CASE REPORT

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Long-Term Efficacy and Safety of Efavirenz Dose Reduction to 200 mg Once Daily in a Caucasian Patient with HIV

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Abstract

A 48-year-old Caucasian male patient presented with severe adverse drug events (ADEs) while being treated with a standard dose (600 mg/day) of efavirenz. The patient's clinical course was favourable; however, he also described intense nightmares, cramps in his legs and anxiety disturbances that made him highly irritable. Measurement of the patient's efavirenz plasma concentrations revealed a mean minimum steady-state concentration during a dosage interval ($C_{min,ss}$) of 12.7 mg/L, which was much higher than that recommended for this drug (therapeutic range 1–4 mg/L). Consequently, the dose of efavirenz was reduced to 400 mg/day, which resulted in a decrease in the frequency of ADEs. Subsequent genotype testing showed that the patient was homozygous for both the *CYP2B6*-G516T (T/T) and *CYP2B6*-A785G (G/G) alleles; these polymorphisms are associated with reduced enzymatic activity and elevated efavirenz plasma concentrations. Because of this and the fact that the patient's mean efavirenz $C_{min,ss}$ was still high (4.6 mg/L), a second dosage reduction was undertaken, to 200 mg/day. This also resulted in a reduction in ADEs. At present, the patient's $CD4^+$ levels remain stable, his viral load continues to be undetectable and the mean efavirenz $C_{min,ss}$ is within the therapeutic range (2.7 mg/L).

Efavirenz is an antiretroviral recommended as a first-line treatment for HIV infection in numerous international guidelines because of its efficacy and favourable tolerability. Nevertheless, this drug has a wide range of neuropsychiatric effects (sleep disturbances, dizziness, sadness, mood changes, irritability, nervousness, impaired concentration, abnormal dreams and somnolence) in up to 40–70% of patients, according to some published reports.[1-3] These complaints usually persist for the first 2–4 weeks of treatment.[4,5] However, some studies show that neuropsychiatric disorders may continue in more than one-half of patients receiving long-term efavirenz therapy.[6]

Adverse drug events (ADEs) have been reported to be more frequent in patients with high efavirenz plasma concentrations.[7-9] However, this association has not been found in other studies[6,10,11] and further research is necessary.

Several studies have revealed that the existence of genetically derived variations in certain proteins involved in either the transportation (P-glycoprotein) or the metabolism (cytochrome P450 [CYP] 2B6, CYP2A6, CYP3A4, CYP3A5, CYP2D6 and other enzymes) of efavirenz[12] could explain its high interpatient pharmacokinetic variability.[13-18] In addition, some studies have demonstrated that high efavirenz plasma concentrations and genetic variations are associated with neuropsychiatric ADEs.[7,8,13,18-21] Thus, this relationship suggests a rationale for evaluating whether reduced efavirenz doses in 'real-world' practice could diminish ADEs without compromising the drug's virological efficacy.[22,23]

To our knowledge, limited information exists on the long-term efficacy and safety of efavirenz dose reduction. We report the case of a Caucasian male patient who presented with severe ADEs while being treated with a standard dose of efavirenz. An efavirenz dosage reduction to 200 mg/day increased safety margins while maintaining the efficacy of long-term therapy.

1. Case Report

A 48-year-old Caucasian male patient was documented as having HIV infection in 1989. A nadir $CD4^+$ lymphocyte level (137/μL) and a peak viral load of 26 032 copies/mL were attained in early 2000, and antiretroviral treatment (ART) consisting of zidovudine, lamivudine and efavirenz was commenced in that year. The patient was coinfected with hepatitis C virus but did not have liver fibrosis.

The patient was commenced on a standard dosage of efavirenz (600 mg/day). However, after only 1 week's treatment, the patient complained of severe ADEs. Furthermore, at all follow-up visits, he continued to describe the presence of intense nightmares (vivid dreams with progressively increasing anxiety, ultimately resulting in the patient waking up), dizziness, anxiety disturbances (nervousness, irritability) and intense cramps in his legs. The patient did not have a previous history of mental disorders and was not taking psychiatric medication at the time of the study.

