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title

Darunavir, promising option in therapy multi-experience HIV-infected patients

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summary

Darunavir was approved in 2006 by the US FDA for patients harboring HIV-1 resistant to more then one protease inhibitor. It belongs to the second generation of protease inhibitors with potent activity against viral strains to all currently available protease inhibitors. Darunavir should always be co-administrated with low-dose ritonavir and with food. Current guidelines suggest that the goal of therapy in all HIV infected patients, including heavily experienced, is full viral suppression. Treatment options for patients infected with multidrug resistant HIV are limited. The results of clinical trials demonstrated that darunavir is effective and well tolerated. The POWER-1, 2, and 3 trials that used DRV/r showed that the compound had a potent effect in heavily pretreated patients. Ongoing studies in treatment-naïve and treatment-experienced will provide more data on the safety and efficacy of darunavir.

key words

protease inhibitor, darunavir, HIV resistance

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Protease inhibitors (PIs) selectively inhibit the cleavage of HIV encoded Gag-Pol protein, thereby preventing the formation of mature virus. The introduction PI-based HAART regimens led to enhanced HIV management and extended patient's life. Since 1996 PI constitute an important component of highly active antiretroviral therapy (HAART). The therapy with the first generation PIs, however, was associated with severe side effects and drug toxicities, higher therapeutic doses due to 'peptide-like' character and the emergence of drug resistance. Current guidelines suggest that the goal of therapy in heavily experienced patients is full viral suppression through the initiation of combination antiretroviral therapy (cART) with multiple active drugs [11, 13] Treatment options for patients infected with multidrug resistant HIV are limited. It has been reported that treatment failure has ultimately occurred in at least half of patients, who initially achieved viral suppression with HAART to undetectable levels. Persistent viral replication has been reported under HAART in 10-40% patients as result of transmission of drug-resistant HIV-1 strains [1, 4, 12, 18, 20,23, 32]. There are at least 26 specific to PI amino acid mutations described by the International AIDS Society (IAS) from the 2006 summary. There are about 15 primary or major mutation that are significant enough to change drug activity, the other so-called minor or secondary mutations that alone are less likely to affect drug activity. Single secondary mutations do not equate with drug resistance, but a combination of mutations result in high level drug resistance. Mutations can also confer resistance to one drug, but enhance the activity of other drug or even drugs [16].

Darunavir (DRV) is one of the second generation PIs and has demonstrated activity in vitro against wild-type HIV-1 and multidrug-resistant strains. It has potent activity against viral isolates that are resistant to all currently available protease inhibitors [8-9]. Darunavir has been a subject of a clinical programme that begun in 2001 [3]. Darunavir was approved in June 2006 by the US Food and Drug Administration (FDA) under its accelerated approval process within six month for the treatment of antiretroviral therapy multiexperienced patients and in those harboring viruses resistant to more then one PI [30]. The recommendation was based on the results of 2 pivotal trials phase 2b studies (POWER-1, and POWER-2) supported by two non randomized trialsTMC114-215 and 208 submitted by Tibotec [17, 21, 24]. Darunavir is administered in combination with low dose (100mg) ritonavir (DRV/r) [30]. DRV/r is now being studied in less treatment-experienced (TITAN) and treatment-naive patients (ARTEMIS).

Darunavir is well absorbed following oral administration. The bioavailability and the effect of different meal types on pharmacokinetics of DRV was evaluated in HIV-negative healthy volunteers. Co-administration with ritonavir in dose 100mg b.i.d. increased systematic exposure to DRV by ~14-fold compared with DRV alone [28, 30]. Administration of drugs in a fasting condition resulted in a decrease in darunavir Cmax and AUClast of approximately 30% compared with administration after a standard meal. Thus DRV should always be coadministrated with ritonavir, and taken with food. [15, 29-30].

Darunavir was studied primarily in two controlled phase IIb clinical trials POWER-1 (TMC114-213) and POWER-2 (TMC114-202) enrolling 605 heavily pretreated multiple PI resistant patients. In the combined analysis of those studies it was shown that patients had received a median of 5 PIs before randomization, only 36% of them in DVR/r group and 39% in comparator group were infected with HIV sensitive to more then 1 PI. A median of 3-8 total protease inhibitor mutations with at least 3 of those being primary mutations were present on baseline. Patients enrolled to POWER-1 and 2 trials were randomized to receive one of 4 doses of DRV/rtv or control PI selected by investigator plus optimized background regimen. Although all doses of DRV/r demonstrated improved efficacy with compared PIs, the best benefit was found in group treated with the 600/100 mg twice-daily dose. The proportion of patients who achieved and maintained HIV RNA below 50 copies/μl was 36% for DRV/r 600/100 b.i.d. vs 7% in the control arm of POWER-2 and 57% vs 16% in POWER-1 [17, 24, 26]. In the combined 48-week analysis a viral load was reduced by a mean value of 1.63 $\log_{10}$ copies/mL in the DRV/r group and 0,36 $\log_{10}$ copies/mL in the comparator group. The best virologic response was connected with the presence of ≤ 1 primary protease inhibitor mutations but even in presence 2 or 3 mutations the response was better then in control group. The studies had shown no dose related toxicities and finally 600/100-mg twice-daily dose was selected for treatment experience patients [25, 27]. The results of 96 week analysis support the findings of POWER-1 and 2 at both 24 and 48 week analysis. The proportion of patients who achieved HIV-RNA < 50 copies/mL at week 96 was 39% of DRV/r patients compared with 9% in the control group. The difference was statistically significant. Enfuvirtide (ENF) use was a strong predictor of antiretroviral response in many previous salvage studies. In POWER-1, and 2 studies the rate of patients using ENF in the optimized background therapy was similar between DRV/r and control groups. ENF was used for the first time by 32% in the DRV/r group and 30% in the comparator groups ad was reused by 14% and 12% respectively. In the analysis the co-administration of ENF in patients naïve to that drug led to strongest replication suppression. The rate of patients who achieved viral load below 50 copies /mL was 58% among patients who started ENF vs 11% among patients without ENF in treatment regimen [31].

POWER-3 study was an analysis of two (TMC114-C215/C208) open label, nonrandomized trials. TMC114-C215 was conducted in 13 sites from different countries all over the world and TMC 114-C208 conducted in the one site in Australia. It was conducted to assess the long-term efficacy and safety of DRV/r in treatment-experienced patients. The POWER-3 trial enrolled 336 adult patients starting treatment with DRV/r 600/100mg b.i.d.; among them 303 were newly recruited patients and 33 patients who had previously participated in the control arm of the POWER-1 or 2 trials. The primary efficacy point was the proportion of patients with ≥ 1 $\log_{10}$ reduction of viral load by week 24. Over a period of six month, reduction of HIV-RNA ≥ 1 $\log_{10}$ was observed in 65% of patients. The reduction of viral load to < 400 copies/mL and < 50 copies/mL was noted in 57% and 40% of patients, respectively [24]. In the 96 week analysis the mean change in HIV RNA from baseline was 1.43 $\log_{10}$ copies/mL, 52% of patients receiving DRV/r had a viral load reduction ≥ 1 $\log_{10}$ and 42% of them had reached HIV-RNA < 50 copies/mL. In the analysis of three POWER studies the presence of 3 or more of mutations as V11I, V32L, L33F, I47V, 150V,154L or M , G73S, L76V, I84V or L 89V was associated with decrease virologic response. When the baseline HIV genotype had 0-2; 3 and more then 4 of those mutations, the proportion of patients receiving DRV/r in the currently recommended dose achieving undetectable viral load, was 50%, 22% and 10% respectively. Co-administration of ENF increased the chance of reaching undetectable viral load [2, 31].

TITAN (Treatment-Experienced Patients Naïve to Lopinavir/Ritonavir) study was conducted to assess non-inferi-

ority of DRV/r compared with LPV/r 400/100 mg b.i.d. in terms of virological response, with both agents given in addition to optimized background regimen. ENF was not allowed in the background regimen. The population was selected to include patients with less advanced disease than those enrolled in the POWER studies. TITAN was conducted in 159 centers in 26 countries. The investigators from the study reported additional information on resistance patterns among patients who experienced virologic failure. In TITAN study DRV/r was non inferior to LPV/r in term of viral response in treatment experienced patients. Of 595 patients enrolled to the study, 82% were harboring HIV susceptible to ≥ 4 were PI and 31% were PI naïve. In the 48 week intent-to-treat (ITT) analysis 77% in DRV/r arm and 68% in LPV/r arm achieved HIV-RNA below 400 copies/mL. Overall 25% of randomized subjects discontinued treatment, among them 7% due to an adverse event and 6% due to virological failure. A higher proportion of the patients who failed DRV/r retained susceptibility to other PIs compared with those who failed LPV/r. Among virological failures 21% patients treated with DRV/r and 36% in LPV/r arm developed primary protease inhibitor mutations. In patients with virologic failure, DRV/r was associated with lower rates of development of additional resistance mutations and loss of phenotypic susceptibility to antiretrovirals than lopinavir/ritonavir.

Of those patients who were at structured treatment interruption at screening, 73,4% in the DRV/r arm and 67.6% in the control arm achieved HIV-RNA < 400copies/mL at week 48. This observations might suggest superior potency of DRV/r, although participants had to be LPV/r naïve, a small proportion had reduced susceptibility to LPV due to previous exposure to other PIs. The findings from TITAN study confirmed the observations from POWER studies that DRV/r has a high barrier to resistance. DRV/r was associated with a low rate of developing mutations conferring resistance to other antiretroviral drugs. The incidence of withdrawal due to an adverse event was low and was similar between treatment arms Safety profile was similar in both arms with occurrence grade 3 and 4 adverse event in 27% in DRV/r arm and in 30% in LPV/r [14, 19].

The ARTEMIS (TMC114-C211) study was designed to compare the efficacy, safety, tolerability resistance characteristic and pharmacokinetics of DRV/r at the dose 800/100mg once daily with LPV/r in the daily dose 800/100mg in treatment naïve patients infected with HIV-1. 843 patients were screened for eligibility and 689 randomized. A total of 689 patients were enrolled to the study and 343 were randomized to the DRV/r arm. Median baseline CD4 count was 137 cells/μL for DRV/r and 141 cells/μL for LPV/r. In the 48-week analysis 84% patients treated with DRV/r and 78% in LPV/r arm achieved undetectable viral load. The increase in CD4 count was very similar for both treatment arms. Rate of discontinuation was less frequent with DRV/r versus LPV/r (12% versus 16%). The main reason for this difference is driven by a difference in discontinuations due to virological failure [7, 10, 17, 22].

Darunavir on the dose 800/100md given once daily was effective and well tolerated it has been shown a favorable safety profile and was associated with less of a risk of common gastrointestinal toxicities than LPV/r [10]. The results were presented in the EACS 2007 and ICAAC 2007.

Antiretroviral therapy has been associated with long term toxicities. In a number of studies the safety of darunavir boosted with low dose of ritonavir (DRV/r) in HIV-1 infected patients was evaluated.

The evaluation of safety data in the 96 week combined analysis the three POWER studies 1-3 patient population revealed no unexpected safety findings associated with DRV/r treatment. The majority of adverse events (AEs) were grade 1 or 2 as per ACTG (AIDS Clinical Trial Group Classification). Treatment with DRV/r 600/100mg b.i.d. was generally well tolerated by treatment-experienced patients over 96 weeks with no new safety concerns identified. The most frequently reported treatment-emergent AEs (regardless of severity and causality) were diarrhea, nausea, nasopharyngitis and headache, each of which occurred in no more than 25% of patients [6].

The serious AEs (SAEs) were reported in 125 (27%) patients; the most commonly observed were pneumonia (2%), acute renal failure (1%), vomiting (1%) and pyrexia (1%). All other SAEs occurred in < 1% of patients.

