Eur J Med Res (2011) 16: 85-92

Changes in Lipid Profiles after Switching to a Protease Inhibitor-containing cART – Unfavourable Effect of Fosamprenavir in Obese Patients

M. Gyalrong-Steur, J. R. Bogner, U. Seybold

Infektionsabteilung der Medizinischen Poliklinik, Campus Innenstadt, Ludwig-Maximilians-Universität, München, Germany

Abstract

Objective: One focus in the medical care of HIV-infected patients today is cardiovascular risk reduction. Metabolic disturbances occur frequently in patients taking protease inhibitors (PI) and are a major risk factor for atherosclerosis. With few published head-to-head studies substance-specific differences concerning metabolic effects are insufficiently defined. Therefore this cohort study directly compared the metabolic profiles of boosted atazanavir (ATV/r), fosamprenavir (FPV/r) and saquinavir (SQV/r).

Methods: Data from a cohort of 124 HIV patients initiating a boosted regimen with one of the PIs at the University of Munich (LMU) infectious diseases outpatient clinic were retrospectively analyzed. The main outcome measures were median absolute total cholesterol levels and median relative change of total cholesterol levels after six months of PI-therapy. A multivariate linear regression model was built to identify and control for potential confounders of the association between PI-therapy and serum cholesterol level.

Results: 84 patients were treated with ATV/r, 23 patients received FPV/r and 17 patients SQV/r. Demographically the cohort constituted a representative sample of HIV-infected patients in Germany. There were no statistically significant differences between the comparison groups at baseline.

After six months of therapy median serum cholesterol in the ATV/r group dropped significantly from 204 mg/dl to 186 mg/dl, while in the FPV/r and SQV/r groups a rise in serum cholesterol levels was observed from 179 mg/dl to 204 mg/dl and from 173 mg/dl to 209 mg/dl respectively. The multivariate linear regression model identified a significant interaction between BMI at baseline and treatment with FPV/r: patients with higher BMI showed more prominent increases in serum cholesterol while taking FPV/r compared to patients with lower BMI.

Conclusion: This cohort study demonstrated the most favourable impact on serum cholesterol levels and thus cardiovascular risk for ATV/r compared to FPV/r and SQV/r under real-life conditions. Given the statistical interaction detected between FPV/r and BMI further studies assessing metabolic profiles of different antiretroviral drugs in specific patient populations are urgently needed.

Key words: HIV, cART, protease inhibitor, atazanavir, fosamprenavir, saquinavir, lipids, cholesterol, triglycerides, glucose, metabolism, body mass index, dyslipidemia, obesity, cardiovascular risk, multivariate linear regression, statistical interaction

Abbreviations:

ATV/r	boosted atazanavir
BMI	body mass index
cART	combination antiretroviral therapy
FPV/r	boosted fosamprenavir
LPV/r	boosted lopinavir
PI	protease inhibitor
PLHA	people living with HIV/AIDS
RTV	ritonavir
SQV/r	boosted saquinavir

Introduction and Objectives

Metabolic and cardiovascular health issues are becoming an increasing problem in Germany and other industrialized countries. Cardiovascular complications [1-8] now are among the leading causes of mortality in these countries [9-12].

Since the introduction of combination antiretroviral therapy (cART) mortality due to AIDS-defining illnesses has considerably decreased among people living with HIV/AIDS (PLHA), resulting in an increase of life expectancy to almost that of the general population [13, 14]. Therefore non-HIV-related causes of death, among them cardiovascular diseases, are becoming more relevant among PLHA [14-17]. In addition, both HIV-infection itself [18-21] and various antiretroviral drugs are also associated with increased cardiovascular risk [22-24]. Elevated serum cholesterol has been shown to be a major cause for atherosclerosis in numerous studies [3-5, 8] and this association has also been confirmed in PLHA [25].

With a broad spectrum of antiretroviral drugs available, the focus of HIV therapy today lies on managing the patients' overall health situation, including metabolic and cardiovascular as well as quality of life issues [26]. Choosing antiretroviral drugs with a favourable metabolic profile is the primary specific intervention recommended to minimize the cardiovascular risk burden in HIV-patients even before identification of oth-

er modifiable cardiovascular risk factors potentially requiring drug therapy [27].

