Once-daily dosing of nevirapine in HAART

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Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens provide simpler and more easily tolerated treatment alternatives to protease inhibitor-based regimens, potentially improving adherence. Long-term viral suppression relies on adherence to a prescribed antiretroviral treatment regimen. Simplification of dosing schedules has prompted investigations into once-daily dosing regimens; nevirapine once-daily dosing strategies are currently under investigation. The DAUFIN study compared zidovudine/lamivudine 300 mg/150 mg plus nevirapine 200 mg twice daily with lamivudine 300 mg, tenofovir 245 mg and nevirapine 400 mg once daily. The study was stopped after early virological failure was observed in 8/36 (22.2%) once-daily patients. Baseline characteristics in once-daily patients with and without virological failure indicated significantly higher median plasma viral load and significantly lower median CD4+ cell counts. Presented nevirapine plasma trough levels were not stratified by virological failure or success. Resistance mutations accumulated while on treatment; high rates of K65R mutations and severe NNRTI resistance profiles might be indicative of ongoing viral replication caused by suboptimal nevirapine plasma trough concentrations under non-adherence to the treatment regimen. Non-B-subtype infection (subtype A or C not stated) was observed in 4/10 patients with virological failure. The DAUFIN study was prematurely stopped without predetermined cessation criteria, presented data are not complete, and results should be interpreted with caution.

Nevirapine pharmacokinetics make it suitable for once-daily dosing. However, due to rash and concerns over liver toxicity, nevirapine once daily might best be administered in patients with undetectable viral load after initial treatment with nevirapine twice daily. The NODy study will evaluate the efficacy and safety of switching to nevirapine once daily compared with remaining on twice-daily treatment.

Keywords: DAUFIN, twice daily, efficacy, safety

Introduction

Current guidelines recommend the use of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with either a non-NRTI (NNRTI) or a ritonavir-boosted protease inhibitor (PI) for treating antiretroviral (ARV)-naive HIV-infected patients. Complex dosing schedules, high pill burden and toxicities associated with the use of early PIs may affect tolerability and adherence. However, ritonavir-boosted PIs have a high barrier to resistance and require the accumulation of several mutations before significant resistance occurs. In contrast, NNRTIs have a low barrier to resistance, with only one point mutation required to confer resistance. Nonetheless, NNRTI-based ARV therapy has become increasingly popular because it provides clinicians and patients with a simpler and more easily tolerated treatment option. NNRTI-based ARV therapy is also recommended as a preferred option for treatment-naive patients in current guidelines. In an effort to simplify dosing schedules further, the feasibility of once-daily dosing of drugs licensed for twice-daily dosing, e.g. nevirapine, is being explored.

The DAUFIN study

DAUFIN, a randomized, open-label, non-inferiority trial, compared zidovudine/lamivudine 300 mg/150 mg plus nevirapine 200 mg twice daily with lamivudine 300 mg, tenofovir 245 mg and nevirapine 400 mg once daily. Seventy-one HIV-1-infected, ARV-naive patients (CD4+ cell counts <350 cells/mm3) were enrolled (n = 35 and n = 36 in the twice-daily and once-daily groups, respectively), with no restrictions on HIV-1 viral load (VL). The primary endpoint was percentage of patients with VL <400 copies/mL at 96 weeks.

Preliminary data from the DAUFIN study showed unexpectedly high rates of early non-response, with a high incidence of...
K65R and, to a lesser extent, M184V resistance mutations occurring in ARV-naive HIV-1-infected individuals who received once-daily lamivudine 300 mg, tenofovir 245 mg and nevirapine 400 mg.6

The study was stopped after early virological failures [defined as <2.0 $\log_{10}$ copies/mL decrease in plasma VL (pVL) by week 12, or rebound $>1$ $log_{10}$ of pVL at week 12 after initial decrease] were observed in 8/36 (22.2%) once-daily patients. Two late virological failures (defined as an increase in pVL after undetectable pVL was established) were also observed; one in the once-daily group and one in the twice-daily dose group. Comparison of HIV baseline (BL) characteristics in once-daily patients with and without virological failure indicated significantly higher median pVL (262 747 copies/mL versus 51 189 copies/mL; $P = 0.002$) and significantly lower median CD4$^+$ cell counts (110 cells/mm$^3$ versus 223 cells/mm$^3$; $P = 0.004$) in virological failures. The authors claimed that virological failure in the once-daily regimen could not be explained by lower nevirapine plasma trough concentrations. However, presented nevirapine plasma trough levels were not stratified by virological failure or success. If nevirapine plasma trough levels for individual virological failures were found to be below the expected 4–5 mg/L level,3 this might suggest poor adherence to the treatment regimen.

