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Leading article

NNRTIs—a new class of drugs for HIV

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The non-nucleoside reverse transcriptase inhibitors (NNRTIs), nevirapine and efavirenz, are now licensed for the treatment of human immunodeficiency virus (HIV) infections. A third compound, delavirdine, is licensed in the USA and available in Europe on expanded access programmes. The place of NNRTIs in HIV therapy is determined by their pharmacology, their potency and their acceptability to patients.

The pharmacologist's perspective

The NNRTIs are a disparate group of compounds that act by blocking HIV-1 reverse transcriptase by direct binding. They require neither intracellular phosphorylation nor significantly affect other enzyme systems. As the three drugs differ structurally they have different pharmacokinetic properties. Both efavirenz and nevirapine have long half-lives, such that efavirenz is given once daily and nevirapine twice daily (once daily for the first 2 weeks). Delavirdine requires a three times daily dosing regimen. All are well absorbed after administration without food restrictions, and efavirenz and nevirapine in particular have mean trough plasma concentrations well in excess of the IC_{90} of wild-type virus strains. Given the importance of maintaining viral suppression this gives a degree of 'forgiveness' if a dose is taken late. However, if therapy in combination with short-acting compounds is stopped abruptly, effectively, monotherapy may result, with the potential for development of resistant strains of virus.

Ideally, antiretroviral drugs should achieve inhibitory levels in other body compartments (e.g. the central nervous system and genital tract). Fortunately nevirapine and efavirenz have both been shown to penetrate CSF, with minimum concentrations above at least the IC_{50} of wild-type virus.[1–3] Nevirapine is also known to penetrate into semen.[4] There are few data on the penetration of delavirdine into CSF.[5] Nevirapine crosses the placenta and is present in breast milk.[6–7] Initial reports suggest a role for single-dose nevirapine in the prevention of vertical transmission in breast-feeding women in less developed countries.[8] There are no published data on penetration of delavirdine into human breast milk and efavirenz has shown marked teratogenic effects in cynomolgus monkeys and should not be used during pregnancy or lactation.

The physician's perspective

The initial combination of drugs for a treatment-naïve patient must be potent enough to reduce viral load to undetectable levels and increase CD4 cell counts. Evidence of a reduction in clinical progression is also desirable but, in practice, the low number of events in patients under treatment makes obtaining these data largely impractical. Other important considerations when choosing a regimen will be side-effects, simplicity of dosage, the ease with which drug resistance develops and potential interactions with other compounds used by the patient. Until recently, a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) with a protease inhibitor (PI) was the accepted first-line treatment for HIV infection. Evidence is now accumulating that antiviral regimens containing an NNRTI and two NRTIs can also produce a sustained reduction in viral load and increased CD4 cell counts in a high proportion of patients. The DMP 266-006 trial compared zidovudine and lamivudine, in combination with either efavirenz or indinavir, in a cohort of 1266 asymptomatic or mildly symptomatic patients. At 48 weeks the efavirenz arm gave significantly better results than the indinavir-containing arm. First analysis to 72 weeks of the full cohort demonstrates statistically significant superiority for the NNRTI arm when analysed for time to treatment failure and durability of response.[9] Importantly this treatment regimen retained its potency in patients with pre-treatment viral loads of over 100 000 RNA copies/mL. This was, however,

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an open-label study and the superiority of the efavirenz-containing arm may, in part, be due to better adherence to the simpler regimen. Other studies are in progress with efavirenz in combination with NRTIs and the initial data look encouraging.

The INCAS study[10] was the first to suggest that nevirapine, zidovudine and didanosine was a potent combination and long term follow-up (over 3 years) has demonstrated continued viral suppression.[11] Early data from the Atlantic study, which has three arms, (two NRTIs and nevirapine, three NRTIs, and two NRTIs plus a PI), have been presented.[12] Patients were all HIV-treatment naïve with a high median baseline CD4 cell count. There were no significant differences between the arms at 48 weeks although the triple NRTI arm patients with high viral loads at entry were less likely to attain suppression to <50 RNA copies/mL.

