS

We conducted an open-label, multicenter study including 87 patients of clinical practice with refractory PsA treated with TOFA.

2.1 Patients and Enrollment Criteria

We included all the patients with PsA diagnosis who had received at least one dose of TOFA at the Rheumatology Division of 25 national referral centers of Spain between January 1, 2015 and December 31, 2019. The ethical approval for the study protocol was originally obtained from the Institutional Review Committee at Hospital Marqués de Valdecilla in Santander, Spain (Approval Number: 2019.177) and was subsequently approved by the remaining participating centers.

PsA diagnosis was based on CASPAR criteria (33). Refractory PsA was defined when the patient did not achieve clinical low disease activity or remission despite the use of b-DMARDs or Apremilast.

All patients were refractory to at least one b-DMARD or to cs-DMARDs in addition to Apremilast. TOFA was used at the standard dose of 5 mg taken orally twice daily. Since TOFA therapy was an off-label indication for PsA, before EMA approval in June 2018, written informed consent was requested and obtained for those patients.

Following the Spanish Biologic Treatment Administration National Recommendations, the presence of infectious diseases was ruled out before starting treatment with TOFA (34). To exclude latent tuberculosis, a tuberculin skin testing and/or an interferon assay (quantiFERON) as well as chest radiography were performed. In positive cases, prophylaxis with isoniazid was initiated for at least 4 weeks before using the biologic treatment and was maintained for 9 months. Patients with active malignancies were excluded.

2.2 Outcome variables

The outcome variables were efficacy, corticoid-dose sparing effect, retention rate and safety of TOFA therapy.

The main efficacy outcomes were improvement in the $DAS28_{ESR}$ (35) and Disease Activity in Psoriatic Arthritis Score (DAPSA) (36). DAPSA is the result of the sum of the number of painful joints, number of swollen joints, C Reactive Protein (CRP), the patient's global assessment of arthritis (as measured on a visual-analogue scale that ranges from 0 to 100 mm) and the patient's assessment of arthritis pain (as measured on a visual-analogue scale).

The secondary outcome was skin efficacy, which was assessed by the improvement on the psoriasis area-and-severity index (PASI) score (range from 0 to 72, higher scores indicating more severe disease) (36,37).

For the purpose of comparing the clinical profile of our cohort of patients with those from RCT, information was retrieved from the results of the TOFA arm (5 mg/12 h) of OPAL BEYOND RCT (20).

2.3. Data collection and Statistical Analysis

Information was retrieved from the patient's clinical records in each participating center according to a predefined protocol. To minimize entry error, all data was double checked. Information was stored in a computerized database.

All continuous variables were tested for normality, and results were expressed as mean±standard deviation (SD) or as median and interquartile range (IQR) as appropriate. The chi-square (χ^2) test and the Student'st-test or U-Mann-Whitney test were used for comparison of qualitative and quantitative variables, respectively. For comparisons among quantitative follow-up data related to baseline, paired Student's t-test or Wilcoxon's signed rank test were used. Medians were compared by quantile regression analysis.

The outcome variables were assessed and compared between baseline (at TOFA onset), and at 1 and 6 months.

Retention rate at month 6 was estimated using Kaplan-Meier non-parametric survival data analysis in which the event was discontinuation of the drug due to inefficacy or toxicity.

Statistical significance was set at $p<0.05$. Analyses were performed using SPSS 23.0 (IBM Corporation, Armonk, NY, U.S.) and Stata SE 14.2 (StataCorp, College Station, TX, US).

2.4 Role of the Funding source

This study was not funded by any drug company. It was the result of an independent initiative of the investigators.

3. RESULTS

3.1. Baseline main clinical features at Tofacitinib onset

We studied 87 patients (28 women/ 59 men) with a mean age of 52.8±11.4 years **(Table 1)**. All patients fulfilled CASPAR criteria for PsA diagnosis. The pattern of joint involvement of PsA was peripheral (n=60), mixed (n=26) and axial (n=1).