An NNRTI mutation (K101E) was present at BL in one patient with early virological failure.6 The remaining patients with virological failure, for whom BL resistance-mutation data were available (BL data not presented for two patients), were infected with wild-type virus at BL and accumulated resistance mutations while on treatment.6 High rates of K65R mutations (6/9 once-daily patients) and severe NNRTI resistance profiles (five subjects with two or more mutations, seven subjects with Y181C/A) were observed in virological failures. This might be attributed to the ongoing viral replication caused by suboptimal nevirapine plasma trough concentrations under non-adherence to the treatment regimen. Four out of 10 patients (one twice daily; three once daily) with virological failure were infected with non-B subtypes. Rapid selection of the tenofovir resistance-associated K65R mutation can occur in subtype C viruses (i.e. a non-B subtype).8 Rey et al.6 did not clarify whether non-B subtypes were subtype A or C. This is relevant because infection with subtype C may predispose patients to developing tenofovir resistance6 and contribute to virological failure.

Comparisons were made between DAUFIN data and results from a small trial in which tenofovir, lamivudine and nevirapine once daily resulted in high virological failure rates in ARV-naive patients with BL VL > 100 000 copies/mL, largely due to the Y181C mutation and nevirapine-associated resistance.9 The latter results should be interpreted with caution because patients lost to follow-up were counted as treatment failures, a rigorous statistical assessment which may have overstated the true rate of virological failure.

Importantly, no negative interactions have been observed between nevirapine and tenofovir10 or nevirapine and lamivudine.7 In another study, patients with long treatment histories, advanced disease and prior evidence of suboptimal ARV therapy were switched from other ARV regimens to tenofovir/ nevirapine due to toxicity or for regimen simplification.11 Neither high virological failure rates [7/77 (9%)] nor unexpected numbers of adverse events were observed in switching patients. Virological failure could be attributed to either or both poor adherence and suboptimal pre-treatment in 6/7 (85.7%) failing patients.

The DAUFIN study enrolled few subjects and was prematurely stopped without predetermined cessation criteria. It is necessary to emphasize the statistical importance of having set endpoints and criteria for study cessation. The small study scale raises the possibility that results presented were attributable to chance. Data presented by Rey et al.6 are also not complete and, given that concern for patient safety is foremost, presenting data in this manner can inappropriately change ARV usage.

**Long-term safety and efficacy of nevirapine-based therapy**

The prolonged use of nevirapine-based regimens in routine clinical settings has been established as safe and effective when treating HIV-1-infected individuals.

Recently, a multicentre, cross-sectional and observational study, performed in 12 tertiary-care hospitals in Catalonia, Spain, assessed the long-term safety, metabolic and viral efficacy of a nevirapine-containing highly active ARV therapy (HAART) regimen in 613 HIV-1-infected adults for at least 2 years.12 This study does not state whether nevirapine regimens involved once- or twice-daily dosing. Patients treated for ≥2 years with a nevirapine-based approach were enrolled with the aim of demonstrating that in patients who initially tolerate the regimen, nevirapine remains a safe treatment in the long-term. Hepatitis B or C co-infection was present in 31% of patients. Only 5.7% of all adverse events could be attributed to nevirapine use during the study; predominantly liver toxicity. Notably, liver toxicity was generally mild and accounted for very few discontinuations (1.1%). Grade 3/4 transaminase elevations were infrequent, occurring in <2% of all patients. Mean lipid values were stable over time, with a significant improvement in triglycerides and HDL cholesterol values. Additionally, a durable immunological response was observed in all patient groups (median CD4+ cell count increased from BL by 224 cells/mm$^3$ in ARV-naive patients, 77 cells/mm$^3$ in switch patients and 134 cells/mm$^3$ in salvage patients).

In some nevirapine patients with high CD4+ cell counts, symptomatic, serious hepatic events (with concomitant rash in some cases) have been observed. Current guidelines recommend that nevirapine be administered only in female and male patients with CD4+ cell counts <250 and <400 cells/mm$^3$, respectively.3 Although patients initiating nevirapine-based HAART may be at increased risk of hepatotoxicity, data have shown that clinically relevant hepatotoxicity related to nevirapine use occurs early. In patients tolerant of nevirapine during the early stages of treatment, long-term exposure appears safe, even in those co-infected with hepatitis C virus.12