Twenty patients (4%) died during the treatment period (n = 2 in POWER 1, n = 4 in POWER 2 and n = 14 in POWER 3). All deaths were considered to be unrelated or doubtfully related to study medication. The overall mortality rate was 2.5 per 100 patient-years exposure and did not increase over time. The majority of deaths (15 [75%]) occurred in patients with baseline CD4 cell counts of < 50 cells/mm3, a factor known to be associated with a higher risk of mortality [6, 26].

The most common AEs of grade 3 or 4 of which 11% were considered as at least related to DRV/r were: diarrhea, vomiting, nausea, and headache. The incidence of treatment required diarrhea seen in evaluated population was low and similar to what was described in earlier safety analysis. All of the most common AEs were reported in no more then 3% patients.

Favorable lipid results were observed in all POWER studies In the cross trials analysis there were no significant differences among the groups. Abnormalities from plasma parameters in most patients were mild to moderate. A decrease of mean triglycerides level were observed for patients who switched from LPV/rtv at baseline to DRV/r or other PI [2, 21, 31]

Efficacy and safety of DRV/r in patients with HCV or/and HBV co-infections

The efficacy and safety of DRV/r was evaluated in subanalysis of HIV infected heavily experienced patients with HCV or HBV co-infection. In POWER-2 study co-infected patients were excluded. A total of 697 (634 DRV/r vs 63 comparator PI) POWER 1 and 3 patients were assessed for HBV or HCV co-infection status: More common was co-infection with HCV then HBV (7-11% vs 5% of subjects).

A 24-week analysis has shown that DRV/ r was generally well tolerated and the efficacy was similar in hepatitis virus co-infected and non-coinfected patients. The proportion of patients with active co-infection and without co-infection initiating treatment at the dose of DRV/r 600/100mg b.i.d. and reaching < 50 copies/mL of plasma HIV-1 RNA at 24 weeks was 46% (n = 46) and 42% (n = 261), respectively. Most liver-related adverse events seen in co-infected patients were due to asymptomatic elevation of liver cell parameters: ALT (alanine aminotransferase), AST (aspartate aminotransferase), bilirubin and gamma glutamylotransferase (GGT). The majority of this laboratory abnormalities were grade 1 or 2. The overall incidence of liver related AEs was similar in patients with active HCV

or HBV co-infection compared with patients without co-infection [25].

The results from the TITAN study revealed similar observations and support those of the POWER studies.

In the TITAN study the proportion of co-infected patients was 15% (in DRV/r arm – 18%, LPV/r arm 13%). The overall incidence of liver-related AEs was higher in patients with HBV and/or HCV co-infection than in those without co-infection, but similar in both treatment groups. DRV/r was generally well tolerated in HBV and/or HCV co-infected LPV/r-naïve patients. In patients with co-infection, grade 3 or 4 increases in ALT and AST were less frequent in the DRV/r group (12% and 10%, respectively) than in LPV/r-treated group (25% and 22%, respectively [5].

The tolerability of once-daily DRV/r in patients co-infected with hepatitis B or C virus (HBV/HCV) was evaluated in ARTEMIS study. The percentage of patients with H**CV** or HBV co-infection in this study was 13% (n = 91). The number of patients with HBV and /or HCV was similar in the both groups (43 in DRV/r arm and 48 in LPV/r arm). In non-co-infected patients, the incidence of grade 3/4 increases in ALT or AST was low and comparable for both treatment groups (ALT: ≤ 1%, AST: ≤ 2).The overall incidence of liver-related AEs was higher in patients with HBV and/or HCV co-infection than in those without co-infection. Grade 4 increases in ALT or AST were not observed in DRV/r co-infected patients, but incidences of 13% and 8%, respectively, were reported in LPV/r co-infected patients, grade 3 increases in ALT or AST were comparable in both treatment groups (ALT: 14% for DRV/r and 15% for LPV/r; AST: 9% for DRV/r and 8% for LPV/r). In both treatment groups, the incidence of hyperbilirubinaemia was higher in co-infected than in not co-infected patients. The overall incidence of hyperbilirubinaemia (all grades) in non co-infected patients was more frequent in the LPV/r group than in the DRV/r group [22].

Of the 558 patients included in the week 48 efficacy analysis 32 of 43 (74%) patients with active HBV and/or HCV co-infection and 255 of 300 (85%) patients without co-infection achieved HIV-1 RNA reduction < 50 copies/mL in the DRV/r arm. The rate of the virologic response in the LPV/r arm was 67% (32 of 48 patients) and 80% (239 of 298 patients) respectively [22].

Once-daily DRV/r was generally well tolerated in HBV and/or HCV co-infected treatment-naïve patients with clinically stable hepatitis disease. These results support those with DRV/r in the POWER studies (treatment-experienced patients) and TITAN study (LPV-naïve, treatment-experienced patients), and usual clinical monitoring of patients with chronic HBV and/or HCV receiving once-daily DRV/r 800/100mg is considered adequate. No safety issues have been identified for HBV/HCV co-infected patients. Ongoing Phase III studies in treatment-naïve and treatment-experienced patients will provide more data on the safety of DRV/r.

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title

Enfuvirtide – new clinical data of the management of HIV-infected patients

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summary

Enfuvirtide (FUZEON, T-20) is an antiretroviral drug which received marketing authorisation for the treatment of patients infected with HIV-1. The introduction of enfuvirtide represents an important advance in the treatment of therapy-experienced patients with HIV-1 infection. Studies of newer antiretrovirals provide further evidence of the efficacy of enfuvirtide in treatment-experienced patients. It is a useful addition to anti-HIV therapeutic strategies also to the novel class drugs such integrase inhibitors or CCR5 co-receptor inhibitors.

key words

enfuvirtide, fusion inhibitors, HIV infection, antiretroviral treatment

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Enfuvirtide (FUZEON, T-20) is an antiretroviral drug which on 13 March 2003 received marketing authorisation from the FDA for the treatment of patients infected with HIV-1. The indications for treatment with enfuvirtide include patients previously treated with other antiretroviral drugs who have not achieved therapeutic efficacy, i.e. HIV viraemia level < 50 copies/mL (1,28). The indications for the European Union Member States also include additionally documented (based on genotypic or phenotypic test) resistance to at least one of the products from the NRTIs, NNRTIs and PIs group, or persistent intolerance of the previously used therapeutic regimens (21, 28).

The introduction of enfuvirtide represents an important advance in the treatment of therapy-experienced patients with HIV-1 infection.

Mechanism of action

Enfuvirtide is a synthetic peptide corresponding to a sequence of 36 bases forming a group of seven repetitive elements of 2 sequences of HIV-1 gp41 glycoprotein. Enfuvirtide competitively binds to the first heptad repeat (HR1) region of gp41, preventing the conformational transformation of a six-helix bundle, and as a result, it inhibits the process of HIV entry into the cell (1, 3, 17). The extracellular mode of action and unique antiviral target results in several benefits, including the absence of cross-resistance with other antiretroviral agents, as well as decreased risk of systemic toxicity and drug interactions. Treatment response to enfuvirtide is not affected by viral tropism for CCR5 and CXCR4 coreceptors (1, 3, 18).

In vitro antiviral activity

In vitro studies on the efficacy of inhibition of HIV infection transmission from the infected cells to cells free from HIV infection in the isolates have been performed using various drug concentrations (3, 10, 13).

The inhibition of infection transmission in 90% of cell isolates was found with the concentration range of 2 to 80 ng/mL (17). However, IC_{50} (the concentration required to inhibit infection in 50% cell isolates) fluctuated from 18 to 1260 ng/mL. In other experimental works, the following IC_{50} values have been reported: in the range of 29 to 982 ng/mL, 2.5 ng/mL, 12 and 14 ng/mL, respectively. Enfuvirtide cytotoxicity in cell cultures was only seen when the drug concentration was higher by 10^4 to 10^5 than the concentration required to inhibit infection of non-infected cells (13, 17). It means that the difference between the therapeutic concentration and the toxic concentration of the drug is very large. Some investigators report that HIV sensitivity to the drug is independent of the co-receptor type used. Some investigators have found a reverse relationship – a significantly higher drug concentration is required to inhibit the multiplication of HIV having the CCR5 co-receptor (R5, with tropism to macrophages) than to inhibit the multiplication of HIV having the CXCR4 co-receptor (X4, with tropism to T cells) (10, 17, 18). However, two phase III clinical trials have not shown significant differences in the virological responses between patients infected primarily with the R5 type and those with a primary predominance of the X4 type (13, 14). The R5 HIV strain usually predominates in the first phase of infection and accompanies HIV transmission, whereas the X4 strain is usually associated with infection development and accompanies its later stage.

Pharmacodynamic studies in cell cultures have shown synergistic effects of drugs added to the study drug, used in combined treatment of HIV infection: zidovudine, lamivudine, nelfinavir and indinavir. Moreover, a synergistic or additive effect was shown following the addition of efavirenz (6,9, 22).

Resistance

In vitro studies have shown that when passaging a culture of HIV-infected cells in the presence of increasing drug concentrations, a HIV mutation occurs in the highly conservative sequence (glycine-isoleucine-valine [GIV]) consisting in an exchange of amino acids at the positions 36 and 38 in the HR1 region of the gp41 glycoprotein. HIV strains with two substitutions (glycine to serine at position 36 [V38M], GIV → SIM) remain resistant to enfuvirtide at concentrations exceeding 10 μg/mL. The strains with a single substitution (G36S) present medium sensitivity to enfuvirtide, requiring concentrations of 0.5 to 1 μg/mL for a 10-fold reduction in the HIV level. Enfuvirtide concentration of 0.1 μg/mL is sufficient for a reduction in a "wild" HIV strain (5, 11, 12, 19).

In vivo HIV strains with reduced sensitivity to enfuvirtide have been isolated from patients receiving this drug in clinical trials. These strains show lower virulence and shorter survival time than the "wild" strain (mean 2.7 to 8.5 months since stopping enfuvirtide administration). Resistance to antiretroviral drugs from the other groups has no affect on cross-resistance to enfuvirtide (12, 13, 19).

Primary resistance to enfuvirtide in untreated patients occurs occasionally. The enfuvirtide-resistant strains have mainly been isolated in patients previously treated with this drug in combination with the other antiretroviral products. The studies have shown that a single mutation in gp41 at positions 36, 38, 40 and 43 correlates with a reduced sensitivity to enfuvirtide by 3 to 450 times. Sensitivity to enfuvirtide of isolates having two mutations at positions 36, 40, 42, 43, 44 and 45 is 30 to 632 times lower (5, 10, 11, 12, 19).

Enfuvirtide remains the active drug in the cultures of HIV-infected cells, despite observed resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs).

Immunosuppressive effect

In vitro, enfuvirtide inhibits the production of IL-12 produced by human monocytes in response to T-cell-dependent and T-cell-independent stimulation following HIV infection. The concentration of enfuvirtide necessary for this *in vitro* process is lower or equal to the concentration required for the suppression of HIV multiplication in an *in vitro* culture. IL-12 production suppression is selective. No suppression of the production of other cytokines such as TNF-α, TGF-β or IL-10 has been shown (3, 10). The clinical effect of this process has not been fully explained.

Pharmacokinetic properties

In studies, after 14 days of using enfuvirtide concomitantly with other antiretroviral products, it was shown that the drug reached C_{max} equal to 5.0 μg/mL; the time necessary to achieve the maximum serum concentration (t_{max}) was 4.1 hours; AUC_{12} (area under the concentration curve 0-12 hours) was 48.7 μg/h/mL, and the minimum concentration was 3.3 μg/mL (4, 9, 26).