Protease inhibitors (PIs) are an essential part of modern cART and recommended as part of first-line HIV-therapy in different guidelines [28-31]. However, unfavourable metabolic effects like elevation of serum lipids, impaired glucose tolerance, and increased risk of myocardial infarction have mainly been associated with this drug class [22, 24, 25, 32-37]. The metabolic effects, especially the impact on serum lipids, is a class effect of PIs, however there seem to be substance-specific differences [24]. Thus, knowledge of the different metabolic profiles of the various PIs offers the possibility to optimize cART efficacy while keeping cardiovascular risk as low as possible. Several newer PIs show fewer metabolic side effects than have been observed for ritonavir-boosted lopinavir (LPV/r) or ritonavir (RTV) in therapeutic dosage [24, 32-35, 38-41]. Especially atazanavir (ATV) so far has shown a relatively favourable lipid profile [42-45]. Saquinavir (SQV) as well has been observed to have few negative effects on the serum lipids [46-49]. Data about the metabolic properties of fosamprenavir (FPV) are conflicting [50-52].

Currently available data do not allow for a concluding assessment of the differences of the various PIs' effect on lipid and glucose metabolism and cardiovascular risk. Moreover, to date little is known about the various interactions of the PIs‘ metabolic effects with other patient characteristics such as body mass index (BMI), blood pressure, or smoking habits, which influence a patient's metabolic situation as well.

The aims of the present study were to directly compare the three PIs ATV, FPV and SQV, for which favourable metabolic profiles have been observed in different studies, with regard to their influence on metabolic parameters affecting cardiovascular risk as well as assessing possible interactions of the PIs with patient characteristics like BMI and blood pressure.

Methods and Statistics

This study took place at the Ludwig-Maximilians-University of Munich infectious diseases outpatient clinic. The University of Munich ethics committee approved the study. All HIV-infected patients seen between January 1, 2000 and March 31, 2008 were screened for their eligibility. All adult patients initiating therapy with ATV 300 mg qd, FPV 700 mg bid, or SQV 1000 mg bid within a RTV-boosted cART-regimen (ATV/r, FPV/r or SQV/r) for whom a follow-up of at least six months was available were included into the analysis. Double-PI therapy and changes of the cART regimen as well as initiation or changes of a lipid-lowering medication during the first six months of PI-therapy were not allowed.

Patients were usually seen at the clinic every three months. At these visits serum levels of cholesterol, triglycerides, and glucose, CD4 cell count and viral load, as well as blood pressure, weight, and current medication were routinely documented. All demographic, HIV-related, and metabolic data were extracted from patient files and the outpatient clinic database.

Cardiovascular risk was calculated for each patient at baseline and after 6 months of PI therapy using the HeartScore-tool developed by the European Society of Cardiology in the version specific for Germany [2, 3, 53]. The Score value is calculated on the basis of age, gender, smoking behaviour, systolic blood pressure and serum cholesterol level and describes the risk of a fatal cardiovascular event within the next 10 years. According to European Joint Task Force guidelines a patient is considered at high cardiovascular risk if the score is above 5% [3, 54].

This study was carried out as a retrospectively analyzed cohort study, the main outcome measures were median absolute total cholesterol levels and median relative change of total cholesterol levels after 6 months of PI-therapy.

To identify potential confounding variables influencing the association between PI-therapy and serum cholesterol level a multivariate linear regression model was designed. The outcome variable was serum cholesterol level after 6 months of therapy with one of the PIs, main predictor variables were PI used and baseline cholesterol. Collinearity was ruled out by assessing variance inflation. Potential confounding covariates known from the literature were assessed, variables shown to be confounders were included in the final model. All parameters in the final model were tested for two-way interaction.

All statistical analyses were performed using SPSS™ software, version 15.0 (SPSS, Munich, Germany). For comparison of the cohorts Kruskal-Wallis-H-test and Chi^2-test were used, as applicable. Intra-group analyses of the changes of parameters over time were performed using the Wilcoxon-test for metric variables and the McNemar-test for categorical variables.

