Early onset hypercholesterolemia induced by the 2nd-generation tyrosine kinase inhibitor nilotinib in patients with chronic phase-chronic myeloid leukemia

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ABSTRACT

Despite a well-recognized clinical benefit of the 2nd-generation tyrosine kinase inhibitor nilotinib in patients with imatinib-resistant/-intolerant or newly diagnosed chronic myeloid leukemia, recent evidence suggests that nilotinib has a propensity to increase the risk of occlusive arterial events, especially in patients with pre-existing cardiovascular risk factors. Given the key role of lipids in cardiovascular diseases, we studied the plasma lipid profile and global cardiovascular risk prior to and during nilotinib therapy in a series of 27 patients in the setting of a prospective single center study. Data from a minimum 1-year follow up showed that nilotinib significantly increased total, low- and high-density lipoprotein cholesterol within three months. Consequently, the proportion of patients with non-optimal low-density lipoprotein cholesterol increased from 48.1% to 88.9% by 12 months, leading to cholesterol-lowering drug intervention in 22.2% of patients. The proportion of patients with low levels of high-density lipoprotein cholesterol decreased from 40.7% to 7.4% by 12 months. In contrast, a significant decrease in triglycerides was observed. Global cardiovascular risk worsened in 11.1% of patients due to diabetes or occlusive arterial events. Whether hypercholesterolemia was the main driver of occlusive arterial events was uncertain: a longer follow up is necessary to ask whether nilotinib-induced hypercholesterolemia increases long-term risk of atherosclerotic diseases. Nevertheless, given key atherogenic properties of low-density lipoprotein cholesterol, we conclude that when prescribing nilotinib, commitment to detect lipid disorders at baseline and during follow up is mandatory given their frequency, requirement for changes in lifestyle or drug intervention, and potential for long-term cardiovascular complications.

Introduction

Imatinib, the first tyrosine kinase inhibitor (TKI) targeting the BCR-ABL1 oncoprotein, has proven remarkably successful in chronic phase (CP)-chronic myeloid leukemia (CML). On the basis of high rates of responses and a favorable safety profile, long-term progression-free and overall survival has become a reality for most imatinib-treated patients.[1,2] Yet, it appears that imatinib must be discontinued in up to one-third of CP-CML patients because of drug resistance and/or unacceptable side effects.[1] Fortunately, several new generation TKIs with unique activity and tolerability profiles have been developed and have emerged as efficient salvage therapies in this setting. Nilotinib, a 2nd-generation TKI with greater potency and affinity for the BCR-ABL1 oncoprotein than imatinib, also active against a wide range of imatinib-resistant ABL1 kinase domain mutant clones, was originally approved for use at 400 mg twice daily in patients with CP- or accelerated phase (AP)-CML in whom imatinib has failed in 2007.[3,4] In patients with newly diagnosed CP-CML, a phase II trial conducted by the GIMEMA CML working party showed that nilotinib was able to rapidly induce high rates of cytogenetic and molecular responses.[5] The efficacy of nilotinib in adults with newly diagnosed CP-CML was then demonstrated in the open-label international phase III randomized ENESTnd trial (Evaluating Nilotinib Efficacy and Safety in Clinical Trials Newly Diagnosed Patients). In ENESTnd, nilotinib induced significantly higher rates of cytogenetic and molecular responses and decreased rates of progression to AP and blast crisis as compared to standard therapy with imatinib 400 mg once daily, leading to a conditional approval of the drug at 300 mg twice daily in the front-line setting in 2010.[6-8]

Despite an overall favorable safety profile, various lines of evidence agree in suggesting a specific association between nilotinib exposure and increased risk of developing occlusive arterial diseases. Severe occlusive arterial events, including peripheral artery disease (PAD), coronary artery disease or ischemic cerebrovascular events, have been reported during clinical trials, retrospective studies and real-life experience.[8-16] In most of these studies, nilotinib-treated patients with pre-existing risk factors for atherosclerotic cardiovascular diseases (CVD) or established CVD appeared to be particularly susceptible to develop occlusive arterial events. Thus it is difficult to reliably estimate the excess risk of occlusive arterial events induced by nilotinib, which may depend on many factors, such as length of nilotinib exposure, type and duration of pre-existing risk factors for CVD, presence of established CVD, and awareness of the importance of primary or second-

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ary CVD prevention. In addition, the mechanism by which nilotinib may cause or aggravate pathological processes involved in occlusive arterial diseases is currently unknown.