In patients who received a single dose of the drug (90 mg intravenously) it was shown that the mean bioavailability of the product was 84.3% (2, 24).

No differences in bioavailability have been shown depending on the drug administration site: in the thigh, arm or abdomen (9, 26). It means that the patients can freely change the drug administration site without any effect on its pharmacokinetic properties.

Clinical studies involving adults (over 18 years of age) and children (aged 12-16 years) have shown that the pharmacokinetic properties of enfuvirtide do not depend on the degree of sexual maturity (according to the Tanner scale), age, weight or body surface (24, 26).

In the concentration range of 2 to 10 μg/mL, enfuvirtide is in 92% bound to plasma proteins. These are mainly albumins and, to a lesser extent, α-1 globulins (16, 20).

Enfuvirtide has low distribution volume. For a single intravenous dose of 90 mg it is equal to 5.5 L, which means that the drug reaches serum C_{max} relatively rapidly (20).

As enfuvirtide is a peptide, it should be expected that it will be metabolised similarly to the other amino acids. *In vitro* studies on human microsomes have shown that enfuvirtide is not metabolised by cytochrome P450 (CYP) (20).

In vitro studies on human microsomes and hepatocytes have shown that enfuvirtide undergoes NADPH-independent hydrolysis to deaminated metabolites (without nitrogen residues). The concentration of these metabolites in the serum constitutes 15% of the parent drug concentration (9).

Following the administration of a single dose of enfuvirtide (90 mg), the mean half-life and elimination time ($t_{1/2}$) is 3.8 hours (9).

No changes in the dosage are recommended based on the body weight or gender; however, the studies on serum concentration of the drug have shown that enfuvirtide clearance is 20% higher in men than in women, and that it decreases along with the body weight reduction similarly in both genders. An increase in the body weight causes an increase in enfuvirtide clearance in men but not in women. However, no relationship has been found between the drug clearance and race (black race, Caucasian race, Asian race) (26).

Potential drug interactions

As enfuvirtide is not metabolised using cytochrome P450 (CYP), possible drug interactions are unlikely; therefore, the drug is relatively safe in combination with products metabolised by CYP1A2, CYP2E1, CYP3A4, CYP2D6 and CYP2C19. Most antiretroviral drugs from other groups are metabolised by these isoenzymes (6, 26).

No adverse drug interactions have been observed when enfuvirtide was used in combination with ritonavir (CYP3A4 isoenzyme inhibitor), rifampicine (inducer of many CYP enzymes) and saquinavir combined with ritonavir (22).

Therapeutic efficacy

The therapeutic efficacy of the dose administered subcutaneously twice daily was evaluated in 43 clinical trials in adults and children. 23 trials have already been completed and 20 are ongoing. Some of the completed trials are presented below.

TORO 1 and TORO 2 trials

The efficacy of enfuvirtide in combination with the other antiretroviral drugs was evaluated in two phase III trials (**T**-20 vs. **O**ptimised **R**egimen **O**nly – TORO), i.e. TORO 1 and TORO 2. These trials lasted 48 weeks, both were randomised, open-label, multicentre. Over 1000 patients with advanced HIV infection were included in the two trials. The inclusion criterion for the TORO 1 study was treatment with all three classes of antiretroviral drugs (NRTIs, NNRTIs, PIs) for at least 6 months, and for the TORO 2 study – for at least 3 months, and documented drug resistance for at least one class of drugs. Patients included in the study were randomised to two groups: the first group remained on drugs from the specified groups, where based on the results of drug-resistance tests the optimum combination was selected, and the other group received enfuvirtide 90 mg BID in addition to this selected regimen (7, 8).

Patients with advanced HIV infection were included in these two trials: the mean baseline HIV viraemia levels were $5\log_{10}$ HIV-RNA copies/mL, the mean baseline number of CD4 cells was 76 cells/mL in the TORO 1 study and 98 cells/mL in the TORO 2 study, and the mean treatment time was 7 years using 12 antiretroviral drugs in one patient, on average (27).

The efficacy analysis in week 48 has shown a reduction in HIV viraemia levels by 1.48 $\log_{10}$ in the group of patients receiving enfuvirtide compared to HIV viraemia level reduction by 0.63 $\log_{10}$ in the group of patients without added enfuvirtide (a statistically significant difference). Moreover, a significantly higher percentage of patients receiving enfuvirtide achieved a reduction in the viraemia levels < 400 copies/mL (34.0%) compared to patients who have not received enfuvirtide (13.0%). For the viraemia level of < 50 copies/mL, these data were as follows: 23.0% in the enfuvirtide group vs. 8.0% in the group without the study drug (statistically significant differences) (7, 8, 27).

The treatment efficacy analysis in week 96 has shown that HIV-RNA < 50 copies/mL was achieved by 17% patients and HIV-RNA < 400 copies/mL by 27% of patients in group treated with enfivirtide. There are no comparative data between the 2 arms because all the patients treated in the optimized background arm (OB) were switched to arm with enfuvirtide at week 48 (7, 8, 27).

The a logistic regression analysis of the TORO 48-week data identified that some patients are more likely to benefit from enfuvirtide treatment. To independent positive predictive factors for virological response to enfuvirtide belong:

- Baseline CD4 cell count of at least 100 cells/μL;
- Baseline plasma HIV-1 RNA level under 5 $\log_{10}$ copies/mL;
- A history of 10 or fewer prior antiretrovirals; and,
- Two or more active antiretrovirals in optimized background regimen.

DUET-1 and DUET-2 trials

It was a phase III, randomised, multicentre, double-blind study of etravirine combined with darunavir boosted with ritonavir, in combination with a selected NRTI, with

(or without) enfuvirtide, compared to placebo plus darunavir boosted with ritonavir in combination with a selected NRTI with (or without) enfuvirtide in patients with multi-drug resistance and advanced HIV infection. The first group (with etravirine) consisted of 599 patients, the other group (with placebo) – 604 patients. The mean baseline HIV viraemia level was 4.8 $\log_{10}$ copies/mL (in both groups), the mean baseline CD4 number was 100 cells/mL in the first group and 108 cells/mL in the second group. Over 2/3 patients (67% vs. 62%) used 10 to 15 antiretroviral drugs until the time of inclusion in the study (4, 25).

The study DUET-1 and DUET-2 evaluated the efficacy of etravirine versus placebo; however, the results of the analysis in week 48 are interesting; it was a comparison of using versus non-using enfuvirtide in the so-called Optimised Background Therapy (OBT) (4, 25).

Among the patients of the first group (who received etravirine), 52% used enfuvirtide before, and 27% used it for the first time. Exactly the same percentage of patients using enfuvirtide was found in the second group (receiving placebo).

The treatment efficacy analysis in week 48 has shown that HIV-RNA < 50 copies/mL was achieved by 75% patients who received enfuvirtide for the first time, compared to 57% patients who have never used enfuvirtide or used it another time (a statistically significant difference). The above results are for the group of patients receiving etravirine. In the group of patients receiving placebo these values were: 61% and 33%, respectively (a statistically significant difference). As shown, the use of enfuvirtide for the first time as the drug added to a regimen containing new antiretroviral drugs significantly improves the therapeutic efficacy (4, 25).

RESIST 1 and RESIST 2 trials

Both these studies evaluated the efficacy of tipranavir boosted with ritonavir among patients with multi-drug resistance, mainly in the class of protease inhibitors. These were phase III multicentre, randomised, open-label, trials. A significant advantage of the above studies was that they lasted 96 weeks (20, 23).

The treatment efficacy evaluation was analysed in week 48 and 96. The use of tipranavir boosted with ritonavir was compared with the use of another selected protease inhibitor. In both groups (with the study drug – group I and with another protease inhibitor – group II), the optimised background treatment (OBT) included enfuvirtide. As many as 76% of patients in group I and 74% patients in group II had used enfuvirtide before (20, 23).

These two studies involved 1483 patients: 746 to the group of tipranavir boosted with ritonavir and 737 to the group with another protease inhibitor. The immune and clinical characteristics of the enrolled patients show that they were in an advanced stage of HIV infection. The percentage of patients with HIV viraemia > 100,000 copies/mL in group I was 37.4%, in group II – 39.2%, disease suggesting AIDS was diagnosed in 56.8% patients in group I and in 55.1% patients in group II, and the mean CD4 number in both groups was 195 cells/mm^3 (20, 23).

Moreover, the inclusion criterion in this study was the occurrence of significant primary mutations concerning protease inhibitors: 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, 90M, and mutations in codons: 33, 82 and 90.

Surprising results were obtained when comparing the therapeutic efficacy of tipranavir combined with enfuvirtide included in the OBT. It became apparent that the two drugs have a synergistic effect and mutually boost their antiretroviral effect. The percentage of patients who achieved viraemia < 50 copies/mL among those who have not received enfuvirtide was 20.4%, and among patients who received enfuvirtide – as many as 34.7% (a statistically significant difference). The improvement in immune parameters among patients receiving enfuvirtide was also spectacular: mean increase in the CD4 number by 122 cells/mm^3. To compare, the mean increase in the CD4 number in the group of patients who have not received enfuvirtide was only 49 cells/mm^3 (a statistically significant difference) (20, 23).

The results obtained in week 48 were comparable to the results from week 96 and they confirmed a high efficacy of enfuvirtide combined with tipranavir boosted with ritonavir (20, 23).

POWER 1 and POWER 2 trials.

Both these studies evaluated the use of a new protease inhibitor, darunavir (TMC114) boosted with ritonavir, intended for patients diagnosed with significant primary mutations in the protease gene. The studies lasted 48 weeks and were multinational, randomised, phase IIB trials, and from week 24 – open-label (the selected darunavir-ritonavir dose was 600/100 mg BID). The total duration of these two studies was 144 weeks (23).

1331 patients were enrolled in the "screening" phase. 674 patients were randomised. The final evaluation in week 48 included 131 patients from group I receiving darunavir/ritonavir at a dose of 600/100 mg BID, and 124 patients from group II, receiving another protease inhibitor (23).

The mean duration of HIV infection in group I was 12.0 years, and in group II – 12.9 years. The mean baseline HIV viraemia levels in group I was 4.6 $\log_{10}$ copies HIV-RNA/mL, and in group II – 4.5 $\log_{10}$ copies/mL. The mean CD4 number was 153 cells/mm^3 and 163 cells/mm^3, respectively (23).

The baseline phenotypic tests to determine the drug resistance to protease inhibitors have shown that 64% patients enrolled in group I and 61% of those enrolled in group II were infected with HIV strains resistant to all available drugs from this group (excluding tipranavir which had not been approved by the FDA at the time the study was started) (23).

The use of enfuvirtide, as a drug included in the OBT in both groups, was similar. For group I: for the first time in 32% patients, again – in 14%. For group II: for the first time in 30% patients, again – in 12% (23).

The efficacy analysis in week 48 showed that 58% patients receiving enfuvirtide (for the first time) with darunavir/ritonavir achieved viraemia levels < 50 copies/mL. To compare, in the group of patients who received darunavir/ritonavir without enfuvirtide this percentage was 44%. In the group of patients receiving another protease inhibitor with enfuvirtide (for the first time), this percentage was 11% vs 10% in a group without enfuvirtide. No differences were shown when the two groups (with darunavir and another protease inhibitor) were compared to patients who received enfuvirtide again (15% and 7%, respectively). These results show the synergistic effect of darunavir/ritonavir with enfuvirtide, occurring particularly when enfuvirtide is used for the first time in the therapeutic regimen (23).

BLQ Study

Based on the results of the POWER 1 and POWER 2 studies concerning the efficacy of the combination of darunavir/ritonavir with enfuvirtide in patients treated with 3 classes of ARV drugs (evaluation of outcomes in week 24 of

the study POWER 1 and 2), the BLQ study was constructed. It was a prospective, multicentre, single-arm, open-label study involving 63 patients (3, 4).