Delavirdine has been studied in combination with zidovudine and lamivudine in treatment-naïve patients and was superior to the control arms of dual therapy, although this is clearly not the standard of care at present.[13,14] Unlike efavirenz and nevirapine, delavirdine is a P-450 inhibitor and, thus, it improves the pharmacokinetics of indinavir. Studies of delavirdine and indinavir in various combinations are still under way and, although preliminary results look promising, more data are awaited.[15]

Drug interactions are a major consideration in the treatment of HIV infection. Individual drugs may alter the pharmacokinetics of the other components of the regimen or interact with prescribed, over-the-counter, or recreational drugs consumed by the patient. This may result in subtherapeutic concentrations of antivirals and the potential for resistance development, or a reduced efficacy of concomitant drugs. Alternatively, enhanced drug-related toxicities may occur. Nevirapine is an inducer of hepatic cytochrome P-450 whereas delavirdine is an inhibitor of the system. Efavirenz seems to both induce and inhibit. There is, therefore, the potential for interaction with any drug (including PIs, oral contraceptives, cisapride and terfenidine) metabolized by this route. Detailed information on drug interactions involving antiretrovirals can be found at the Liverpool University Department of Pharmacology website[16] and should be consulted before prescribing.

The commonest side-effect of NNRTIs is rash, which occurs in the first few weeks and usually resolves. Normally, treatment can be continued with the use of antihistamines, and possibly steroids. The incidence of rash with nevirapine and delavirdine is nearly 20% but is lower with efavirenz. The major side-effects reported with efavirenz are neuropsychiatric; 52% of patients report insomnia, vivid dreams and, rarely, hallucinations and 'psychosis-like' reactions. These symptoms occur during the first days of therapy, shortly after dosing, and last a few hours only. They usually resolve within 2 to 4 weeks. Most patients tolerate them if given sufficient information and support. Splitting, escalation or reduction of doses has no effect on CNS side-effects. Abnormal liver-function tests have also been reported for these drugs, particularly with nevirapine. Early clinical experience suggests that a patient experiencing side-effects with either efavirenz or nevirapine can sometimes be switched to the other drug without recurrence of the same problem. To date no long-term or unexpected side-effects have arisen from these drugs although further follow-up is required, particularly with regard to lipodystrophy.

Regarding NNRTIs, the area of greatest concern for physicians is the low genetic barrier to drug resistance. The acquisition of only a single mutation, leading to the K103N substitution in reverse transcriptase, appears to confer cross-class resistance to all three available agents. As this mutation emerges quickly with inadequate viral suppression, use of these drugs as part of a potent regimen is essential. As indicated above, this may be relevant when stopping therapy and if suboptimal penetration into 'sanctuary sites' occurs.

How then can physicians use NNRTIs to their best advantage? Clearly there is a role for the use of dual NRTIs with either efavirenz, nevirapine or, possibly, delavirdine (although better data are required) in the initial therapy for naïve or minimally nucleoside-exposed patients. This option has become particularly attractive as a PI-sparing regimen. The desire to avoid the use of PIs, especially in early disease, has been driven by the emergence of the lipodystrophy and metabolic disturbances which seem to be associated (although not exclusively) with PI-containing regimens. For patients with established lipodystrophy, replacing a PI with an NNRTI sometimes results in improvements in metabolic abnormalities and body habitus without loss of viral control.[17–19] The place of NNRTIs in second-line and salvage therapy is being extensively investigated. Clinical experience suggests that once one NNRTI has failed, success is unlikely with another of the presently available compounds, this is supported by the common finding of the K103N substitution in the HIV of failing patients.[20]

The patient's perspective

The ideal treatment regimen from the patient's point of view is simple and effective, with no food restrictions and easily incorporated into their daily routine. In addition, side-effects and interactions with recreational substances such as alcohol should be minimal. Most importantly, treatment should not produce characteristic changes in appearance that clearly identify the patient as HIV-positive. The facial and limb fat wasting with central adiposity associated with PIs has severely affected the social functioning and self-confidence of many patients who are otherwise well in spite of advanced disease. Patients report that adherence, which is so important for good virological control,[21] is easy with NNRTIs. The simplest licensed regimen (zidovudine, lamivudine and nevirapine) requires only two pills twice daily and the combination of efavirenz, zidovudine and

lamivudine one pill in the morning and four pills at night with no food restrictions. In contrast PI-containing combinations are much more complex. Some interactions with recreational drugs do occur, e.g. nevirapine increases methadone requirements,[22] and many more data are required.

The future

Nevirapine and efavirenz have quickly found a place in the management of HIV infections. Doctors find them easy to prescribe and patients find them easy to take. National guidelines are being changed to include their use. One possible concern is the overlapping side-effect profile (rash) with other new HIV drugs. This applies to amprenavir and to abacavir which has a potentially serious hypersensitivity reaction, of which rash is a component. New NNRTIs are in development, which appear active against K103N-containing mutants; in the meantime, the existing compounds are a welcome addition to our armamentarium.

One final note of caution—HIV physicians have learned over the last 10 years that treatment strategies formulated today will almost certainly have been proved incorrect by tomorrow!

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