Nilotinib has been demonstrated to induce metabolic disturbances, such as hyperglycemia in a substantial proportion of patients, via a mechanism that may involve insulin resistance.[6,17] As high blood cholesterol is a major risk factor for atherosclerotic CVD,[18,19] a clear impact of nilotinib toward lipids has not been published, although dyslipidemia is mentioned as an uncommon side effect by the manufacturer and product instructions advise assessing lipid profile prior to initiating nilotinib therapy and as clinically indicated during treatment.[20] This gap in our knowledge urged us to search for modifications in the plasma lipid profile upon treatment with nilotinib in CML patients without base-line co-medication with lipid-lowering agents.

Methods

Patients

Adults with CP-CML were selected based on adequate hepatic or biliary function (SGOT, SGPT, alkaline phosphatase <2.5 fold upper normal limit (UNL), total bilirubin <1.5 fold UNL), absence of lipid-lowering drugs at baseline and nilotinib treatment frontline or after imatinib. Atherosclerotic CVD, concomitant medications and cardiovascular risk factors (age, sex, body mass index (BMI), smoking, arterial hypertension, diabetes mellitus (DM), chronic kidney disease (CKD)) were collected in all patients. Once nilotinib was initiated, visits were performed after one, three, six, nine and 12 months, and every 3-6 months thereafter. Minimum and median follow up since nilotinib initiation were 12 and 19 months (range 12-63 months), respectively.

Metabolic analyses

Total cholesterol (TC), low- and high-density lipoprotein cholesterol (LDL-C and HDL-C) and triglycerides (TG) were measured prospectively under fasting conditions within four weeks before nilotinib treatment, every three months for 12 months, and then annually unless otherwise indicated. LDL-C was estimated using the Friedewald equation. Fasting glucose, glycosylated hemoglobin, creatinine and thyroid stimulating hormone were measured to rule out secondary dyslipidemia. Metabolic analyses at baseline and at three months were also performed in a ponatinib-treated control group of CP-CML patients without hypolipemic drugs (n=8).[21]

Cardiovascular disease risk estimation and management of high cholesterol

The 2012 European Society of Cardiology (ESC) guidelines were used to assess the 10-year risk of fatal CVD at baseline and throughout therapy.[18] The risk assessment model is based on cardiovascular history, CVD risk factors and Systematic Coronary Risk Evaluation (SCORE). SCORE relies on age, sex, systolic blood pressure, TC, tobacco use and country of origin. Patients were categorized into 4 risk groups: 1) very high (documented CVD, asymptomatic atherosclerosis, DM with organ damage or ≥1 CVD risk factor, severe CKD or SCORE ≥10%); 2) high (elevated single CVD risk factors, DM without other CVD risk factors or organ damage, moderate CKD or SCORE of ≥5% and <10%); 3) moderate (SCORE ≥1% and <5%); and 4) low (SCORE <1%). For CVD risk stratification, imaging techniques were not used to search for evidence of pre-clinical atherosclerosis. HeartScore was calculated to analyze the impact of HDL-C on CVD risk.[18,22] Changes in lifestyle and/or drug treatment for dyslipidemia were based on LDL-C and CVD risk.[18] Optimal LDL-C levels were less than 0.7 g/L, less than 1 g/L and less than 1.15 g/L in case of very high, high or moderate/low CVD risk, respectively.[18]

Responses to tyrosine kinase inhibitors

Responses were monitored according to European LeukemiaNet (ELN) recommendations.[23,24] Molecular monitoring was performed according to ELN recommendations for *BCR-ABL1* mRNA quantification and international standardization (IS), providing that the BCR gene breakpoint occurred in the major (M)-breakpoint cluster region.[25] ABL1 kinase domain mutations were analyzed according to ELN recommendations.[26]

Statistical analyses

The effect of TKI on lipids was evaluated using Student's paired t-tests. Two-tailed $P<0.05$ was considered statistically significant. In case of introduction of lipid-lowering medications, subsequent measurements were excluded from analyses

Study conduct

The study was approved by the Institutional Review Board of HUPVNS, Paris 7 University, France, and conducted in accordance with applicable regulatory requirements. Informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Results