Patients who had not received darunavir or enfuvirtide, with HIV-RNA viraemia > 2000 copies/mL and treated with 3 classes of ARV drugs (NRTIs, NNRTIs, PIs). Patients received darunavir/ritonavir at a dose of 600/100 mg BID plus enfuvirtide at a dose of 90 mg BID plus an active OBT regimen selected by the investigator. The purpose of the study was to determine the factors predicting the therapeutic efficacy of the combination of darunavir/ritonavir with enfuvirtide. To this end, the baseline (BL) phenotypic and genotypic sensitivity of the HIV strains to darunavir (stratification into 3 sensitivity groups), CD4 and CD8 numbers, HIV-1 RNA levels, CD4+ and CD8+ activation markers, as well as HIV tropism (CCR5, CXCR4, dual/mixed) were determined (3, 4).

The results after 24 weeks have shown that 64% patients achieved HIV viraemia < 50 copies/mm^3. The mean reduction in the viraemia levels was -2.39 $\log_{10}$ copies/mL.

The group of 63 patients was divided into 3 groups, depending on the sensitivity to darunavir/ritonavir: high (17 patients), medium (18 patients) and low (17 patients). The mean reduction in HIV viraemia levels was most pronounced in the high-sensitivity group (-2.61 $\log_{10}$) whereas the mean increase in the CD4 number (+84 cells/mm^3) was strongest in the low-sensitivity group (3,4).

The viral tropism was also determined: 21 patients were found to have the "dual/mixed" tropism, 24 – CCR5, and only 1 patient had CXCR4. A better virological response was found in patients with the CCR5 tropism: 67% patients in this group achieved viraemia < 50 copies/mL compared to 57% patients in the group showing mixed/dual tropism (3, 4).

Too small a size of each group was a significant limitation for the analysis of results of the BLQ study.

Motivate 1 and Motivate 2 trials

These studies evaluated the use of a drug from the new group (CCR5 co-receptor inhibitors) – Maraviroc, combined with OBT including at least one active antiretroviral drug. It was a phase III multicentre, randomised, double-blind study (until the week 24 phase), placebo-controlled trial (22).

Patients with HIV-RNA viraemia > 5000 copies/mL infected with HIV-1 with CCR5 tropism, treated or not with antiretrovirals, were included in the study. Among those treated with ARV, patients with known resistance to one or more products from each class of drugs (NRTIs, NNTRIs, PIs) or resistance to at least two or more protease inhibitors were enrolled in the MOTIVATE study. The presence of virus with CXCR4 or "dual/mixed" tropism was the exclusion criterion (22).

The studies had 3 arms: maraviroc OD plus OBT (414 patients), maraviroc BID plus OBT (426 patients) and placebo plus OBT (209 patients) (22).

The mean baseline CD4 lymphocyte number was: in arm 1 – 195 cells/mm^3, in arm 2 – 189 cells/mm^3 and in arm 3 – 187 cells/mm^3. The mean baseline HIV viraemia level in all arms was the same and was equal to 4.8 $\log_{10}$ copies of HIV-1/mL. The evaluation of the therapeutic efficacy, depending on the product used, included in the OBT, was performed in week 24 of the study (22).

The first place was taken by enfuvirtide which was used by 40.6% (arm 1), 42.7% (arm 2) and 43.5% (arm 3) of patients. The other used drugs were: fosamprenavir, lopinavir, atazanavir and tipranavir (22).

In the efficacy analysis both maraviroc arms demonstrated substantially greater efficacy vs placebo arm across all subgroups. Moreover, higher proportion of patients achieved undetectable HIV-1 RNA in group treated with enfuvirtide when they were naive or had no evidence of resistance to the drug (22).

The percentage of patients who used enfuvirtide for the first time and achieved HIV viraemia level < 50 copies/mL in week 24 was: 63.7% in arm 1, 53.2% in arm 2 and 36.2% in the placebo arm. However, the percentage of patients who had previously used enfuvirtide and/or showed resistance to enfuvirtide and who achieved HIV viraemia level < 50 copies/mL, was 31.1%, 33.8%, and 6.3%, respectively (22).

Benchmark 1 and Benchmark 2 trials

These were randomised, double-blind, placebo-controlled phase III trials of the use of raltegravir, a drug from the new class of integrase inhibitors, plus OBT, in patients with multi-drug resistance. 703 patients were enrolled in the studies (352 to the BENCHMARK-1 study and 351 to the BENCHMARK-2 study). The efficacy analysis was performed in week 48. It is planned to extend the study and to repeat the efficacy analysis in the study week 156 (20, 21).

The patients were divided into two groups: group I received raltegravir combined with OBT, group II – placebo combined with OBT. The mean baseline HIV viraemia levels in both groups was 4.7 $\log_{10}$ copies/mL, and the mean baseline CD4 number was 102 and 132 cells/mm^3, respectively. In both groups of patients, AIDS was diagnoses in 90% patients, and the mean ARV treatment duration was 10 years (20, 21).

The analysis of treatment efficacy in week 48 in the group of patients using enfuvirtide with or without darunavir is interesting (20, 21).

In the group of patients who used both enfuvirtide and darunavir for the first time, the percentage of patients who achieved HIV viraemia level < 50 copies/mL was 89% for those receiving raltegravir and 68% for those receiving placebo (20, 21).

In the group of patients who used enfuvirtide for the first time but without darunavir, the percentage of patients effectively treated was 80% for those receiving raltegravir and 57% for those receiving placebo (20, 21).

In the group of patients who did not receive enfuvirtide but used darunavir for the first time, the percentage of effectively treated was 69% and 47%, respectively (20, 21).

In the group of patients who received neither enfuvirtide nor darunavir in their OBT, the percentage of effectively treated was significantly lower and was equal to 60% and 20%, respectively (20, 21).

The above analysis shows that the efficacy of enfuvirtide added to a regimen of ARV drugs is higher than the efficacy of added darunavir (80% vs. 69% in the group of patients receiving raltegravir and 57% vs. 47% in the placebo group). The highest efficacy was shown for the combination of enfuvirtide and darunavir (20, 21).

SAFETY AND TOLERABILITY

The data on side effects of enfuvirtide have been collected based on many clinical trials in large cohorts of patients (adults and children). Enfuvirtide is generally well tolerated. In clinical trials, most adverse events have been mild to moderate in intensity. No exacerbation of other

common antiretroviral toxicities by enfuvirtide has been observed. Constitutional adverse events, especially gastrointestinal events, were less common in the enfuvirtide-treated patients in the TORO studies versus those treated with optimized background alone. These events included diarrhea, nausea and fatigue (2, 15, 27).

As enfuvirtide is administered parenterally in the form of subcutaneous injection, 89% patients experience reactions at the administration site: thighs, arms or abdomen. These reactions include: pain and discomfort at the puncture site, reddening (erythema), hardening of the skin and subcutaneous tissue, tumours of the subcutaneous tissue, skin infections at the drug administration site. 11% of patients who experience the above side effects received analgesics, and 4.4% patients discontinued the treatment with enfuvirtide (20, 22, 24).

Bacterial pneumonia has been seen in a higher percentage of patients treated with enfuvirtide as compared to the other HIV-infected patients treated with antiretroviral drugs. The relationship between the incidence of pneumonia and the use of enfuvirtide is unclear. Perhaps it is a clinical manifestation of the Immune Reconstitution Inflammatory Syndrome (IRIS) but these data must be confirmed based on further observations (23, 24, 25).

The other possible side effects of enfuvirtide include: peripheral neuropathy, sinusitis, ear infections, lymphadenopathy, insomnia, depression, difficulties in concentration, nightmares, decreased appetite, nausea, diarrhoea, complete lack of appetite (anorexia), weakness, dizziness, myopathy, constipation, pancreatitis, flu-like symptoms, heartburn, blepharitis, renal calculosis, diabetes, hypertriglyceridaemia, haematuria (23, 24, 25)

Hypersensitivity to enfuvirtide is relatively rare. It usually occurs after repeated administration of the drug and is manifested by typical adverse symptoms: rash, fever, dyspnoea, chills, nausea and vomiting, myalgia, hyperidrosis and reduced blood pressure (23, 24, 25).

Enfuvirtide belongs to category B of drugs in the FDA classification, which means that animal experiments have shown no risks for the foetus but there are no controlled trials in women. It also means that the benefits from using enfuvirtide in a pregnant woman exceeds the risk of adverse effects in the foetus (23, 24, 25, 28).

Conclusions

1. Enfuvirtide is a drug that targets HIV by inhibiting viral fusion with the host cell. Thus far, it has provided antiviral, immunological and clinical benefits, has a low toxicity, and contributes to improved quality of life in patients with HIV.
2. It is a useful addition to anti-HIV therapeutic strategies also to the novel class drugs such integrase inhibitors or CCR5 co-receptor inhibitors.
3. Although enfuvirtide treatment is beneficial at later stages of disease, patients have improved outcomes with the earlier use of enfuvirtide. The data from TORO shown that it should be considered earlier in the management of HIV and that it should not be reserved until late in the disease when its use may effectively be limited to monotherapy [28].

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title

The role of nevirapine in the antiretroviral therapy

authors

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summary

In the presented multicenter study an attempt was made to evaluate the role of nevirapine used in treatment of HIV-seropositive patients in both groups: naive as well as experienced. The therapeutic effect was evaluated while analysing the HIV-RNA level and the increase in CD4 cell count. The reasons for which the new schema with nevirapine was introduced in experienced patients were as well analysed. Among these reasons were mainly side effects of different character. On the basis of the obtained results very good virologic response was reported in both groups, naive and previously treated. Immunologic response in both populations discussed was similar though the initial level of CD4 was two times lower in naive patients in comparison with experienced population.

key words

HIV infection, nevirapine, undetectable viremia, CD4 cell count, side effects of antiretroviral drugs

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Introduction

Nevirapine appeared as the first among those of non-nucleoside inhibitors of reverse transcriptase which are in use. Despite this fact, its role does not diminish but, on the contrary, is even much more substantial. As the prolongation of life length of HIV-infected people has become much more noticeable, another crucial problem appears: civilisation diseases such as hypertension and coronary heart disease concerning the whole population (1, 2). Their main underlying causes are disruptions in lipids metabolism. These disruptions, in case of seropositive patients, are aggravated by numerous antiretroviral drugs, especially protease inhibitors (3, 4, 5). The clinical consequence of abnormalities in lipids is lipodystrophy among patients treated with HAART which, to the significant extent, negatively affects the quality of their life**.** Application of nevirapine possessing good lipid profile, has in this case remarkable significance (4, 6). The next and vital advantage of nevirapine is widely known and corroborated: getting pregnant during treatment with nevirapine as well as its application in vertical prophylaxis among women previously non-treated is the recommended and safe option. As a consequence, nevirapine is the chief component of ART and can be then applied to young women in period of procreation (7, 8).

Aim of study

The aim of this study was to characterize and to evaluate effectiveness of ART treatment with application of nevirapine carried out in a group of seropositive patients from different centres in Poland.

Patients and methods

Studied population consisted of 278 HIV-infected patients treated with ART including nevirapine. The factors analysed were: sex of patients under treatment, average time of treatment and patients' therapeutic history (naive/experienced patients). In both groups of patients the immune (CD4 cell count/mm^3) and viral (HIV-RNA copies/ml) responses to treatment were tested**.** Data were collected two times: firstly, at the moment of the introduction of the schema with nevirapine and then, during continuation of the therapy between May and September 2007. Due to differences in data, it was assumed that detectable viremia signifies the interval between 400 and 3 1400 000 copies/ml. In case of experienced patients the analysis concerned the reasons for which the change for the therapy including nevirapine took place. Due to incomplete data, the number of persons undergoing the analysis was changing dependently of the problem being studied.