The mean±SD time from PsA diagnosis to TOFA onset was 12.3±9.3 years. The main clinical features at the time of TOFA onset were arthritis (95.4%), skin involvement (48.3%), enthesitis (32.2%), nail involvement (19.5%) and dactylitis (18.4%) **(Table 2)**.

Before TOFA, all patients had received at least one cs-DMARDs (mean number, 2.26±0.86) and one b-DMARDs (mean number, 3.6±1.9). Previous cs-DMARDs were methotrexate (MTX) (n=72), leflunomide (LFN) (n=48), and sulfasalazine (SSZ) (n=39). Previous b-DMARDs were the following: etanercept (n= 58), adalimumab (n=54), secukinumab (n=54), ustekinumab (n=39), golimumab (n=37), infliximab (n=31), certolizumab (n=30), and ixekizumab (n=2). Apremilast was used in 17 patients. Also, 44 (50.6%) patients had received oral prednisone or equivalent (maximum mean dose;15.8±13.9 mg/day).

3.2. Tofacitinib treatment and efficacy

TOFA was initiated at standard dose of 5 mg twice daily. Prednisone (mean dose;7.8±4.9 mg/day) was associated in 44 cases (50.5%). Combined therapy with MTX (n=30), LFN (n=15) and SSZ (n=6) was used in 48 cases (55.2%). In the remaining 39 patients (44.8%), TOFA was used as monotherapy.

Following TOFA therapy, patients experienced a rapid and maintained joint improvement **(Table 2)**. The main outcomes ($DAS28_{ESR}$, DAPSA), showed a significant improvement at first month of TOFA that was longer maintained **(Figure 1)**. Likewise, PASI score showed a trend for improvement throughout follow-up, although no statistically significant differences were achieved **(Table 2)**.

CRP decreased from 1.90 [0.34-5] to 0.5 [0.1-2.24] (p= 0.004) at the first month. A sparing corticosteroid-dose effect was also observed. TOFA led to a reduction of the prednisone dose from 7.83±4.93 mg/day to 6.67±3.77 mg/day (p=0.006) at the first month **(Table 2)**.

Regarding concomitant use of cs-DMARDs, there were no changes in their mean dose throughout the study (data not shown).

3.3. Tofactinib retention rate and adverse-effects

TOFA retention rate at month 6 was 77% (CI 95%; 65.2-86.3 %). No serious adverse events were observed after a mean follow-up of 6.5±5.69 months. 21 (24.13%) patients experienced at least one mild adverse event including gastrointestinal symptoms (n=17), upper respiratory tract infection (n=4), tract urinary infection (n=2), headache (n=2), cutaneous infection (n=1) and sleep disturbances (n=1). TOFA was discontinued in 29 of 87 patients (33.33%) due to inefficacy in most cases. No thrombotic events were observed, and the mean levels of hemoglobin, lymphocyte, neutrophils, platelets, lipids and transaminases levels were stable throughout the follow-up **(Table 3)**. However, mild lymphopenia was reported in 3 patients and worsening of lipid profile in 3 other patients.

3.4. Comparative study of our cohort of patients from clinical practice and patients from the OPAL BEYOND clinical trial.

Patients from our clinical practice cohort (n=87) were compared to those included in the arm with standard TOFA therapy (5 mg twice daily) of the OPAL BEYOND trial (n=131) **(Table 1)**.

There was a higher proportion of men in patients from clinical practice (67.8 % vs 51.1 %, p=0. 015). Also, they were older (52.8±11.4 vs 49.5±12.3 years, p=0.047) and had a longer duration of PsA (12.3±9.3 vs 9.6±7.6 years, p= 0.020). A non-significant increased functional disability (HAQ-DI; 1.4±0.7 vs 1.3±0.7; p=0.507) was observed in patients from clinical practice. In our series, patients had received a higher number of b-DMARDs prior to TOFA than patients from OPAL BEYOND trial **(Table 1)**.

The count of tender and swollen joints, PASI Score, as well as the proportion of patients with enthesitis and dactylitis, was higher in patients from the OPAL BEYOND trial **(Table 1)**.

