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REVIEW

Clinical utility and consumer considerations for the use of once-daily nevirapine extended release for HIV infection treatment

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Abstract: An extended-release formulation of nevirapine (NVP-XR) has been developed with the aim of simplifying antiretroviral treatment regimens and improving patients' adherence with a single daily intake. The VERxVE and TRANxITION clinical trials have demonstrated the noninferiority of NVP-XR compared with nevirapine immediate-release (NVP-IR) on viral load after 24 and 48 months of treatment. The tolerance profiles of NVP-XR and NVP-IR are similar. Simplifying the treatment dosage for NVP would likely improve adherence to antiretroviral treatments.

Keywords: nevirapine extended release, HIV infection, antiretroviral therapy, efficacy, safety

Introduction

Highly active antiretroviral therapy (HAART) has improved the prognosis of patients with human immunodeficiency virus (HIV) infection by significantly reducing related morbidity and mortality.[1,2] Early treatment protocols, many of which are still recommended, contain two nucleoside reverse transcriptase inhibitors (NRTI) and one nonnucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI).[3–5] NNRTIs currently included in treatment regimens comprise nevirapine (NPV), efavirenz, and rilpivirine. Although NPV is used mostly to substitute PIs in patients with high cardiovascular risk in developed countries,[5] it is still included in first-line treatment regimens in low-income countries.[3] Given its short plasma half-life, NVP immediate-release (NVP-IR) must be administered twice a day to achieve a 24-hour effective plasma level.[6] In order to simplify ART regimens and improve adherence to prescribed medications, the extended-release formulation of NVP (NVP-XR), which allows a single daily intake, has been developed and tested in two Phase III clinical trials. The aim of the current review is twofold: (1) To highlight the clinical utility and efficacy of NVP-XR; (2) To assess the impact of NVP-XR on patients' safety by shedding light on the main side effects of NVP-XR and the expected gain in term of treatment adherence.

Historical perspective

Nevirapine is a member of the NNRTI family that was introduced as a component of the triple ART in 1996 (Viramune; Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT, USA). Since then, it has been used in its immediate-release (IR) form alongside NRTIs. Following an induction phase at 200 mg in a single intake per day for 2 weeks, NVP-IR is administered twice per day at 200 mg per intake during the continuation phase.[7]

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Early clinical trials comparing a single daily dose of NVP-IR 400 mg vs 200 mg twice per day, or vs another NNRTI with longer half-life, revealed high rates of virologic failure among patients treated with single daily intake.[8–10] For instance, in the DAUFIN randomized, open-label trial,[8] a twice-daily combination of zidovudine (300 mg), lamivudine (150 mg), and NVP-IR 200 mg was compared with an once-daily combination of lamivudine (300 mg), tenofovir (245 mg), and NVP-IR (400 mg). This study was prematurely terminated after the inclusion of 35 and 36 patients respectively in each of the study arms, due to a treatment failure rate of 22.2% among those in the NVP-IR single daily intake arm of the study.[8] By contrast, in a prospective nonrandomized study published in 2009, assessing the efficacy and tolerance of a once-daily combination of NVP-IR (400 mg), tenofovir (300 mg), and emtricitabine (200 mg), Weberschock et al[11] found a virologic efficacy in 84.6% of patients who were still on treatment after 72 weeks of follow-up, and reported important side effects in 11.4% of patients. In spite of the nonrandomized nature and the lack of a control arm in the study by Weberschock et al,[11] there were suggestions for the efficacy and tolerability of regimens based on a once-daily NVP regimen. Therefore, in order to simplify treatment protocols, the NVP-XR (Viramune 400-XR; Boehringer Ingelheim Pharmaceuticals, Inc), which allows a single daily intake of 400 mg, was approved by the US Food and Drug Administration in March 2011.[12]

Pharmacology of nevirapine extended-release formulation

Nevirapine belongs to the class of NNRTI agents that act by inhibiting the reverse transcriptase (RT) of HIV-1. Unlike NRTI, NVP does not act through a competitive mechanism, but by directly binding to the catalytic site of RT, leading to the inhibition of the DNA polymerase, which is essential for RNA and DNA activities.[13,14] NVP-XR was developed from a hydrophilic polymer called hypromellose 2208, to allow a controlled and extended release of NVP in the intestinal tract.[15] NVP-IR is very well absorbed in the digestive tract, with a bioavailability rate as high as 90%. Compared with NVP-IR, NVP-XR is slowly absorbed in the digestive tract, with a bioavailability rate of 72%.[12] The minimal plasmatic concentration of 2920 ng/mL achieved after a single dose of 400 mg of NVP-XR and the 24-hour time to maximum concentration, are compatible with a single daily intake using this formulation.[12] NVP undergoes a biotransformation process involving cytochrome P450 to yield several hydroxylated metabolites. This biotransformation is achieved in large part by cytochrome CYP3A.[7]