In 2005, the patient was enrolled in a therapeutic drug monitoring (TDM) programme, which involved collection of one blood sample during each visit to the hospital. Samples for measurement of plasma drug concentrations were collected at steady state (more than 4 weeks after the initiation of efavirenz treatment), usually at the midpoint of the dosage interval. Efavirenz concentrations were assessed quantitatively by high-performance liquid chromatography (HPLC). Determination of efavirenz plasma concentrations revealed a mean minimum steady-state plasma concentration during a dosage interval ($C_{min,ss}$) of 12.7 mg/L, which was much higher than that recommended for this drug (therapeutic range, 1–4 mg/L).[7]

Accordingly, in March 2006, a reduction in efavirenz dosage took place (to 400 mg/day) on the basis of the results of a pharmacokinetic analysis. For this analysis, which assumed an open, one-compartment model with a fixed absorption constant and first-order elimination,[18] the apparent oral clearance and apparent volume of distribution for efavirenz were individually estimated using Bayesian algorithms. The population pharmacokinetic parameters were obtained from our own population and were incorporated into PKS® software (Abbott Diagnostic, Chicago, IL, USA). This software allowed us to predict dose adjustments and subsequent plasma concentrations at different times using the population pharmacokinetic parameters and two or three efavirenz plasma concentrations obtained from the patient.

Evaluation and quantification of the evolution of the patient's ADEs were achieved by semi-structured interviews with the patient at every follow-up visit. This interview included questions about common presumed efavirenz-related ADEs (cognitive effects, affect/mood changes, anxiety, psychotic and sleep disturbances) and was based on two validated questionnaires (the Pittsburgh Sleep Quality Index[24] and the Hospital Anxiety and Depression Scale[25]). An overall ADE score, expressed as a percentage of the maximum possible score (45 points), was generated.

After the first efavirenz dose reduction, the patient reported a decrease in both the frequency

of his nightmares and the intensity of his cramps. He also commented that his irritability level had reduced. As anticipated, because of these improvements with regard to ADEs, our patient reported a high level of satisfaction with the new dose.

In May 2007, after having obtained informed consent from the patient and ethical approval from the Institutional Review Board of the University Hospital of Salamanca, Spain, the patient underwent genotype testing. These tests showed that the patient was homozygous for both the *CYP2B6*-G516T (T/T) and *CYP2B6*-A785G (G/G) alleles (table I). This genotype analysis was determined using PHARMAchip® (Progenika Biopharma, Bilbao, Spain), a DNA chip that analyses 91 polymorphisms present in 33 genes involved in phase I and II enzymatic metabolism, as well as transporters, neurotransmitter receptors and others.

Based on the patient's genotype analysis and the fact that mean efavirenz $C_{min,ss}$ was still high (4.6 mg/L) in July 2008 a second dosage reduction took place (to 200 mg/day). One month later the patient commented that his anxiety, nervousness and irritability had diminished considerably. In addition, before dose adjustment, he had also complained of numbness in the calves, which has since disappeared completely. In August 2009, the patient's $CD4^+$ levels remained stable, his viral load remained undetectable and mean efavirenz $C_{min,ss}$ (2.7 mg/L) was within the therapeutic range at every follow-up visit (figure 1).

It is necessary to emphasize that the patient's adherence to treatment was always optimal (100%) during the entire period of analysis, according to treatment dispensary records and responses to the simplified medication adherence questionnaire (SMAQ).[26] Likewise, during the entire observation period, the absence of concomitant medication interfering with the pharmacokinetic profile of efavirenz was assured.[27]

2. Discussion

To our knowledge, this is the first case of efavirenz dosage reduction to 200 mg/day that has demonstrated an increased safety margin while also maintaining the efficacy of long-term therapy in a patient of Caucasian extraction; until now, such procedures have been described only in patients of African[28] and Japanese[22] extraction. In addition, the duration of follow-up (45 months) is longer than in previously documented case reports.

Our patient experienced important ADEs with a standard dosage (600 mg/day) of efavirenz, despite the fact that the drug was always taken before going to bed and that the effect of diet was minimized since the patient took the drug at least 2 hours after his evening meal (as per the manufacturer's recommendations) and thereby avoided any possible food-drug interactions.[4]

Subsequently, the evolution of ADEs (figure 1) showed a direct proportional relationship between efavirenz plasma concentrations and ADE score, expressed as a percentage of the maximum possible score. Thus, this leads to the conclusion that the ADEs described in our patient could have been a consequence of elevated efavirenz plasma concentrations.