Regarding treatment, patients in clinical practice required more frequently corticosteroids (50.6 vs 28.0%; p=0.001) but less concomitant cs-DMARDs. In the OPAL BEYOND trial all patients received combined therapy with a stable dose of a single cs-DMARD whereas TOFA was used as monotherapy in 39 (44.8 %) patients in our series **(Table 1).**

Besides the clinical differences shown above there was good response both in the RCT as well as in clinical practice.

4. DISCUSSION

We present the first series published of patients with PsA treated with TOFA in clinical practice. Our series had a longer evolution of the disease and were more commonly refractory to conventional therapy. Despite these differences, TOFA showed clinical efficacy and was well-tolerated, making it a promising new agent for the comprehensive treatment of PsA.

Diagnosis of PsA is often delayed, resulting in significantly worse outcomes, including radiographic damage and impaired functional status (38,39). Fortunately, during the last 15 years, a range of new treatment options have been developed, which have improved outcomes for patients with PsA (40). These therapeutic agents are directed toward different specific disease pathways (41–43). As therapeutic options evolve, tailored therapies can be used depending on the most PsA affected domain (44). However, there is a striking similarity regarding joint involvement efficacy for most current therapies, with only 50 to 60% of patients meeting the primary outcome measure (ACR20) regardless of the drug mechanism of action (43)**.**

As previously mentioned, TOFA has shown efficacy in RCT for PsA refractory to cs-DMARD (OPAL Broaden) (45) and to TNF inhibitors (OPAL Beyond) (20).In the OPAL Beyond trial, at 3 months, the rates of ACR20 response with the 5-mg of TOFA were

significantly higher compared to placebo (p<0.001), as well as, the mean changes from baseline in HAQ-DI score (p<0.001). The 10-mg dose of TOFA, but not the 5-mg dose, was superior to placebo with respect to the rate of PASI75 response (p<0.001) and the mean changes. Improvement in enthesitis and dactylitis could not be tested for statistical significance but were in the same direction as the findings for the primary endpoints. In the OPAL Balance (46) post hoc analysis of pooled data from two phase 3 studies, a significantly greater proportion of TOFA-treated patients achieved PASI75 response at month 3 compared to placebo (32.1-43.7% vs. 14.3%; $p \leq 0.05$) and significant improvements in enthesitis and dactylitis were also observed. The efficacy across various PsA disease domains including ACR, HAQDI, PASI75, Leeds Enthesitis Index, dactylitis Severity Score and pain response were maintained up to 30 months (46).

Like in the OPAL Beyond trial (20), our patients experienced a rapid and maintained improvement in joint activity indexes (DAS28, DAPSA). A trend toward improvement of PASI score was also observed. In addition, a sparing corticosteroid-dose effect was achieved.

TOFA has also shown a good safety profile in phase 3 trials and in the long-term extension study. At 36 months, adverse events were reported in 79.6% patients, but only 13.8% patients had serious adverse events. TOFA was discontinued in 8.6% patients due to adverse events (46). Burmester *et al.* (47) has recently published a study including 5799 patients which compared the incidence rates of adverse events in TOFA clinical trials and real-world observational data of patients receiving csDMARD, bDMARD, or apremilast. This molecule showed a similar safety profile to that of other systemic therapies in real-world settings, except for the increased risk of Herpes Zoster (47). Noteworthy, we observed a lower frequency of minor adverse events in our study in comparison to the OPAL BEYOND trial and no serious adverse events were reported. In this regard, adverse events occurred in 55% of the patients from the OPAL BEYOND trial whereas they were reported in 24.13% of the patients from our clinical practice. The types of adverse events were similar to those observed in TOFA clinical trials with

gastrointestinal symptoms (n=17) and upper respiratory tract infection (n=4) being the most commonly reported. Mild lymphopenia was reported in 3 patients. The fact that TOFA was administered in monotherapy in almost half of the patients in our series whereas all patients from the OPA BEYOND trial received TOFA along with cs-DMARDs may explain the lower frequency of adverse events in the clinical practice.

We observed a retention rate to TOFA of 77% (CI 95%; 65.2-86.3 %) at 6 months. Of note, most of our patients had previously received at least one anti-TNFα or other (non-anti-TNFα) bDMARD, which may reflect that these patients had a more aggressive disease.