Results

Patients and Baseline Characteristics

During the study period 444 patients starting a PI-containing regimen were seen at the outpatient clinic, 124 patients met eligibility criteria for inclusion into the analysis. Of these, 84 patients (68%) initiated therapy with ATV/r, 23 patients (19%) initiated therapy with FPV/r, and 17 patients (14%) with SQV/r. The remaining patients were excluded because they were treated with a different PI (199 patients), received a double-PI-regimen or an unusual dosage of the PI (87 patients), or insufficient follow-up was available (34 patients). Additional follow up documentation of 24 months after starting PI-therapy was available for 86 patients. The baseline demographic and clinical characteristics of the patients are shown in Table 1. There were no significant differences with regard to demographic characteristics, HIV disease characteristics, antiretroviral therapy, or cardiovascular risk factors between the 3 groups receiving different PI-based cART at baseline.

Metabolic Profile and Cardiovascular Risk

The changes of different metabolic parameters examined during the first 6 months after initiating therapy with one of the PIs are shown in Table 2.

Table 1. Baseline demographic and clinical characteristics of patients starting a new PI-based cART regimen.

		Starting therapy with	ATV/r	FPV/r	SQV/r	p[a]
Characteristic						
Number of patients		N	84	23	17	
DEMOGRAPHIC CHARACTERISTICS						
Male patients		n (%)	62 (74)	18 (78)	14 (82)	0.72
Age (years)		Median	43	44	41	0.69
		(IQR[b])	(37; 54)	(38; 50)	(35; 50)	
Caucasian patients		n (%)	66 (79)	21 (91)	14 (82)	0.71
HIV risk category	**MSM[c]**	n (%)	41 (49)	14 (61)	12 (70)	0.76
	heterosexual	n (%)	17 (20)	4 (17)	2 (12)	
	other	n (%)	26 (31)	5 (22)	3 (18)	
HIV DISEASE CHARACTERISTICS						
Duration of known HIV infection (years)		Median	8.8	10.5	8.8	0.41
		(IQR)	(5.4; 12.8)	(6.3; 15.3)	(4.7; 10.5)	
Previous AIDS		n (%)	34 (40)	8 (35)	9 (53)	0.53
CD4 cell count (cells/µl blood)		Median	343	320	262	0.59
		(IQR)	(221; 496)	(138; 595)	(81; 551)	
Patients with undetectable viral load[d]		n (%)	37 (44)	8 (35)	6 (35)	0.73
ANTIRETROVIRAL THERAPY						
Previous cART exposure		n (%)	79 (94)	20 (87)	16 (94)	0.50
Previous PI exposure		n (%)	55 (66)	15 (65)	14 (82)	0.40
Cumulative cART exposure (years)		Median	6,9	7,3	5,2	0.30
		(IQR)	(3.2; 8.7)	(3.8; 9.6)	(3.5; 8.7)	
previous cART	**no cART**	n (%)	15 (18)	8 (35)	1 (6)	0.35
	other PI	n (%)	40 (48)	11 (48)	10 (59)	0.69
	NRTI and/or NNRTI only	n (%)	29 (35)	4 (17)	6 (35)	0.12
CARDIOVASCULAR RISK FACTORS						
BMI		Median	23,7	23,6	21,5	0.50
		(IQR)	(21.3; 25.4)	(20.5; 25.1)	(19.3; 23.2)	
Current smoker		n (%)	39 (46)	9 (39)	6 (35)	0.23
Arterial hypertension[e]		n (%)	35 (42)	11 (48)	6 (35)	0.73
Diabetes mellitus		n (%)	7 (8)	1 (4)	0 (0)	0.40
Current lipid-lowering therapy		n (%)	5 (6)	2 (9)	2 (12)	0.67

[a]: Kruskal-Wallis-H-test for metric variables, Chi²-test for categorical variables; p-value for inter-group comparisons
[b]: inter quartile range
[c]: Men having sex with men
[d]: less than 50 copies per ml of plasma
[e]: diastolic blood pressure ≥90mmHg and/or systolic blood pressure ≥140mmHg or antihypertensive medication

At the time of starting PI-based therapy, the median serum cholesterol level was highest at 204 mg/dl in the ATV/r-group. In the FPV/r- and SQV/r-groups the median values were 179 mg/dl and 173 mg/dl, respectively. The differences between the groups were not statistically significant (p= 0.19; inter-group comparison). After six months of therapy the median serum cholesterol level significantly decreased to 186 mg/dl in the patients taking ATV/r (p= 0.009; intra-group comparison). The median value rose to 204 mg/dl in the patients taking FPV/r (p= 0.03; intra-group comparison), and to 209 mg/dl in the patients taking SQV/r (p= 0.15; intra-group comparison). At month 6 of therapy there was a trend towards a lower median serum cholesterol in patients taking ATV/r (p= 0.055; inter-group comparison) (Fig. 1). Regarding the relative change of the serum cholesterol levels at month 6 compared to baseline values, a significant difference between the PI groups was seen (p=0.0002; inter-group comparison): In the ATV/r-group serum cholesterol had decreased by -6%, in contrast to both the FPV/r- and SQV/r-group, in which a respective

Table 2. Changes in the metabolic and cardiovascular profile during PI-therapy.