Patients' characteristics and response to therapy

Twenty-seven patients diagnosed with CP-CML and treated with nilotinib entered this prospective single center study (Table 1). Of these, 7 were initially treated within a multicenter clinical trial (CAMN107ECI01, EudraCT n. 2009-17775-19). Median age at diagnosis was 48 years (range 19-69 years); 15 patients (55.6%) were males. Sokal risk group was low in 13 (48.1%), intermediate in 11 (40.7%), and high in 3 (11.1%) patients. EUTOS score was low in 23 (85.3%) and high in 4 (14.8%) patients. Major route chromosomal abnormalities in addition to the Philadelphia (Ph) chromosome (ACAs)[27] defined as trisomy 8, Ph duplication, isochromosome 17q or trisomy 19 were present at diagnosis in 3 patients (11.1%). Only one patient (3.7%) had variant *BCR-ABL1* transcripts (e1a2). Nilotinib was given upfront in 22 patients (81.5%) and after first-line imatinib in 5 (18.5%). Median time from diagnosis to treatment with nilotinib was 0.8 months (range 0.4-4.3 months) in the former and 16 months (range 1-48 months) in the latter, with a median duration of prior imatinib treatment of 15 months (range 2-46 months). Reasons for switching from imatinib to nilotinib included non-hematologic intolerance (n=1), lack of major molecular response (MMR: *BCR-ABL1* IS ≤0.1%) (n=1), primary cytogenetic resistance (n=2) and secondary molecular resistance associated with a F317L ABL1 kinase domain mutation (n=1). Initial nilotinib dosing regimen was 300 mg twice daily in 24 patients (88.9%) and 400 mg twice daily in the 3 imatinib-resistant patients (11.1%). None of the patients required nilotinib interruption or dose reduction during the first year of therapy. By 12 months of nilotinib therapy, a complete cytogenetic response (CCyR: Ph1=0%) and a major molecular response (MMR) were obtained by 25 of 27 (92.6%) and 24 of 26 (92.3%) patients, respectively. Three patients discontinued nilo-

tinib because of intolerance (n=1), resistance (n=1) and TKI discontinuation study while in deep molecular response (n=1). Median duration of exposure to nilotinib was 19 months (range 12-48 months) and median follow up since nilotinib initiation was 19 months (range 12-63 months).

Cardiovascular disease risk factors and risk groups at baseline

Base-line CVD risk factors included age 55 years or over in men and 65 years or over in women in 8 patients (29.6%), active smoking or stopping smoking during the previous year in 6 patients (22.2%), non-optimal LDL-C levels in 13 patients (48.1%), overweight (BMI ≥25 kg/m^2) in 14 patients (51.9%), obesity (BMI ≥30 kg/m^2) in 3 patients (11.1%), arterial hypertension in 2 patients (7.4%) and type 2 DM in 1 patient (3.7%) (Table 2). None of the patients had severe CKD or prior history of symptomatic atherosclerotic CVD. The 10-year fatal CVD risk was low in 13 patients (48.2%), moderate in 9 patients (33.3%), high in 4 patients (14.8%), and very high in 1 patient (3.7%) (Table 2).

Lipid profile during nilotinib therapy

At baseline, mean plasma TC concentration was 1.80 g/L (standard deviation (SD): 0.38). At three months, TC had risen by a mean of 0.45 g/L with mean plasma TC concentration of 2.24 g/L (SD: 0.47) (Figure 1A). There was a statistically significant difference in TC levels between baseline and at three months (P<0.0001). Analyses of LDL-C and HDL-C revealed that both fractions were involved in TC elevation after nilotinib initiation. Compared to base-line concentrations, LDL-C had indeed increased by a mean of 0.33 g/L at three months. Mean LDL-C concentrations at baseline and three months were 1.13 g/L (SD: 0.30) and 1.46 g/L (SD: 0.38), respectively (P<0.0001) (Figure 1B). Consequently, the proportion of patients with non-optimal LDL-C levels increased from 48.1% at baseline to 88.9% at three months and only 3 of 14 patients with optimal LDL-C levels at baseline maintained such optimal levels at three months. Compared to base-line concentrations, HDL-C had increased by a mean of 0.14 g/L at three months. Mean HDL-C concentrations at baseline and three months were 0.44 g/L (SD: 0.15) and 0.58 g/L (SD: 0.18), respectively (P<0.0001) (Figure 1C). As a result, the proportion of patients with low HDL-C (<0.4 g/L) decreased from 40.7% at baseline to 7.4% at three months, and that of patients with a high TC/HDL-C ratio (≥4) decreased from 63% at baseline to 48.1% at three months. After three months, no further significant modifications in TC, LDL-C and HDL-C were observed, with mean TC, LDL-C and HDL-C concentrations at 12 months of 2.18 g/L (SD: 0.35), 1.37 g/L (SD: 0.26) and 0.62 g/L (SD: 0.23), respectively (Figure 1A-C).