Data were presented as means, range and median (95% CI). The significance of differences was calculated by the non parametric, Mann-Whitney U test. Statistical analyses were performed with Statistica 8.0 for Windows software.

Results

Population under study consisted of 278 patients: 181 men and 80 women (no data for 17 patients). There were 149 patients classified into the naive group. The remaining 129 patients had earlier undergone the antiretroviral treatment. The mean time of the therapy was 40 months for naive patients and 42 months for experienced.

The viral response to treatment was tested in 122 naive and 118 experienced patients. Undetectable viremia was found in 115 naive and 98 experienced patients (94.3% and 83% respectively). The mean time of the treatment in both of these groups with virological treatment success was similar: 43 months in the naive group and 46 months in the experienced group. Detectable viremia, on the other hand, was found in 7/5.7% of naive and 20/17% of experienced patients. The mean time of the treatment was: 57 months in the naive group and 36 months in the experienced group.

The mean level of HIV-RNA before the introduction of the therapy with Nevirapine was: 192244 copies/ml for naive and 41801 copies/ml for experienced patients (Fig. 1).

Figure 1. HIV-RNA load at the beginning of NVP-treatment

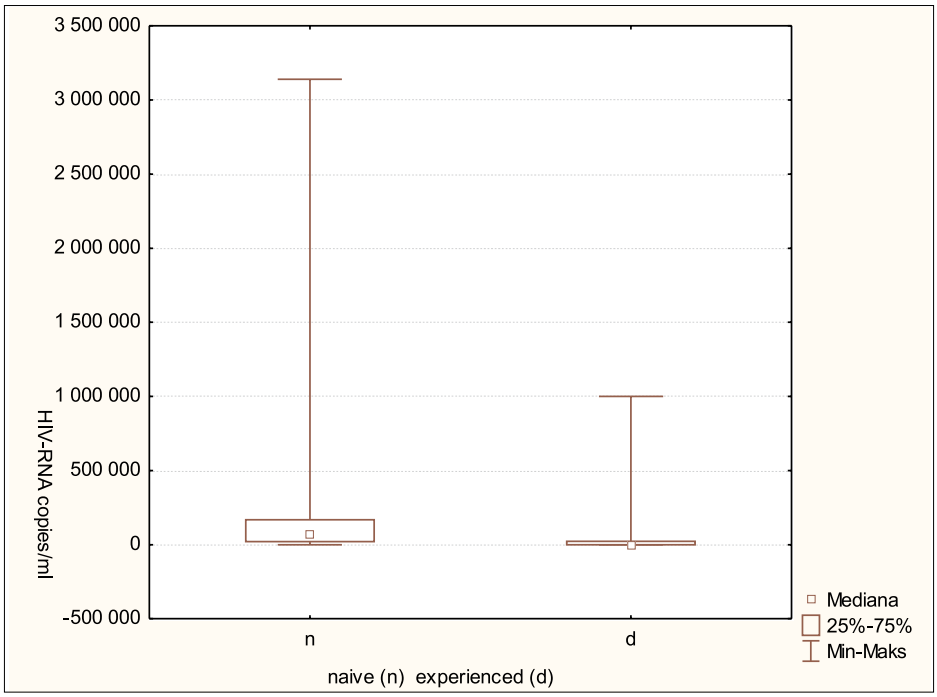


Figure 2.
HIV RNA load during NVP – schema treatment

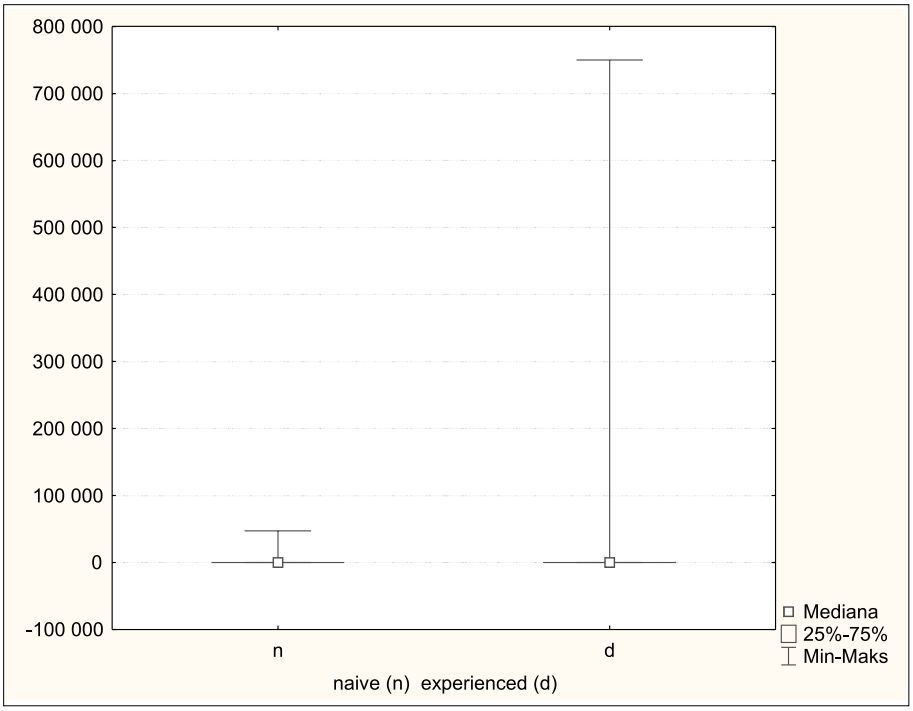
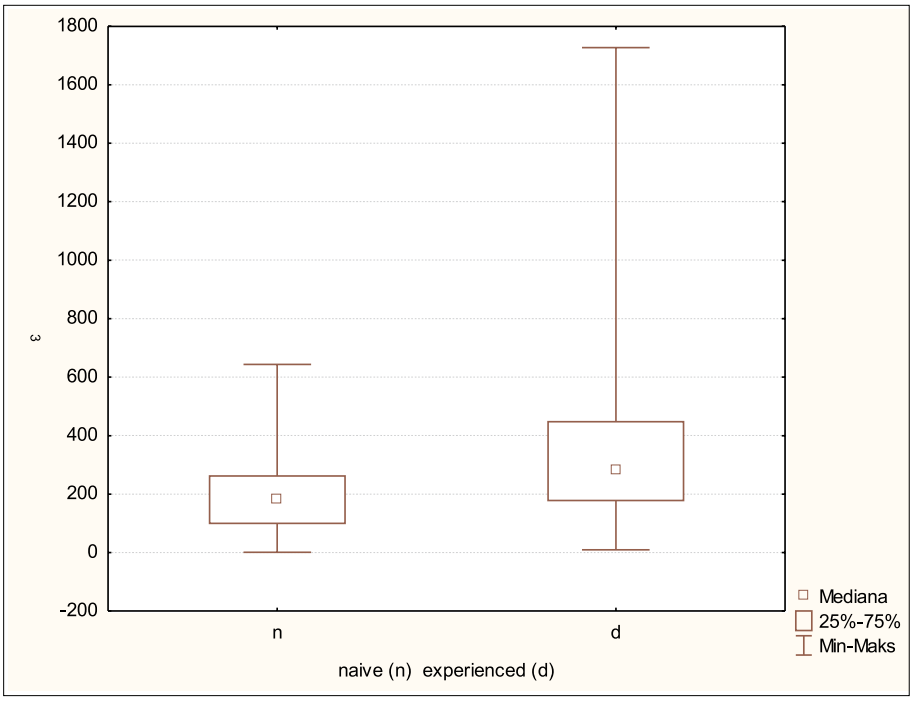


Figure 3.
CD4 cell count at the beginning of NVP – schema



The subsequent mean level of viremia during the antiretroviral therapy was 985 and 14796 respectively ($p < 0.05$) (Fig. 2).

The mean CD4 cell count before the introduction of the therapy with nevirapine was: 188 for naive and 336 for experienced patients (Fig. 3). The last CD4 cells count during the treatment of the populations studied was 469 and 473 respectively and this difference was statistically non-significant (Fig. 4).

Figure 5 presents the reasons for a change of the therapeutic schema which consequently resulted into the introduction of the one including Nevirapine. The dominating reason were side effects associated with the previous therapy. In 15 cases they were described as gastrointestinal problems. Incidental circumstances such as, for example, nephrolithiasis were found in the next 15 cases. In 10 cases disruptions in lipids metabolism with/without lipodystrophy gave the reason for the change of the therapeutic schema. CNS adverse effects after Efavirenz were detected in 6 cases. The remaining side effects were described in a very general way which made their classification into the particular group just impossible (15 cases).

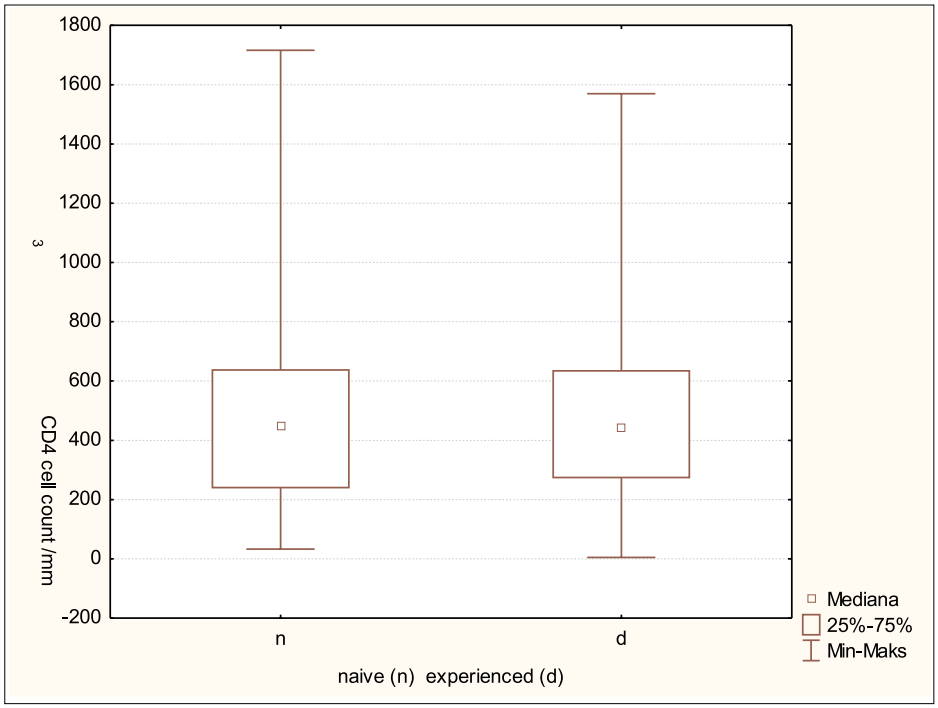


Figure 4.
CD4 cell count during NVP – schema treatment

The next reason for the change of the therapeutic schema was virological treatment failure (in 18 patients). The remaining reasons for the change of the therapy were: nonadherence, treatment interruption and pregnancy (in 8, 7 and 6 cases respectively). The reason for the change of the schema was not stated in 11 cases.

While analysing the course of treatment with NVP – regimen in both groups of patients, it has to be highlighted, that severe side effects (skin rash, increase in aminotransferase levels) in grade 3/4 were not observed.