PI group		**ATV/r**	**FPV/r**	**SQV/r**	**p-value[a]**
Characteristic					
Number of patients		**84**	**23**	**17**	
Serum cholesterol					
at baseline [mg/dl]	Median	204	179	173	0.19
	(IQR)	(159; 251)	(148; 217)	(143; 221)	
at month 6 [mg/dl]	Median	186	204	209	0.055
	(IQR)	(157; 228)	(177; 284)	(164; 278)	
relative change at month 6	% (Median)	-6	+21	+8	0.0002
Serum triglycerides					
at baseline [mg/dl]	Median	187	136	205	0.20
	(IQR)	(113; 334)	(87; 289)	(143; 366)	
at month 6 [mg/dl]	Median	186	169	218	0.90
	(IQR)	(119; 280)	(122; 239)	(120; 342)	
Serum glucose					
at baseline [mg/dl]	Median	90	87	89	0.70
	(IQR)	(82; 101)	(83; 97)	(78; 99)	
at month 6 [mg/dl]	Median	91	90	97	0.17
	(IQR)	(83; 101)	(83; 103)	(89; 118)	
High cardiovascular risk[b]					
at baseline	n (%)	23 (27)	2 (9)	2 (12)	0.088
at month 6	n (%)	20 (24)	3 (13)	3 (18)	0.50

[a]: Kruskal-Wallis-H-test for metric variables; p-value for inter-group comparisons
[b]: risk of developing a fatal cardiovascular event over the next ten years >5%, according to the HeartScore [2, 3, 53]

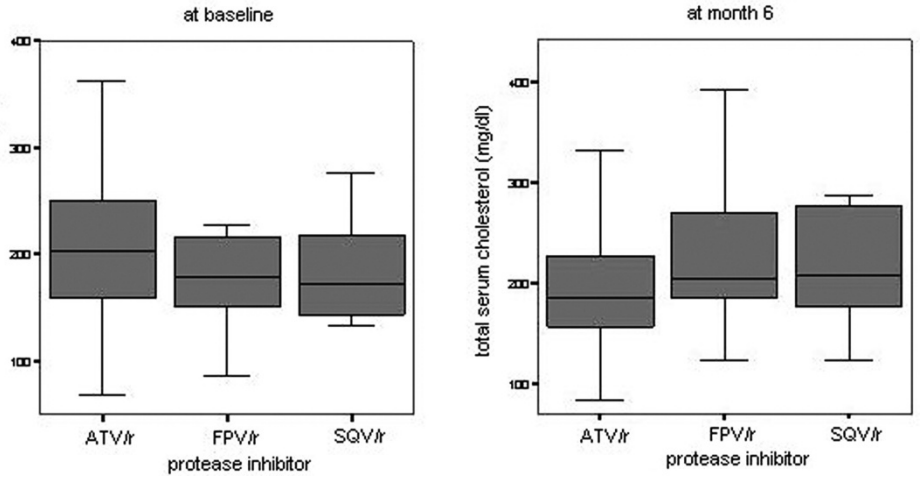

Fig. 1. Change of serum cholesterol levels in the course of the therapy.
In the boxplot, the central line represents the median, the box denotes the inter quartile range, the whiskers encompass the 1,5-fold inter quartile range, outliers are not indicated

increase of +21% (p= 0.0002; comparison of ATV/r and FPV/r) and +6% (p= 0.016; comparison of ATV/r and SQV/r) was observed. No significant difference could be found between the patients taking FPV/r and those taking SQV/r (p= 0.28; comparison of FPV/r and SQV/r) (Table 2).