In contrast to cholesterol, TG concentrations decreased by a mean of -0.35 g/L between baseline and three months, with mean TG concentrations at baseline and three months of 1.32 g/L (SD: 0.75) and 0.97 g/L (SD: 0.64) (P<0.0004) respectively, and no significant change beyond three months (mean TG concentration at 12 months 0.96 g/L (SD: 0.7)) (Figure 1D). High TG (>1.5 g/L) was observed in 9 patients (33.3%) at baseline and in only 2 patients (7.4%) at three months including 1 with type 2 DM at baseline and 1 who developed type 2 DM after the start of nilotinib.

Lipid profile after nilotinib discontinuation

We had the possibility to assess the reversibility of nilotinib-induced hyperlipidemia in 1 additional female patient with CP-CML in whom nilotinib 300 mg twice daily was discontinued without replacement by any CML drug treatment due to a wish to become pregnant and who did not receive any lipid-lowering agent. Lipid profile

Table 1. Characteristics of nilotinib-treated patients.

Parameters	Results
Number of patients	n=27
Median age at CP-CML diagnosis	48 years (range 19-69)
Male sex	n=15 (55.6%)
Sokal risk group	n=13 (48.1%)
Low	n=11 (40.7%)
Intermediate	n=3 (11.1%)
High	
EUTOS risk group	
Low	n=23 (85.3%)
High	n=4 (14.8%)
Major route ACAs	n=3 (11.1%)
Major *BCR-ABL1* transcripts	n=26 (96.3%)
Indication for nilotinib	
First-line therapy	n=22 (81.5%)
Second-line therapy	n=5 (18.5%)
Reasons for second-line nilotinib	
Non-hematologic intolerance to imatinib	n=1 (3.7%)
Lack of MMR on imatinib	n=1 (3.7%)
Resistance to imatinib	n=3 (11.1%)
Median time from diagnosis to nilotinib initiation	
First-line nilotinib	0.8 month (range; 0.4-4.3)
Second-ine nilotinib	16 months (range; 1-48)
Median duration of prior imatinib	15 months (range; 2-46)
Initial nilotinib dosing regimen	
400 mg twice daily	n=3 (11.1%)
300 mg twice daily	n=24 (88.9%)
Responses to nilotinib by 12 months	
CCyR	n=25 (92.6%)
MMR*	n=24 (92.3%)

*Patients with Major BCR-ABL1 transcripts type only.

Table 2. Base-line CVD risk factors and 10-year fatal cardiovascular disease risk group.

Parameters	Results
Age (years) ≥55 in men and ≥65 in women	8 (29.6%)
Active smoking or ceased during the previous year	6 (22.2%)
BMI ≥25 kg/m^2	14 (51.9%)
BMI ≥30 kg/m^2	3 (11.1%)
Arterial hypertension	2 (7.4%)
Type 2 DM	3 (3.7%)
Non-optimal LDL-C levels	13 (48.1%)
CVD risk group	
Low	13 (48.2%)
Moderate	9 (33.3%)
High	4 (14.8%)
Very high	1 (3.7%)

determined two months prior to and after nilotinib discontinuation showed a decrease of both TC and LDL-C from 2.24 g/L to 1.92 g/L and 1.42 g/L to 1.06 g/L, respectively, while HDL-C and TG remained stable. This decrease in TC and LDL-C after nilotinib cessation was confirmed three months later (*data not shown*).

Lipid profile upon treatment with other tyrosine kinase inhibitors

We asked whether TC, LDL-C and HDL-C elevation was specific to nilotinib or a characteristic shared by other TKIs. Plasma fasting lipids were thus studied at baseline and at three months in 8 additional patients not receiving lipid-lowering drugs and who were treated with ponatinib. The latter is indeed associated with cardiovascular safety issues.[21] Blood lipid profile was determined in agreement with recommendations from regulatory agencies. No significant early modifications in TC, LDL-C, HDL-C and TG were observed (Figure 2A-D).