This study has certain limitations derived from the retrospective design. In addition, the follow-up period was relatively short (6.5±5.69 months) mainly because TOFA could not be prescribed until September 2019 in Spain. Furthermore, this is a single arm study so in the absence of comparative data, it is purely descriptive. Another limitation of this study was the use of DAS28-ESR as this is a rheumatoid arthritis outcome measure. However, we have included DAPSA to address this limitation. Moreover, we are aware that retention rates may be artificially higher in patients with refractory disease who have fewer therapeutic options.

In conclusion, our data support that TOFA is effective, rapid and relatively safe in daily clinical practice for refractory PsA despite the clinical differences with patients included in the OPAL BEYOND trial.

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FIGURE LEGEND

Figure 1. Improvement in disease activity indexes in 87 patients with refractory psoriatic arthritis following TOFA therapy. **(A)** Disease Activity Score-28 with erythrocyte sedimentation rate ($DAS28_{ESR}$). **(B)** Disease Activity in Psoriatic Arthritis Score (DAPSA). Bars represent median values with 95% confidence intervals; p-compared with baseline,* $p< 0.01$

Table 1. Baseline characteristics of 87 patients with refractory psoriatic arthritis of clinical practice and the arm of standard TOFA therapy (5 mg/12h) of OPAL BEYOND Clinical trial.

	CLINICAL PRACTICE (N=87)	**CLINICAL TRIAL** *Gladman D, et al [20].* (N=131)	**p**
Baseline demographic parameters			
Age, years (mean±SD)	52.8±11.4	49.5±12.3	0.047
Sex, n (%)	59M/28F (67.8/32.2)	67M/64F (51.1/48.9)	0.015
Disease Characteristics			
Duration of psoriatic arthritis, year (mean±SD)	12.3±9.3	9.6±7.6	0.020
HAQ-DI *	1.4±0.7 (n=26)	1.3±0.7	0.507
Swollen joint count, mean±SD	5.7±5.8	12.1±10.6	< 0.001
Tender joint count, mean±SD	8.0±6.6	20.5±13.0	< 0.001
Enthesitis, n (%) **	28 (32.3)	83 (63)	< 0.001
Dactylitis, n (%) ***	16 (18.4)	66 (50)	< 0.001
PASI score, median [IQR] ****	5.0 [1-14]	7.6 [0.6–32.2]	-
Elevated CRP, n (%) *****	55 (63.2)	85 (65)	0.002
Oral glucocorticoid use, n (%)	44 (50.57)	37 (28.0)	0.001
Concomitant synthetic DMARD, n (%) Methotrexate Leflunomide Sulfasalazine Others	48 (55.2 %) 30 (34.4) 15 (17.2) 6 (6.9) 0(0)	131 (100%) 98 (75) 12 (9) 21 (16) 2 (2)	< 0.001
Previous use of anti-TNFα, mean±SD	2.4±1.4	1.7±1.0	< 0.001
Previous use of other biological no anti-TNFα, n (%)	68 (78.2)	11 (8)	< 0.001
TOFA in monotherapy, n (%)	39 (44.8)	0 (0)	< 0.001

CRP: C-reactive protein; DMARD: disease modifying antirheumatic drug; HAQ-DI: Health Assessment Questionnaire–Disability Index; IQR: interquartile range; PASI: Psoriasis area-and-severity index; SD: standard deviation; TNF: tumor necrosis factor; TOFA: tofacitinib. * Scores on HAQ-DI range from 0 to 3, with higher scores indicating greater disability. ** The presence of enthesis was considered when Leeds Enthesitis Index >0. *** The presence of dactylitis was considered when Dactylitis Severity Score >0 **** PASI score ,range from 0 to 72, higher scores indicating more severe disease.***** An elevated level of CRP was defined as a level of more than 0.5 mg /dl in clinical practice and more than 0.287 mg /dl in OPAL Beyond trial .

Table 2. Improvement in efficacy outcomes at 1st and 6th months after Tofacitinib onset in 87 patients with refractory psoriatic arthritis.