In the further course between 6 and 24 months after initiating PI therapy cholesterol levels in patients on ATV/r were continuously lower than in the other groups. In the ATV/r-group the median serum cholesterol at month 24 was 198 mg/dl, in the FPV/r- and SQV/r-group the values were 228 mg/dl and 214 mg/dl, respectively.

The median serum triglyceride level at baseline in the FPV/r-group was at 136 mg/dl and thus in the favourable range below 150 mg/dl [3, 4, 55, 56]. In the patients starting therapy with ATV/r and SQV/r the median baseline values for the triglycerides were 187 mg/dl and 205 mg/dl, respectively. After the first 6 months of PI therapy the median value in the ATV/r-collective remained basically unchanged at 187 mg/dl whereas an increase to 169 mg/dl in the FPV/r group

and an increase to 218 mg/dl in the SQV/r group were observed. However, neither the inter-group differences nor the changes over time within the different PI groups were statistically significant (Table 2).

Median serum glucose values showed no significant variation between the comparison groups and no relevant changes over the time course of the therapy with the PIs. The majority of the patients in all three groups had normal fasting serum glucose levels below 110 mg/dl throughout the study period (Table 2).

At baseline the proportion of patients with high cardiovascular risk, i.e., a HeartScore-risk of >5% [2, 3, 54], was highest at 27% in the group starting therapy with ATV/r. In the FPV/r-group and SQV/r-group the prevalence was 9% and 12%, respectively. After 6 months of PI therapy the proportion of high-risk patients was slightly lower in the ATV/r-group at 24%. In the other groups a trend towards a rise to 13% and 18% could be observed in the patients taking FPV/r and SQV/r, respectively (Table 2).

There were no statistically significant differences between the PIs regarding their efficacy in suppressing HIV. Less than half of the patients in all PI-groups had a non-detectable viral load at baseline. After 6 months of therapy the proportion had risen to >70%. The median CD4-cell count was between 262 and 343 cells/µl at baseline and rose to values between 292 and 400 cells/µl after 6 months of therapy.

Multivariate Linear Regression

Among the covariates tested only BMI at baseline was identified as confounding the association between PI group (ATV/r vs. SQV/r vs. FPV/r) and cholesterol level at month 6 and therefore was included in the final model. In addition, significant interaction between treatment with FPV/r and BMI at baseline was detected (Table 3).

Table 3. Multivariate linear regression model for serum cholesterol levels after 6 months of PI-therapy.

Parameter	Coefficient	p-value	R^2 [a]
intercept	59.9	0.071	
Therapy using ATV/r	reference		
Therapy using SQV/r	34.5	0.007	
Therapy using FPV/r	-83.8	0.15	
FPV/r×BMI at baseline	5.6	0.021	
BMI at baseline	1.5	0.26	
Serum cholesterol at baseline	0.5	< 0.001	
			0.49

a: Coefficient of determination of the regression model

The effect of this interaction can be illustrated by dichotomizing BMI at the median value of 23.5 kg/m2 (Table 4). While for patients with higher BMI values the use of FPV/r was associated with the highest cholesterol levels after 6 months, for patients with lower BMI predicted serum cholesterol in the FPV/r group was identical to those in the SQV/r group (all compared to therapy with ATV/r).

Table 4. Influence of BMI stratum on the effect of FPV/r on the serum cholesterol level after 6 months of PI therapy.

Parameter	Coefficient	p-value
ATV/r	reference	
SQV/r	36.6	0.004
FPV/r		
for BMI >23.5 kg/m²	58.1	<0.001
for BMI ≤23.5 kg/m²	36.6	0.023
Serum cholesterol at baseline	0.5	<0.001
BMI of >23.5 kg/m² at baseline	15.0	0.13

Discussion

In this cohort study comparing the effect of cART either containing ATV/r, SQV/r, or FPV/r on serum cholesterol levels after 6 months of therapy under real-life conditions we demonstrated the lowest serum cholesterol levels in the ATV/r treated patients. This is even more remarkable considering that at baseline the median serum cholesterol level was highest in the ATV/r group. During the first 6 months of therapy the median serum cholesterol significantly decreased by 18 mg/dl in the ATV/r-group (p=0.009), whereas in the FPV/r and SQV/r-groups an increase in median cholesterol was observed. Thus, in contrast to baseline the serum cholesterol profile at month 6 was most favourable in the patients taking ATV/r. The observed differences of >20 mg/dl in median serum cholesterol between the groups appear clinically relevant, especially in patients at a high cardiovascular risk, even though predefined statistical significance was missed for the bivariate inter-group comparison (p=0.055), likely due to the differences in baseline median cholesterol values between the PI groups. When adjusting for different baseline levels by comparing the median relative changes in serum cholesterol during the first 6 months of therapy the difference between the PI-groups is significant (p=0.0002) and strongly in favour of therapy with ATV/r. Therefore our study confirms the favourable influence of ATV/r on serum cholesterol described in current literature [42-45, 52, 57-60].