Change in cardiovascular disease risk category during nilotinib treatment

We searched for modifications in the 10-year risk of fatal CVD during nilotinib treatment. Overall, a change in CVD risk category occurred in 4 patients (14.8%) during follow up. One patient with a moderate CVD risk at baseline changed to the low CVD risk category at 12 months because of stopping smoking while 3 patients (11.1%) evolved toward a higher risk group. Among the latter, 1 patient with a low CVD risk at baseline, progressed to the high CVD risk group at 12 months due to the onset of type 2 DM requiring intervention with glucose-lowering drugs, 1 patient with a moderate CVD risk at baseline progressed to the very high-risk category due to the onset of symptomatic PAD at 12 months, and the last patient evolved from the high- to the very high-risk category due to the discovery of asymptomatic PAD at 46 months. The last 2 patients had non-optimal LDL-C levels at the time of PAD; however, any direct link between PAD and hyperc-

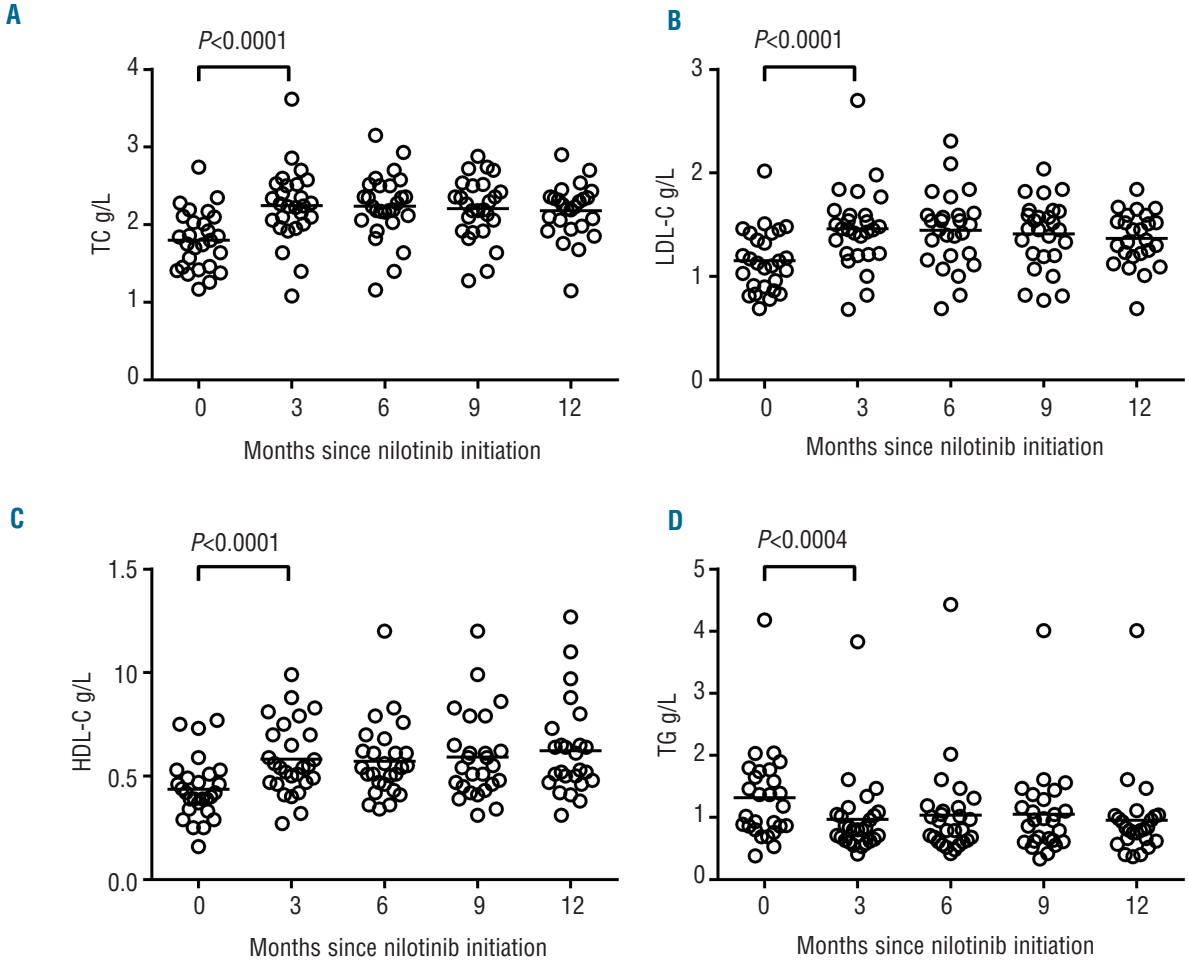

Figure 1. Plasma lipid profile of CP-CML patients prior to and during the first year of nilotinib therapy. Concentrations of plasma TC (A), LDL-C (B), HDL-C (C) and TG (D) in CP-CML patients measured within four weeks prior to nilotinib treatment and every three months for 12 months during nilotinib therapy in the absence of lipid-lowering medication. Empty circles represent data obtained in individual patients and means are represented by horizontal bars. Lipid measurements were excluded from analyses in 1 patient at 9 and 12 months and 1 patient at 12 months due to the introduction of lipid-lowering medications. Two-tailed *P* values <0.05 from Student's paired t-tests comparing data obtained at baseline and 3 months are shown.

holesterolemia remained uncertain, due to the very rapid development of PAD in the absence of prior atherosclerosis in the first case and because of other important CVD risk factors (type 2 DM) in the second case. In order to address the potential impact of cholesterol increase in CVD risk modification, we thus compared SCORE and