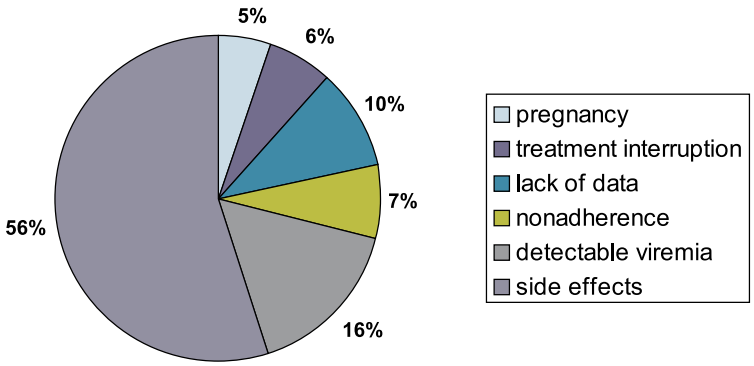


Figure 5. Reasons for ART changes in experienced patients

Discussion

Due to the multicenter character of the study, it is of significant value while evaluating the role of nevirapine, the principal drug used in the antiretroviral therapy. However, presented data are not free from errors characteristic of retrospective studies. This study proved very good virologic effectiveness of the therapeutic schema with nevirapine in the group of naive patients (98% of patients with undetectable viremia) during the mean time 43 months. Statistically significant decrease in HIV-RNA load in naive patients in comparison with experienced group as well corroborates the fundamental role of the first-line therapy in medical history of every HIV-positive patient.

Although the CD4 cell count at the beginning of the study in naïve patients was low (188 cells/mm^3), the increase in its level, protecting against opportunistic infections, was achieved. Clotet highlights the role of nevirapine as an effective and well-tolerated treatment, capable of prolonged, virological and immunological responses (16). Data presented by the other authors also corroborate good effectiveness of nevirapine in the first-line treatment (9, 10, 11). Low mean CD4 cell count at the beginning of the study is in accordance with observations of the authors concerning recognition of HIV infection in the late stage in Polish population (12). Achieving in this situation the significant increase in CD4 level is much more difficult than initiating the treatment when CD4 level is higher (13). The mean CD4 cell count during the continuation of treatment was similar in both groups (469 versus 473 cell count/mm^3). The results presented indicate that attaining effective immunologic reconstitution was possible both in the group of naive as well as of experienced patients.

The undetectable viremia in the experienced group was noted in 83% of patients. This good result corroborates the role of nevirapine on every stage of the antiretroviral therapy. PI-regimen treatment is often associated with side effects, especially metabolic disorders which may affect tolerability and adherence (14). The possibility of modification of the therapeutic schema is very important and efficient. It was proved that the durable, virologic effect can be achieved after the switching from PI-regimen treatment,

efficient so far, to the regimen with nevirapine (4, 5, 6, 15, 16). That is of great importance especially while considering frequency of symptoms of intolerance towards antiretroviral drugs reported by patients (3, 4, 5, 15). Despite including in the study data about side effects, virologic failure and nonadherence in a separate way, it can be stated that these results are not free from a certain error. This error stems from the fact that side effects are actually the very frequent and direct cause of the remaining, above-mentioned phenomena.

Nevirapine like the other drugs presents side effects. The main problem besides development of resistance is hepatotoxicity in the first months of treatment. The prolonged use has been established as safe and the risk of drug-induced hepatotoxicity is low. Less than 2% of 613 patients including in multicentre cross-sectional and observational study in Spain, treated with NVP-regimen for at least 2 years, presented grade 3/4 transaminase elevations (17). Similar, low risk of hepatotoxicity was observed by Maggiolo at al (18).

In conclusion, nevirapine – based ART has become increasingly popular because presents simpler and more easily tolerated treatment option.

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title

Cystatin C as a new biomarker of renal dysfunction in HIV-1 infected patients – preliminary report

authors

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summary

Background. HIV-1 infection and ARV therapy can cause progressive renal dysfunction. The aim of our study was to evaluate serum cystatine C (Cys-C) concentration and their possible relationships with the degree of renal injury in HIV-1 infected patients with or without antiretroviral therapy.
Material and Methods. Study was performed in 34 HIV(+) and 17 HIV(-) individuals. In 20 already treated HIV(+) Cys-C concentration was measured once; in the rest: before, after 3 and 9 months of HAART. Serum Cys-C concentration was measured by ELISA. Plasma urea and creatinine levels were measured. Creatine clearance was calculated by Cockroft-Gault formula.
Results. Serum Cys-C concentration in untreated and treated HIV(+) patients was significantly higher than in control group (441.94 ±121.62 and 513.10 ±94.12 v. 309.9 ±49.4 ng/ml, $p < 0.001$, respectively). After 3 months of HAART Cys-C concentration decreased to 379.74 ±42.15 ng/mL, and after 9 months increased to 384.52 ±41.23 ng/mL.
Conclusion. Cys-C serum concentration is elevated in HIV-1-infected patients. Its decrease during the initial phase of ARV treatment suggests possible association with HIV viremia. HAART is associated with progressive increase of serum Cys-C concentration.

key words

HIV-1 infection, ARV therapy, renal dysfunction, cystatin C, biomarker

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Background

HIV-1 infection of glomerular endothelial and mesangial cells can cause progressive renal dysfunction, which prevalence fluctuates between 3% and 20% [1] and which has known, negative influence on prognosis in these patients. Moreover, in more than 30% of HIV-positive persons proteinuria is observed. Many HIV-associated renal disorders have been detected, among which the most common are: HIV-associated nephropathy (HIVAN), immune complex glomerulonephritis (GN) and thrombotic microangiopathy. These renal lesions could be related to HIV-1 infection and/or potential nephrotoxicity of antiretroviral therapies, such as: acute tubular necrosis, intratubular obstruction or interstitial nephritis. However recently, beneficial effect of antiretroviral therapy (ARV) on slowdown of progression of renal dysfunction was observed [2]. 12-year cohort study demonstrated substantial reduction in HIV-associated nephropathy incidence associated with HAART. Probably, it is linked with the decrease of detected HIV RNA in serum. Actually used standard metrics to define and monitor renal failure such as serum urea, creatinine or creatinine clearance are insensitive, nonspecific and change significantly only after major kidney injury. This is why there is necessity an vital necessitate to find new, more specific renal injury biomarkers.

In the last years, cystatin C (Cys-C, in the past known also as interalia γ-trace, post-γ-globulin and gamma-CSF) was identified as a new promising biomarker helpful for early detection of kidney function impairment. Cys-C is a 13.3-kDa, non-glycosylated protein produced by most mucleated cells. It belongs to the cystatin family which comprises inhibitors of cysteine proteases such as lisosomal catepsine B, H, L, S, papain or ficine [3,4]. Cys-C is freely filtered by the glomerulus and practically completely reabsorbed and catabolised by tubular cells [5]. Cys-C production rate is remarkably constant and therefore its plasma concentration has been proposed as a suitable marker of glomerular filtration rate (GFR). It was found to be a better GFR marker than creatinine, because its serum concentration appear to be independent of sex, age, and muscle mass [6]. Serum Cys-C levels have been already found elevated in chronic glomerulonephritis, diabetic nephropathy or nephritic syndrome.

The aim of our study was to evaluate serum Cys-C concentration and their possible relationships with the degree of renal injury in HIV-1 infected patients with or without antiretroviral therapy.

Material and Methods

Study was performed in 51 individuals: 34 infected with HIV-1 (25 males and 9 females, aged from 21 to 54; mean 37.5 ±23.3) and 17 healthy HIV(-) volunteers (aged from 27 to 45; mean 36 ±20.7). 20 HIV(+) patients (9 in group B and 11 in group C, univocal with CDC classification system) with already started long-term HAART (from 3 to 8 years; mean 5.5), was selected for single measurement of serum Cys-C concentration. Whereas, in remaining 14 HIV(+) patients (5 in group B and 9 in group C, univocal with CDC classification system) who just initiated ARV treatment, Cys-C was measured before the therapy beginning and after three and nine months of HAART administration.

Plasma HIV-1 RNA was evaluated using the RT-PCR Amplicor system. CD4/CD8 T-cell ratio on flow cytometry (Beckton-Dickinson, Franklin Lasek, NJ, USA) had been reported. Serum Cys-C concentration was measured by ELISA (Human Cystatin C ELISA, BioVendor, Heidelberg, Germany) according to manufacturer instructions. To estimate the relationship between degree of renal lesion and serum concentration of Cys-C, plasma urea and creatinine levels were measured. Creatinine clearance was calculated by using of Cockroft-Gault formula. GFR was calculated using MDRD Calculator © 2007 (Stephen Z. Fadem, Nephron Information Center).

The significance of differences was calculated by non-parametric Mann-Whitney U test and t-student test. For correlation analysis, the Spearman non-parametric correlation was used. A $P < 0.05$ was considered statistically significant. Statistical analyses were performed with Statistica 5.1 for Windows software (Statsoft Inc., Tulsa, USA).

Results

Serum Cys-C concentration before start of ARV therapy and in HIV(+) patients on successive long-term ARV treatment, were significantly higher than in control group (441.94 ±121.62 and 513.10 ±94.12 v. 309.9 ±49.4 ng/ml, $p < 0.001$, respectively) (Figure 1). After 3 months of HAART administration Cys-C concentration decreased to 379.74 ±42.15 ng/mL, and than, after 9 months increased to 384.52 ±41.23 ng/mL, but was still significantly higher in comparison to control group (Figure 2). Mean values of plasma urea, creatinine, creatinine clearance, GFR, HIV RNA and CD4/CD8 T-cell ratio in all HIV(+) patients are presented in Table 1. There were no significant differences between studied groups in respect to urea, creatinine, creatinine clearance and GFR values.

Table 1. Mean values of HIV-RNA, CD4/CD8 ratio and selected biochemical indices of renal function and injury in HIV (+) patients

	Group A	Group B	Group C
Urea (mg/dl)	28,61 ±5,81	25,92 ±2,75	23,38 ±10,4
Creatinine (mg/dl)	0,76 ±0,17	0,82 ±0,17	0,72 ±0,16
Creatinine clearance (ml/min)	152,26 ±31,97	129,57 ±43,06	141,70 ±35,62
GFR (ml/min/1,73m^2)	140,93 ±37,10	109,28 ±22,20 p < 0,010	125,20 ±34,41
CD4 (cells/ml)	370,55 ±27,68	319,71 ±16,63 p < 0,001	403,66 ±11,99 p < 0,001
CD8 (cells/ml)	691,80 ±186,70	873,28 ±112,14 p < 0,005	984,9±262,24 p < 0,005
HIV RNA (copies/ml)	36917 ±63980	8424 ±11407	20488 ±26497

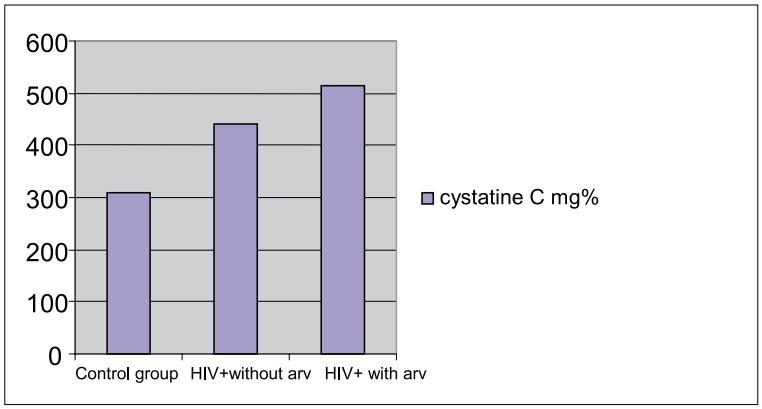

Figure 1.
Serum cystatine C concentration in HIV(+) patients with and without antiretroviral therapy in comparison to control group

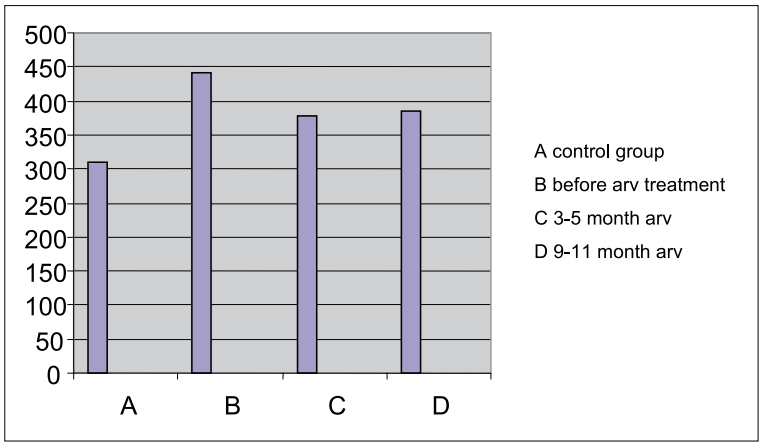

Figure 2.
Serum cystatine C concentration in HIV(+) patients before, after three and nine months of antiretroviral therapy

Discussion

It has been considered that new renal injury biomarkers will permit putting more appropriate diagnosis, predicting of injury severity and safety of therapy. The measurement of serum Cys-C has been already proposed as a simple, reliable and specific marker of GFR, better than plasma urea or creatinine, for patients with diabetes, cardiovascular diseases and acute kidney injury [7]. However, recently its some restraints have been discovered, especially the possibility of false positive results in patients with leukaemia, after renal transplantation or in pregnant women [8, 9]. In literature, there are still not many data about Cys-C concentration in treated and untreated HIV(+) patients.