For SQV/r several trials have indicated a comparatively beneficial influence on serum cholesterol [24, 39, 46, 47], an effect not replicated in our study where treatment with SQV/r was associated with a modest increase in serum cholesterol.

In contrast to the Alert-study [52], our findings confirm the rather disadvantageous effect of FPV/r on serum cholesterol [27] found in several other studies [50, 51, 61]. However, considering the interaction identified in the multivariate linear regression model, this unfavourable effect of FPV/r on serum cholesterol may not be universal but seems to mainly affect patients with a higher BMI. This suggests that while it might be prudent to avoid therapy with FPV/r in obese patients, FPV/r may be a relatively safe treatment option in patients with normal weight.

With serum cholesterol being one of the main established cardiovascular risk factors [3-5, 8], calculated cardiovascular risk within the first 6 months of PI therapy parallelled the changes in cholesterol values: in the group taking ATV/r the proportion of patients with high cardiovascular risk decreased, whereas in the patients using FPV/r and SQV/r the proportion with high cardiovascular risk increased.

The HeartSCORE used here for determining the patients' cardiovascular risk has not been validated in HIV-infected populations so far. However, its advantage over other available cardiovascular risk calculators is its validation specifically in European populations. Furthermore, based on parameters readily available through measurements in clinical routine, it describes the risk of a fatal cardiovascular event rather than other, less clearly defined endpoints [2].

It is well known that atherosclerosis is most strongly associated with levels of LDL-cholesterol [4, 26], which were not available for many patients in this study. However, there is a robust correlation between LDL-cholesterol and total serum cholesterol, therefore the latter can well serve as a surrogate variable for determining a patient's cardiovascular risk profile [4].

Another limitation of the study is the relatively small sample size and the unbalanced distribution of patients between the comparison groups, potentially leading to an impairment of statistical significance of some of the analyses. However, the group of patients examined here can be regarded as a representative sample of HIV-infected individuals in Germany based on their demographic characteristics [62]. Furthermore, different univariate and multivariate approaches to analyze the effect of the examined PIs on serum cholesterol yielded consistent results, demonstrating the robustness of the statistical analyses. An immanent limitation of a non-interventional, retrospectively analyzed study is the potential problem of missing data and incomplete data standardization. This was minimized by the use of different data sources including chart documentation of regular clinic visits scheduled every three months and a standardized patient database established at the clinic since 1997. In addition, a main strength of this study is the analysis of data derived from a real-life patient population. In this way clinical reality can be better represented than by the highly selected patient populations used for interventional studies.

In conclusion, in a real-life patient population we confirmed that treatment of HIV infection with a ATV/r based regimen had a more favourable impact on serum cholesterol levels and therefore cardiovascular risk compared to SQV/r or FPV/r based regimens. FPV/r was associated with the highest increase in serum cholesterol, specifically in overweight patients, whereas its effects on cholesterol may be comparable to SQV/r in patients with a BMI $\leq$23,5 kg/m^2. In the light of growing interest in personalized medicine [63] and with obesity and cardiovascular disease getting ever more prevalent [4, 64-68] this may be an example of how to better tailor cART regimens considering a patient's metabolic and cardiovascular profile.

Based on these results more and larger studies should be undertaken to specifically address the multiple interdependencies between effects of cART and patient characteristics affecting cardiovascular risk.

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Received: November 1, 2010 / Accepted: November 1, 2010

Address for correspondence:
Dr. Miriam Gyalrong-Steur
Infektionsambulanz und Tagesklinik
Medizinische Poliklinik der
Ludwig-Maximilians-Universität – Innenstadt
Pettenkoferstraße 8a
80336 München
Germany
Phone: ++49-151-56168156
Fax: ++49-89-51603550
Email: m_c_gyalrong@hotmail.de