These results show how use of TDM offers an opportunity to develop an optimal and

Table I. Analysis of patient's genotype

Gene	Allele analysed	Genotype	Phenotype (enzymatic activity)
CYP2B6	G516T	T/T	Reduced
CYP2B6	A785G	G/G	Reduced
CYP3A4	1/1B	1/1	Normal
CYP2D6	1, 2, 3, 4, 5[a], 6, 7, 8, 9, 10, 11, 14A, 14B, 15, 17, 19, 20, 25, 26, 29, 30, 31, 35, 36, 40, 41, 1XN[b], 2XN, 4XN, 10XN, 17XN, 35XN, 41XN	2/2	Normal

a Gene deletion.

b Gene duplication.

CYP = cytochrome P450.

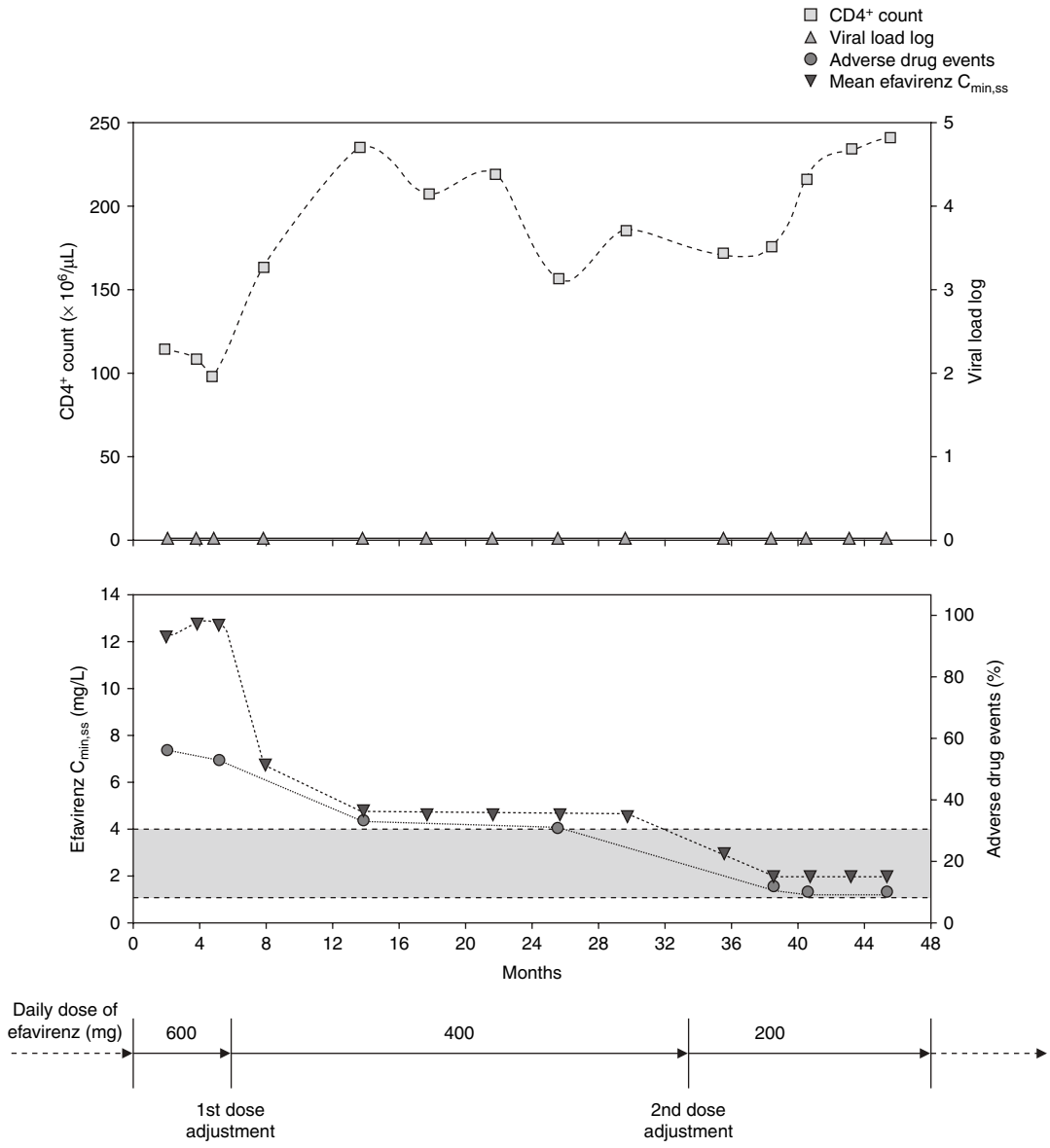

Fig. 1. Evolution of CD4+ cell count, viral load, adverse drug events and efavirenz plasma concentrations in patient undergoing efavirenz dose reductions. The grey shaded area represents the efavirenz therapeutic range. $\mathbf{C_{min,ss}}$ = minimum steady-state plasma concentration during a dosage interval.