In our study we observed significantly higher serum Cys-C concentration and lower GFR in HIV(+) patients in comparison to control group. In the same time, concomitant plasma creatinine and urea levels did not increase. These results can confirm the negative influence of HIV-1 infection and nephrotoxicity of antiretroviral therapy and the low specify of actual renal lesion biomarkers. Our results are in accordance with the data of Odden et al [10] who also observed the higher serum Cys-C concentration in HIV(+) patients, but without concomitant GFR decrease and Kimmel et al. [11] who confirmed positive correlation between HIV viremia and intensity of renal dysfunction. Moreover, Izzedine et al. [12] proved that the renal dysfunction in HIV infection was observed also during undetectable serum HIV viremia.

We observed the fluctuations of serum Cys-C concentration in initial phase and during long-term ARV therapy which are probably linked with the decrease of HIV RNA and/or side effect of ARV drugs.

Conclusions

Cys-C serum concentration is elevated in HIV-1-infected patients, that may confirm its direct relationships with renal lesion. The decrease of serum Cys-C concentration during the initial phase of ARV treatment suggests possible association with HIV infection and HIV viremia. Long-term HAART is associated with the progressive increase of serum Cys-C concentration, that can be related with long-term HIV infection or possible nephrotoxic effect of antiretroviral therapy.

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title

Autoimmune hepatitis in a HIV-infected patent – diagnostic difficulties – a case report

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summary

Autoimmune hepatitis is a rare clinical entity characterized by interface hepatitis, hypergammaglobulinaemia and circulating antibodies. The coexistence of AIH and HIV infection has been reported previously in only 7 cases in the literature. This paper describes a case of a patient with HIV infection, on ARV therapy who developed an icteric hepatitis. Diagnostic challenges and difficulties are presented with comparison to previously described cases.

key words

AIH (autoimmune hepatitis), HIV infection, antiretroviral therapy

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Background

Autoimmune hepatitis (AIH) was first described in 1950s. It is uncommon liver disease characterized generally by 3 features: hepatitis, presence of circulating autoantibodies and high serum gammaglobulin concentration. AIH usually presents as chronic hepatitis, but it can range from asymptomatic to acute or fulminant liver failure. The etiology and pathogenesis of AIH is unclear. Genetic bases of autoimmune hepatitis were studied by many researchers – alleles within and outside the major histocompatibility complex (MHC) are considered of special importance in disease development and therapy outcome (1). Viral infection has long been discussed the most likely etiologic basis for AIH, and many agents have been implicated, especially the hepatitis A virus (HAV), hepatitis G virus (GBV-C) and TT virus (TTV) (2-3). HIV has been very rarely reported to be associated with AIH. This particular infection-disease coexistence has been described in only 7 cases in the literature (4-8). The aim of his paper is to describe a case of a HIV infected patent, with a long-term history of ARV therapy, and diagnostic challenges and difficulties connected with establishment of final diagnosis.

Case report

A 40 year old male, MSM, diagnosed as HIV-positive in 1993, was admitted to the IVth Division of Hospital for Infectious Diseases due to hepatitis, presumably of toxic, ARV – drug-induced etiology. He reported nausea, lack of appetite, general weakness and fatigue for last 3 weeks proceeding hospitalization. At that time he noticed jaundice as well.

Since 1998 the patient has been on ARV-therapy with a history of several changes of drug regimens due to adverse effects or lack of effectiveness. For last four months his ART, adjusted to the results of resistance tests (genotyping), consisted of: lopinavir/r, zydovudine, lamivudine and tenofovir. Before introduction of the current ARV medicines his CD4+ cell count was 101 cells/mm^3. History of alcohol, illicit drug use and smoking was negative. He had a medical history of esophageal hernia and candidiasis, renal stones and episode of acute hepatitis of unknown etiology three years proceeding present case. On admission he presented: icterus, peripheral lymphadenopathy (multiple, enlarged, not painful regional lymph nodes, in diameter < 20 mm) and hepatosplenomegaly. In the work-up for hepatitis the following results were obtained: negative serology for HAV (anti-HAV IgM negative), HBV (hepatitis B surface antigen negative, total core antibody negative), HCV (anti-HCV negative), EBV (anti-EBV IgM negative) and CMV (anti-CMV IgM negative) infection. Negative viral load for hepatitis C virus. The laboratory results were: bilirubine concentration 3x↑UNL (upper normal limit), ALT 6x↑UNL, AST 7x↑UNL, ALP 1,5x↑UNL, GGTP 8x↑UNL, CD4+ 252 cells/mm^3, HIV RNA undetectable. Serum protein electrophoresis revealed hypergammaglobulinemia 2,5x↑UNL. The patient demonstrated positive antinuclear antibody (ANA) in titers 1:2560. Other autoimmune markers were negative.

The abdominal ultrasound and CT-scan were performed revealing hepatosplenomegaly and visceral adenopathy – the presence of enlarged periaortal, perihepatic and upper-abdomen lymph nodes (up to 25 mm in diameter). According to clinical findings the drug – induced hepatitis (due to LPV/r use or mitochondrial toxicity caused by AZT/3TC use), lymph nodes tuberculosis, lymphoproliferative disease and autoimmune hepatitis were taken into consideration in differential diagnosis. The ARV therapy was stopped. Based on blood tests results the lactic acidosis was excluded. Patient underwent gastroscopy, which revealed single esophageal varice. Based on histopathology and microbiological tests results (direct examination, MTD, cultures) of cervical lymph node specimen and bone marrow the lymphoproliferative disease and tuberculosis were excluded. The diagnostic liver biopsy was performed showing chronic hepatitis with mild activity (+2) and mononuclear, portal cell infiltrates (+), without rosettes. According to the criteria of IAIHG (International Autoimmune Hepatitis Group) the patient's score was 16 meeting the criteria for define diagnosis of AIH (9). The patient was started on immunosuppressive therapy consisted of prednisone and azathioprine. In a follow – up the marked improvement of symptoms and normalization of liver tests were obtained. An abdomen ultrasound examination was done at a third and sixth month of immunosuoresive therapy showing decrease in lymph node's size. After achieving the sustained normalization of liver tests the previous regimen of ARV therapy was reintroduced with good tolerance and efficacy (immunological and viral). During one-year follow-up the assay of reduction of maintenance steroid dose resulted in increase of ALT and AST resulted in a need of prednisone dose rise (Fig.1).

Discussion

Autoimmune hepatitis is a rare liver disease affecting all ages, both genders with predominance of female gender. There is no exact epidemiological data on AIH incidence and prevalence. The best available data regarding the prevalence of autoimmune hepatitis in Europe are from Norway. The mean annual incidence of autoimmune hepatitis in this country is 1.9/100,000 and prevalence is 16.9/100,000 (10).

The two main patomechnisms of hepatocyte injury have been implicated in AIH. First is the transformation of activated CD4+ lymphocytes into toxic ones (cell mediated cytotoxicity. Second – the effect of antigen – antibody complexes on the liver cell (cell mediated antibody mediated cytotoxicity) (9, 11). Currently, many researchers believe that the retroviral infection may play a role in the pathogenesis of AIH as a initiator of the disease. The role of retroviruses as causative agents of certain autoimmune diseases like Sjogren's syndrome, primary biliary cirrhosis, multiple sclerosis, diabetes have been discussed. It has been proposed that viral infections may break or overcome self-tolerance and result in inflammation of hepatocytes, especially in genetically predisposed persons (12). Recently, in HIV infection the role of CCR5-coreceptor as a regulator of the inflammatory response was described and can represent a potential novel therapeutic agent for T-cell mediated hepatitis.

In HIV-infected patients the most common causes of abnormal liver tests are: HCV or HBV co-infection, hepatotoxicity of antiretroviral drugs or illicit drugs, opportunistic infections (tbc, MAC, CMV etc) and their treatment and neoplasm (13). Due to this the AIH in HIV-infected patients is very likely underdiagnosed and treated with delay.

Presented case is an example of a need of wide and very detailed diagnostic process in establishment of correct diagnosis of hepatitis. The liver biopsy is the an effective diagnostic procedure enabling diagnosis. The early recogni-