Recently presented long-term data from the 2NN study confirm no statistical differences in treatment failure between nevirapine and efavirenz.13 The 2NN study compared the efficacy and safety of treatment with stavudine and lamivudine, and nevirapine once daily, nevirapine twice daily, efavirenz or the combination of nevirapine and efavirenz in 1216 ARV-naive HIV-1-infected patients at 48 weeks.14 The primary endpoint was the proportion of patients with treatment failure. Week 48
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data showed no significant differences in treatment failure between regimens, although the safety profiles of nevirapine and efavirenz differed and authors advised this to be considered when selecting a treatment regimen. Nevirapine once daily had an ARV efficacy similar to nevirapine twice daily and the authors concluded that it seemed suitable for treatment simplification. Data collected retrospectively for a further 2 years confirmed no significant differences between the treatment regimens through 144 weeks.15

Nevirapine-based regimens represent a low-cost approach to ARV treatment; long-term data, as presented above, will contribute to the development and implementation of safe, effective and economical strategies, which are required to combat HIV globally.

Switching to nevirapine-based therapy

Nevirapine is an effective and well-tolerated treatment, capable of prolonged virological and immunological responses.14 As such, it is possible to switch from a PI-based to a nevirapine-based ARV regimen and maintain viral suppression as shown in the NEFA study, which assessed the strategy of substituting nevirapine, efavirenz or abacavir for a PI in HIV-1-infected patients in whom virological suppression had already been achieved.15 Martinez et al.15 do not state whether nevirapine dosing was once or twice daily. Since nevirapine twice-daily dosing was the standard of care at NEFA study enrolment, it is likely that patients received a twice-daily dosing regimen. NEFA study results indicated a trend towards higher failure rates when abacavir, rather than nevirapine or efavirenz, replaced the PI component of the regimen. Importantly, patients with high CD4+ cell counts were switched to a nevirapine-based regimen in the NEFA study with no significant increases in hepatotoxicity.15 This would indicate that the risk of hepatotoxicity in nevirapine recipients maintaining VL <50 copies/mL is not the same as for treatment-naive patients and is not affected by BL CD4+ cell count. Since adherence is inversely related to the number of doses per day,16,17 attempts to simplify treatment regimens have led to greater interest in once-daily dosing of ARV drugs. Nevirapine has a long half-life and achieves high steady-state plasma concentrations relative to the concentration required to inhibit 50% viral replication in vitro (IC50) of wild-type virus isolated from patients, making it a suitable consideration for once-daily dosing.18 However, due to rash and concerns over hepatotoxicity,14,19 nevirapine might be best administered once daily in patients who have achieved undetectable VL following treatment with nevirapine twice daily. This is a view supported by Cooper and van Heeswijk,18 who recently reviewed the pharmacokinetic, efficacy and safety implications of once-daily nevirapine dosing. They concluded that the benefits of once-daily dosing may be achieved without excess toxicity by switching to once-daily nevirapine after several months of twice-daily administration. Further, this dosing strategy is currently under evaluation in the NODy study. This randomized, open-label study, of 400 patients already on twice-daily nevirapine for at least 3 months, will evaluate the efficacy and safety of switching to once-daily nevirapine compared with remaining on twice-daily treatment.

The cost of treating HIV is an important issue in developed, and especially less-developed, countries. Nevirapine represents one of the most affordable, marketed ARVs for managing HIV-1-infected individuals. In patients with undetectable VL, nevirapine represents a low-cost treatment option for those wishing to switch from a PI-based to an NNRTI-based therapy.

In conclusion, twice-daily nevirapine is highly effective and well tolerated in the majority of ARV-naive individuals. Nevirapine twice daily has a good long-term safety profile; liver toxicity is mild and infrequent and a favourable lipid profile is observed with treatment. Switching from a successful PI-based regimen to one containing nevirapine is associated with maintenance of good virological control and a favourable tolerance profile. Furthermore, switching to a nevirapine-based regimen does not appear to be affected by CD4+ cell counts. Nevirapine pharmacokinetics make it suitable for once-daily dosing, a strategy which will contribute to simplifying treatment regimens and improving adherence. DAUFIN study data on nevirapine once-daily dosing are incomplete, making the unfavourable conclusions drawn by the authors questionable. Importantly, nevirapine-based regimens represent a low-cost approach to ARV treatment, an important consideration in treating HIV worldwide. Improved adherence associated with simplified dosing regimens may also contribute to better efficacy and, hence, better treatment outcomes.

Transparency declarations

I have served as a consultant for Boehringer Ingelheim GmbH. I have also served as a consultant on advisory boards, speakers’ bureaus and in the conduct of clinical trials with Roche, Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Tibotec, Merck and Pfizer.

References