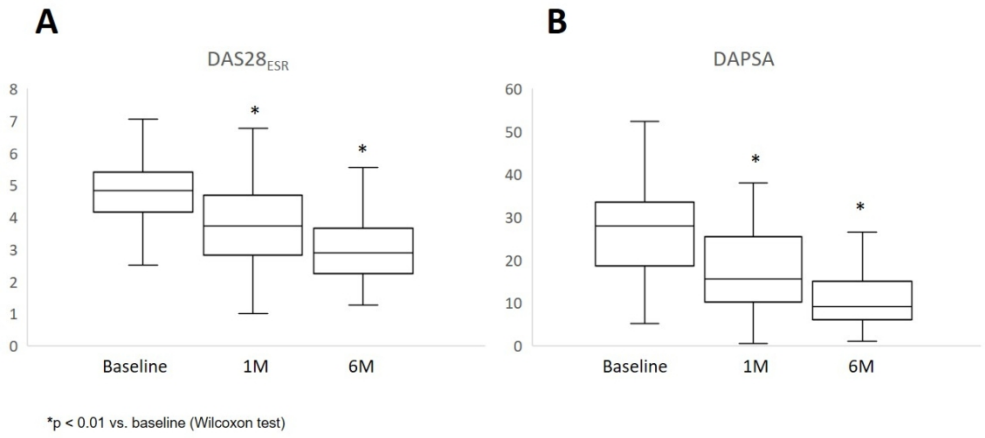
	Baseline (n=87)	**1st month (n=77)**	**6th month (n=52)**
Swollen joint count, median [IQR]	4 [2-8]	1 [0-4]*	0 [0-2]*
Tender joint count, median [IQR]	6 [3-10]	3 [1-5]*	1 [0-3]*
$DAS28_{ESR}$, median [IQR]	4.82 [4.14-5.40]	3.71 [2.82-4.67]*	2.88 [2.24-3.85]*
DAPSA, median [IQR]	28 [18.41-34.05]	15.5 [10.1-25.7]*	9 [6.07-15]*
PASI, median [IQR]	5.0 [1-14]	1.45 [0-7]	0 [0-4]
CRP (mg/dl), median [IQR]	1.90 [0.34-5]	0.5 [0.1-2.24]*	0.5 [0.3-1.24]*
Prednisone dose (mg/day), mean±SD	7.83± 4.93	6.67 ± 3.77*	5.39 ± 2.24*

CRP: C-reactive protein; DAPSA: Disease Activity Index for Psoriatic Arthritis: DAS28ESR: disease activity score-28 erythrocyte sedimentation rate; IQR: interquartile range; PASI: Psoriasis area-and-severity index *p < 0.01 vs. baseline (Wilcoxon test).

Table 3. Laboratory findings at baseline, 1st and 6th months after Tofacitinib onset in 87 patients with refractory psoriatic arthritis.

	Baseline (n=87)	**1st month (n=77)**	**6th month (n=52)**
Hemoglobin (gr/dl), mean±SD	13.3±1.7	13.3±1.4	13.3±1.4
Neutrophils (count/μL), mean±SD	4826±2462.4	5193±3030.6	4711.5±2317
Lymphocytes (count/μL), mean±SD	2443±1151.7	2608±1188.1	2500±1577.5
Platelets (count/μL), mean±SD	258127±106843.7	273864±92855.9	272868±95190
Creatinine (mg/dl), mean±SD	0.79±0.3	0.79±0.3	0.75±0.2
AST (U/L), mean±SD	20.1±10.4	19.9±6.8	22±9.0
ALT (U/L), mean±SD	21.2±15.3	21.0±13.2	20.3±10.5
Cholesterol (mg/dl), mean±SD	197.6±31.8	199.6±42.6	206.3±65.1
HDL (mg/dl), mean±SD	59.3±15.8	64.1±18.6	65.8±17.0
LDL (mg/dl), mean±SD	114.4±31.3	111.0±38.3	113.8±40.9

ALT: alanine transaminase; AST: aspartate transaminase; HDL: high density lipoprotein; LDL: low density lipoprotein.



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