HeartScore by 12 months in the subgroup of 7 patients who remained in the moderate-risk category during follow up and in whom main risk factors other than cholesterol levels did not change. SCORE remained stable between baseline and 12 months in 6 patients (1% in 1, 2% in 4 and 3% in 1) and increased from 3% to 4% in 1 patient. HeartScore (which unlike SCORE takes into account the protective role of HDL-C toward atherosclerotic CVD) remained stable in 2 patients (1% in 1, 2% in 1) and moderately decreased in the 5 other patients (from 2% to 1% in 3, from 3% to 1% in 1 and from 3% to 2% in 1).

Lipid-lowering medications during nilotinib therapy

The rise in LDL-C or the onset of occlusive arterial events observed during treatment with nilotinib triggered the prescription of lipid-lowering drugs in 6 patients (22.2%) of our series, in the setting of a specific consultation with cardiovascular specialists. All received HMG-CoA reductase inhibitors (rosuvastatin n=4, atorvastatin n=2) after a median of 13 months (range 7-48 months) of nilotinib treatment. At the time of statin initiation, the CVD risk was moderate in 1 patient, high in 2 patients and very high in 3 patients. Nilotinib was maintained without any dose reduction in 4 cases. In the 2 remaining patients, nilotinib was discontinued because of symptomatic PAD (n=1) and primary resistance with onset of a T315I mutation (n=1). These 2 patients respectively received imatinib and ponatinib. LDL-C rapidly decreased below target LDL-C thresholds with mean LDL-C concentrations before statin initiation and after three months of 1.64 g/L (SD: 0.51) and 0.77 g/L (SD: 0.34), respectively (P=0.0036).

Discussion

Our prospective study provides new information on lipid profile modifications induced by the 2nd-generation TKI nilotinib. It is indeed the first to reveal that early-onset hypercholesterolemia is a key adverse reaction associated with exposure to this drug in CP-CML patients. Our results highlight a significant rise in TC within three months of nilotinib therapy in a pattern that involves elevation of both LDL-C and HDL-C fractions. As a conse-