Clinical efficacy of nevirapine extended-release

The efficacy and tolerance of NVP-XR have been assessed in two major clinical trials: the VERxVE[16] and TRANxITION[17] trials. VERxVE was a Phase III multinational, randomized, single-blinded parallel arms trial, comparing the efficacy and tolerance of NVP-XR (400 mg once-daily) with NVP-IR (200 mg twice-daily); each arm augmented with emtricitabine (FTC) and tenofovir (TDF) among 1011 adult patients (505 in the NVP-XR arm and 506 in the NVP-IR arm) with HIV infection and naïve to ART drugs.[16] The primary outcome of the study was a sustained virologic response at 48 months of treatment. Sustained virologic response was defined by two consecutive HIV viral load $<$ 50 copies/mL at least 2 weeks apart and without relapse or change in the ART regimen.[16] After 48 weeks of treatment, this study showed a noninferiority of once-daily NVP-XR 400 mg compared with twice-daily NVP-IR, for a predefined margin of −10%. The proportion of patients with sustained virologic response at 48 weeks was 81% (409/505) in the NVP-XR group and 75.9% (384/506) in the NVP-IR group with an adjusted difference of 4.9% favoring the NVP-XR arm.[16]

The TRANxITION trial was conducted to assess the efficacy and tolerance of once-daily NVP-LP 400 mg, subsequent to a transition from an initial twice-daily regime of NVP-IR 200 mg in patients with virologic efficacy. This was a randomized trial (2:1, NVP-XR:NVP-IR) in multinational, double-blinded, noninferiority, and paralleled groups.[17] This study enrolled 295 patients in the NVP-XR group and 148 patients in the NVP-IR group. The main primary outcome was a sustained virologic response at 24 weeks following randomization and was based on a viral load $<$ 50 copies/mL.[17] Persisting virologic response was observed in 93.6% of patients in the NVP-XR arm and 92.6% in the NVP-IR arm, with an adjusted difference of 1% favoring the NVP-XR arm. NVP-XR was noninferior to NVP-IR, based on a margin of 10%.[17]

The two Phase III clinical trials[16,17] have demonstrated the clinical efficacy of NVP-XR compared with NVP-IR (suppression of the viral load or maintenance of a nondetectable viral load) among HIV patients naïve to ART or initially treated with a regimen containing a NVP-IR. Other indicators of comparable efficacy between the two formulations are: the time to the loss of virologic response and increase in CD4 count from the baseline levels.[16]

Tolerance and side effects of nevirapine extended-release

In the VERxVE trial, the incidence of a skin eruption considered to be drug-related was 5.7% in the NVP-XR arm and 4.9% in the NVP-IR arm, with nonsignificant difference. The majority of patients had mild or moderate skin eruption, usually within the first 4 months of starting the treatment. Three patients in the NVP-IR arm developed Stevens–Johnson syndrome against none in the NVP-XR arm.[16] The proportion of patients who developed symptomatic hepatitis was 1.6% and 2.4% in the NVP-XR and NVP-IR arms, respectively ($P > 0.05$).[16] Drug side effects were reported in 11.9%[17] and 19.8%[16] of patients on NVP-XR, and in 2%[17] and 24%[16] of those on NVP-IR in the two published clinical trials, respectively.[16,17] It is also of note that grade 3 and 4 side effects attributable to the trial medications were comparable in the two arms in the two studies. Therefore, the reported frequency of side effects during treatment with NVP-XR is comparable to those observed during treatment with NVP-IR. Compared with NVP-IR, NVP-XR is equally tolerated.

Impact of nevirapine extended-release on the patient: improvement of the adherence to antiretroviral treatment

The reduction of the pill burden significantly improves the adherence to ART.[18] Therefore, transition to NVP-XR formulation, which allows a single daily intake would improve the adherence of patients initially on NVP-IR twice daily, or those directly started on the new formulation. In the two clinical trials of NVP-XR, adherence was similar in the two arms, which in some ways is expected in rigorously conducted randomized controlled trials. Real-life studies will aid in exploring this issue.

Conclusions

The XR formulation of NVP is effective and well tolerated in both HIV patients who are naïve to ART therapy and those initially treated with NVP-IR. The incorporation of NVP-XR in the treatment armamentarium for HIV infection would likely allow a simplification of treatment protocols through single daily intake of the medications and therefore contributing to improving adherence to ART.

Disclosure

The authors report no conflicts of interest in this work.

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