individualized therapy for each patient. They also demonstrate that ADEs should not be always assumed to be an inherent consequence of ART, which may be effective without causing significant toxicity. Furthermore, the findings suggest a need for investigation of the relationship between ART ADEs (lipodystrophy, dyslipidaemias, peripheral neuropathies, etc.) and high plasma concentrations, not only for efavirenz but also for other ARTs.

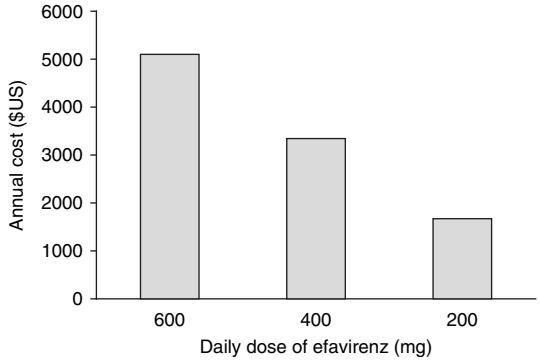

Fig. 2. Comparison of annual cost (year of costing 2009) and daily dose of efavirenz.[37]

The main objective of ART is to achieve virological suppression, and thus restore the efficiency of the immune system to the greatest extent possible. Efavirenz has good antiviral efficacy, but the high interindividual variability of its pharmacokinetics complicates the achievement of long-term benefits with the drug.[29] Differences in the hepatic metabolism of efavirenz seem to explain much of this variability. In our case, genotype testing showed that the patient was homozygous for the *CYP2B6*-G516T and *CYP2B6*-A785G alleles. These polymorphisms are associated with reduced enzymatic activity, which in turn results in increased efavirenz plasma concentrations.[8,9,19-22,30-32] Thus, correct interpretation of pharmacogenetic and pharmacokinetic data could be used to individualize treatment with this drug. In clinical practice, the pharmacogenetic data support the information provided by TDM, which is a reflection of the phenotype expressed by the pharmacokinetic behaviour of the drug in a particular patient and is dependent mainly on hepatic metabolism.[33] This, added to low intrapatient variability in efavirenz plasma concentrations and high interindividual variability,[34] shows not only that TDM could be useful in the clinical management of HIV disease,[35] but also that in clinical practice TDM continues to be the best tool for optimizing the dose regimen of efavirenz.[36]

It is also important to take into consideration the economic implications of dose reductions of the type described in this case report. The cost of treatment with efavirenz in this case decreased by approximately one-third with each dose reduction and, given that the optimal dosage in this patient was 200 mg/day, the annual savings would have been $US3446 per year (year of costing 2009)[37] [figure 2]. Furthermore, the costs associated with the determination of efavirenz plasma concentrations are minimal if we compare these with the savings generated by dose reduction. Thus, the average cost of measuring plasma concentrations is approximately $US40 (year of costing 2009), which includes personnel and technical expenses (technicians and HPLC equipment).[37] Therefore, considering that three determinations of plasma concentration are necessary to ensure that these values reflect the true exposure of the patient to the drug, the total annual cost of the 'diagnosis of overdosage' is approximately $US120 (year of costing 2009). These figures justify implementation of TDM, which would give more patients access to ART because of the savings in treatment costs.

3. Conclusion

Factors that limit efavirenz dose reduction to minimize ADEs in 'real-world' practice are: (i) the low genetic barrier of efavirenz (development of resistance can occur after only a single amino acid substitution); and (ii) the fact that dose adjustment of ARTs guided by TDM has not been extensively studied. However, based upon the findings of the current case, the observed relationship between ADEs and efavirenz plasma concentrations confirms the usefulness of TDM in dose individualization as one way of optimizing the management of long-term efavirenz therapy.

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