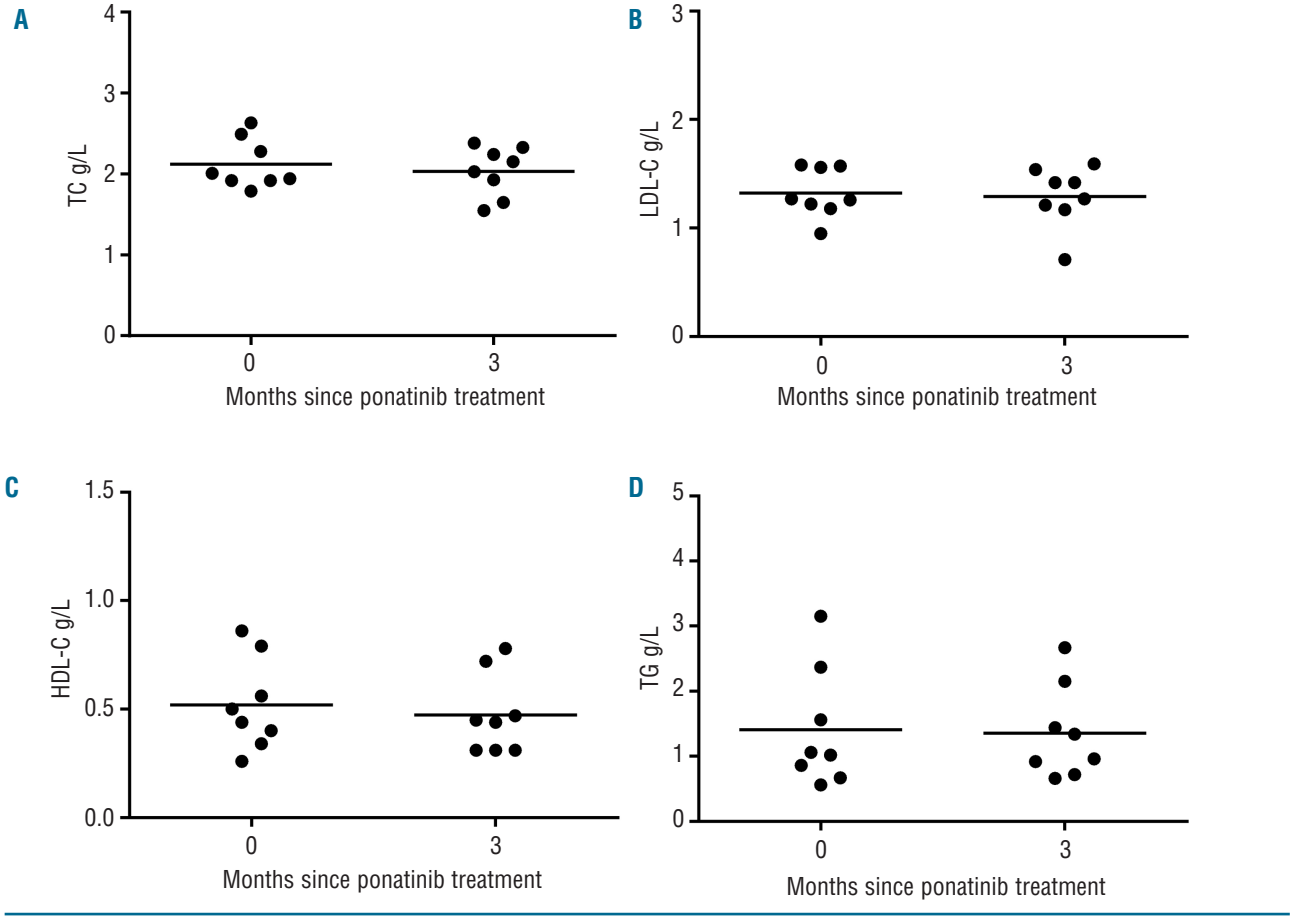

Figure 2. Plasma lipid profile of CP-CML patients prior to and after three months of ponatinib therapy. Concentrations of plasma TC (A), LDL-C (B), HDL-C (C) and TG (D) in CP-CML patients measured within four weeks prior to ponatinib treatment and three months later. Filled circles represent data obtained in individual patients and means are represented by horizontal bars. No significant modifications were observed.

quence, nilotinib substantially increases the need for changes in lifestyle and/or introduction of lipid-lowering medications.

Cardiovascular diseases are a leading cause of morbidity and death worldwide.[28] In Europe, deaths from CVD represent nearly half of all deaths: 52% of all deaths in women and 42% of all deaths in men.[29] Atherosclerosis, the main pathological process underlying CVD, results from complex interactions between multiple non-modifiable and modifiable factors.[30,31] Among the latter, hypercholesterolemia, and especially high LDL-C, the major atherogenic lipoprotein, plays a direct causative role. Importantly, multiple randomized clinical trials provided robust and compelling evidence that lowering LDL-C with lipid-modifying treatments such as statins significantly reduces CVD morbidity and mortality.[32]

In our study, nilotinib exerted a sustained negative impact on LDL-C. While 52% of patients showed optimal LDL-C levels prior to nilotinib initiation, only 11% did so after three months of therapy, regardless of 10-year fatal CVD risk groups. This effect was nilotinib-specific, since no early modification in the lipid profile occurred in control CP-CML patients treated with ponatinib, another TKI raising cardiovascular safety concern.[21] In addition, reversibility upon nilotinib discontinuation was confirmed. Despite these findings, we were not able to definitively establish a positive relationship between rising TC and LDL-C levels and nilotinib-associated occlusive arterial events. However, we recognize that a limitation of our current study resides in the fact that LDL-C was measured indirectly as part of routine clinical practice, and that further and more accurate analyses of the atherogenic lipid burden, including direct measures of LDL-C, non HDL-C, apolipoprotein B or LDL particles, are needed.[33] Alternatively, modifications within the arterial wall other than cholesterol deposition may also be at work, as suggested by ongoing investigations focusing on the impact of nilotinib on endothelial cell properties.[34]

Nevertheless, these lipid abnormalities that we have described in nilotinib-treated patients remain firmly established atherosclerotic CVD risk factors in non-CML populations and an increased predisposition of nilotinib-treated CML patients to the development of atherosclerotic CVD in the longer term cannot be ruled out, especially as the use of TKIs has converted CML from a rapidly fatal leukemia into a chronic and manageable disease with a near to normal life expectancy on life-long treatment.[2,23,35,36] The fact that nilotinib also triggered HDL-C elevation in our study is, in our view, not sufficient to argue against this potential scenario for several reasons, despite the well-known inverse relationship between HDL-C and cardiovascular events.[37] First, inclusion of HDL-C to risk estimation through the HeartScore resulted in stagnation or a very modest improvement in CVD-risk calculation compared to SCORE and did not modify CVD risk categorization in our patients. Second, reduction of CVD through strategies directly targeting HDL-C has not been effective. Third, LDL-C is widely recognized as the primary target for primary and secondary prevention of atherosclerotic CVD.[18,19] In patients at very high CVD risk, LDL-C goal is less than 0.7 g/L and this is achievable with changes in lifestyle together with statin therapy, leading to an important clinical benefit.[18] In patients at high CVD risk, LDL-C goal less than 1 g/L is recommended through changes in lifestyle and/or drug intervention.[18] In patients at moderate or low risk, LDL-C goal is less than 1.15 g/L but physicians should exercise clinical judgment and consider risk and benefits before choosing cholesterol-lowering treatment plans.[18]

In our series, the decision for a rapid introduction of statins was made in 6 patients with LDL-C levels above goals (either worsening from baseline or newly acquired). Statins were shown to be remarkably efficient in reducing nilotinib-induced high LDL-C since patients rapidly reached optimal LDL-C levels. As recommended by the European Society of Cardiology, low-dose aspirin was prescribed only in case of onset of occlusive arterial event or in patients with clinically established atherosclerotic disease.[18] The role of low-dose aspirin in primary CVD prevention is, indeed, unproven whereas the risk of major bleeding has been shown to increase.[18]

To conclude, patients with CP-CML should be screened for lipid disorders prior to and during nilotinib therapy given their incidence, potential for morbidity, and possible long-term atherosclerotic CVD risk. All patients should be instructed on how to adopt a healthy lifestyle and detection of clinical symptoms compatible with atherosclerotic-like manifestations in all arterial areas should be integrated into patient care visits. Consultation with cardiovascular specialists may be organized on an individual basis to search for pre-clinical or clinical atherosclerosis, and to assess CVD risk and indication for dietary intervention or lipid-lowering drugs like statins. Statins not metabolized by the cytochrome P450 isoenzyme 3A4 may be preferred to avoid potentially harmful interactions with nilotinib.[20] Discontinuation of nilotinib and switch to another TKI may be considered in situations where the risk of the drug may outweigh the benefit, such as onset of a severe adverse event like arterial occlusion, persistence of dyslipidemia after adequate therapeutic intervention or statin tolerance issues. Follow up is mandatory to evaluate the long-term atherosclerotic CVD risk in nilotinib-treated patients. Whether nilotinib-induced hypercholesterolemia results from increased hepatic synthesis or impaired clearance from the bloodstream is unknown, and additional studies are required to further dissect the lipid profile and decipher the mechanism of nilotinib-induced hypercholesterolemia.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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