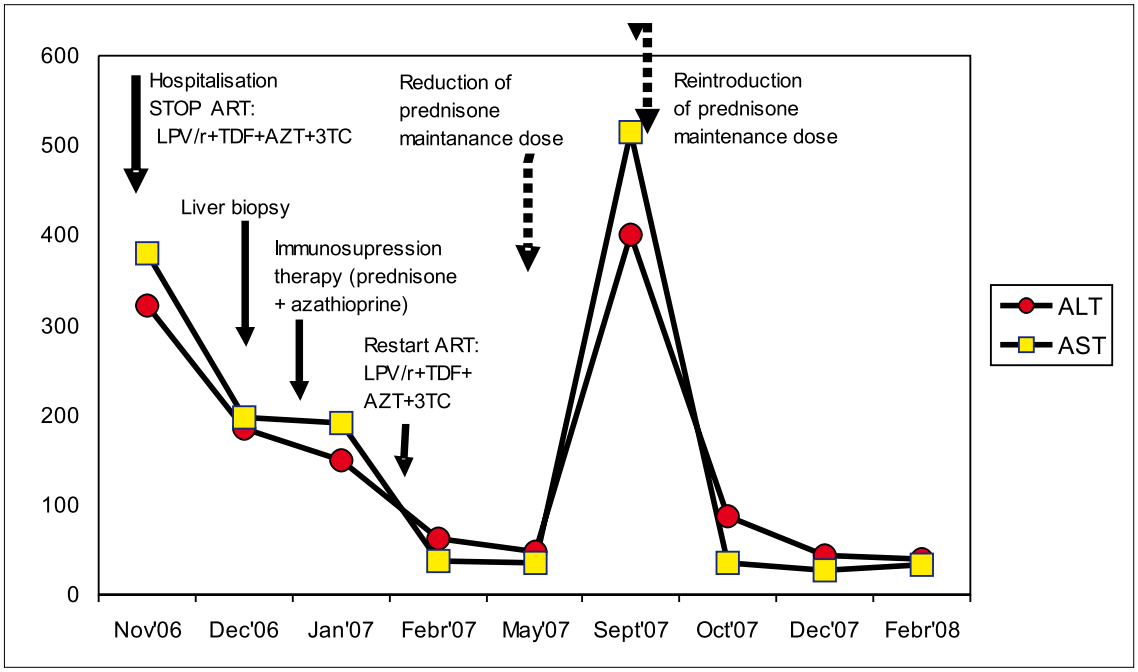

Figure 1. ALT and AST levels over time

tion of AIH gives an opportunity of appropriate, immediate therapy and in consequence postponing the development of liver cirrhosis (14). In described case of AIH it is very likely that exacerbation of hepatitis is due to immunological reconstitution (observed CD4+ cell increase from 101 cells/mm^3 to 262 cells/mm3 during ARV therapy). It is also probable that in a medical history of a patient acute hepatitis of unknown etiology was the first episode of AIH. The diagnosis of AIH in HIV infected patients has been described in only 7 cases in the literature (4-8). Our case is an eighth one. In 2 of 7 previously presented patients the exacerbation of autoimmunity was connected with immune restoration. This observation is consonant with previous theoretical data (7, 8, 15). It is also interesting that in four patients the use of ARV therapy did not influence the AIH outcome. In 4 patient (including currently presented) use of antiretroviral therapy resulted in exacerbation of autoimmune hepatitis (7, 8). Use of antiretroviral therapy improved AIH only in one case (6). All remaining patients experienced worsening of liver disease or HIV medication was the trigger agent of AIH. Immunosuppressive therapy (prednisone, azathiopryna, mycophenolate) was used in all patients as well as antiretroviral agents. It seems that concomitant therapy for AIH and HIV should be a standard of care in this group of patients.

Conclusions

In HIV infected patients diagnosis of autoimmune hepatitis is complicated and needs numerous procedures to exclude other, more common liver diseases. The incidence of AIH in HIV positive patients is unknown and probably very low, but AIH must be taken into consideration in differential diagnosis of liver injury with special caution to those patients who experience immune restoration due to ARV medication. For HIV infected and not infected patients formal criteria for AIH diagnosis and therapy are the same and based on recommendations of IAIHG.

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title

Low level viremia on HAART and newly registered protease inhibitor – a case report

authors

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summary

A case of 38 years old men with partial virologic suppression on HAART is presented. Patient's HAART was started when his CD4 count was 11cells/uL and viremia 275 000 copies/mL. During three years of treatment according to following schemes: 1) AZT, 3-TC, NFV; 2) d4T, 3-TC, NFV; 3) d4T, ABC, LPV/r and 4) d4T, ABC, LPV/r, EFV therapy goal – undetectable viremia was not achieved. Some virologic response was observed – viral load in consecutive tests was: 10800; 2510; 430; 690, 57, 182 and 242 copies/uL respectively but it has never been undetectable. Immunologic response was also unsatisfying – CD4 cells count fluctuated between 100-200 cells/uL. Considering whole patient's history newly registered protease inhibitor darunavir was introduced and therapy goal undetectable viremia was achieved. Concluding: introducing of newly registered drugs may improve ARV therapy and it may help achieving therapy goals in patients with non-complete virologic response on previously available drugs.

key words

HAART ; Non-complete virologic response; darunavir

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Introduction

Achieving undetectable viremia is main goal of antiretroviral treatment in HIV infected patients but there are patients that cannot achieve the goal and only partial suppression of the virus is available. Decision how to treat the patients with non complete virologic response is one of the most important questions in daily practice for those who take care of HIV patients. In some of such patients with marked but not complete suppression of the HIV viremia apparent clinical benefit is observed but it was confirmed that maintaining such situation may cause emerging new viral mutations [1]. More difficult is situation when clinical benefit is not satisfying.

We present a case of patient with non-complete virologic response and not satisfying immunologic response in whom the therapy was switched and newly registered protease inhibitor was introduced.

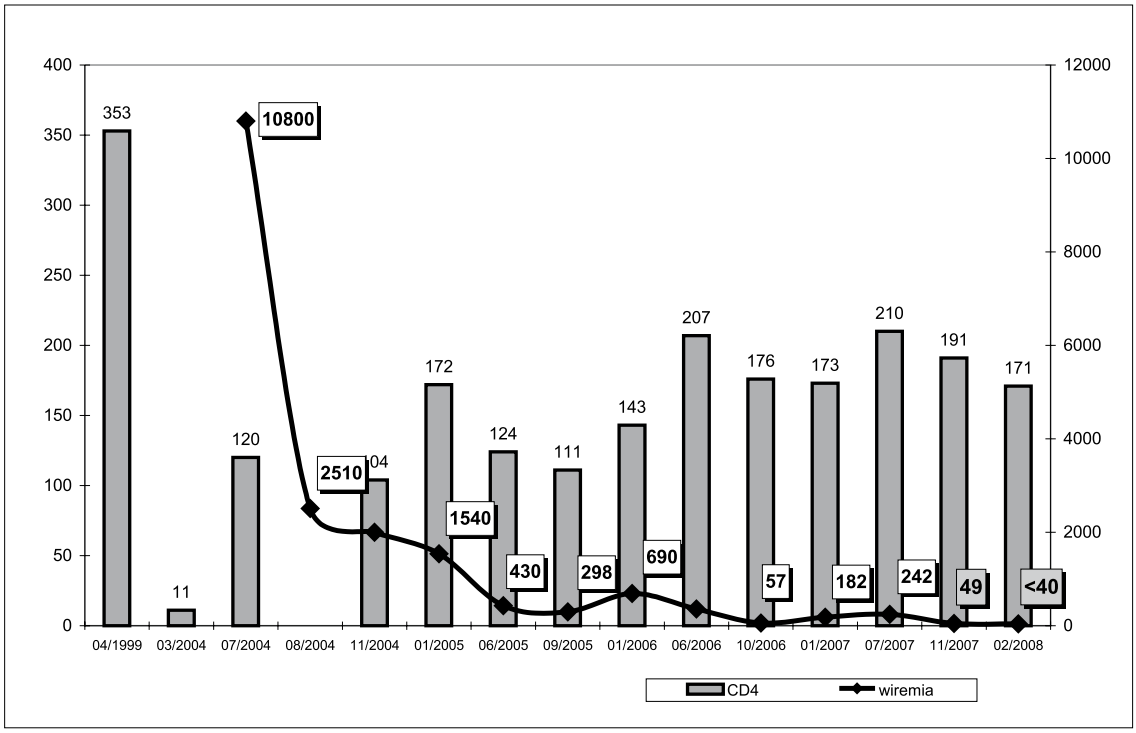
Case report

The case of 38 years old men with partial virologic suppression on HAART is presented. HIV infection was diagnosed at the age 27; probable route of infection was intravenous drug abusing but the patient had also HIV-infected female sexual partner. At time of primary diagnosis the infection lasted not longer than 1,5 of year as HIV antibodies test had been negative one year earlier. No more laboratory analyses were done at primary diagnosis as the patient did not come to the outpatient clinic. Two years later the patient was hospitalized for pulmonary tuberculosis. Additionally chronic hepatits C was diagnosed. His CD4 cells were 354 cells/μL than. Pulmonary tuberculosis was cured but anti-TBC drugs were continued only for 5 months. During consecutive four years the patient was not attending out-patient clinic visits and he was abusing drugs actively.

In March 2004 the patient was admitted to the hospital because of episodes of high fever that had lasted for several days. There was no site of active infection detected but CD4 cell count was 11 cells/uL, therefore AIDS and fever related to the syndrome were diagnosed. HIV viremia was 275 000 copies/ml at this time. Sputum was tested for presence of Mycobacterium tuberculosis infection was excluded. Additionally Hepatitis B Virus infection was diagnosed with HBs and HBe antigens positive and relatively high aminotransferases levels (ALT over 500U/L). Antiretroviral treatment was immediately started with retrovir (AZT), lamivudine (3-TC) and nelfinavir (NFV). After first three months of treatment decrease of viremia up to 10 800 copies/ml and increase of CD4 count up to 120 cells/uL were achieved.

After one month of ARV therapy the patient started to complain of neurological symptoms like paraestesia mainly of left side of the body and hypaesthesia of lower and upper extermitaties. Computed tomography of head was performed but no lesions were detected so multifocal polineuropathy was diagnosed and carbamazepine treatment was introduced. Two months later intensity of neurological symptoms increased so the patient was admitted to the hospital. Magnetic resonance of brain was performed and lesions characteristic for Toxoplasmosis of central nervous system were revealed. Anti-TOXO IgG antibodies test was positive. Toxoplasmosis treatment with pirimethamine and clindamicin accompanied by folinic acid was started. Following the next two months of treatment the patient developed marked anaemia related to bone marrow suppression in the course of retrovir treatment therefore the drug was withdrawn and replaced with stavudine (d4T). Further suppression of viremia was observed before the treatment was changed – HIV viral load 2510 copies/ml, however without CD4 cells count increase – 104 cells/uL. Toxoplasmosis treatment was continued according to previous scheme but drugs doses were decreased as marked improvement of brain lesions was found. After next three months (10th month of ARV treatment) further decrease of viral load (1540 copies/ml) and minor increase of CD4

Figure 1. Course of viremia, CD4 count and treatment



cells count (172 cells/uL) were observed. As virologic suppression and immunologic improvement were not satisfying decision to change the treatment followed. Therapy that consisted of d4T, ABC and LPV/r started. Change of treatment resulted in further viral load decrease, in the third month of new regimen viremia was 448 copies/ml and in sixth month 298 copies/ml. Unfortunately after next three months higher viral load was detected (690 copies/ml) and decrease of CD4 cells count (143 cells/uL) was observed so it was decided to intensify treatment and efavirenz (EFV) was added to the previous therapy scheme. Within next year of treatment viral load decreased to 57 copies/ml and after that started to increase again – 182 copies/ml and 242 copies/ml respectively. Only minor increase of CD4 cells number was observed – 207 cells/uL, 176 cells/uL, 173 cells/uL in consecutive tests.

Considering whole patient's history and lack of anticipated virologic and immunologic response after three year HAART treatment the decision to change treatment was made. As no genotypic tests were available because they were not routinely performed at the time of treatment start and too low viral load was revealed at the time when resistance was suspected newly registered protease inhibitor – darunavir was introduced with lamivudine (3TC) and tenofovir. After first three months of that regimen viral load decreased under 50 copies/ml and after next three months viremia became undetectable so virologic goal of the treatment was achieved. No marked immunologic response is observed (CD4 cells count – 3rd month 191 cells/uL and 6th month 171 cells/uL) but it is anticipated in further tests after complete virologic suppression. The course of virologic, immunologic response and treatment options was presented on figure 1.

Discussion

Treatment of the patients with non complete virologic response is always very difficult. Most often asked question is if and when the treatment should be switched and what treatment opportunities should be chosen. There is a real possibility that treatment options may be lost when viremia will increase to higher levels because of genotypic mutations of the virus [1]. Some patients with low viremia achieve marked immunologic benefit but it was observed that it lasts rather short [2]. The more difficult situation is when neither complete virologic response nor satisfying immunologic response is observed. Additionally when viremia is too low to perform genotypic tests to assess which mutations emerged and which drugs is the virus susceptible for.

In case of our patient we lost possibility to perform genotypic tests. At first phase of the treatment decrease of viremia was so evident that it seemed that the drugs ordered are good enough to achieve therapy goal (see figure 1). Later on low level viremia had been observed but during three consecutive years of treatment undetectable viremia was never achieved and existing results did not allow performing genotypic tests. In parallel immunologic response was not satisfying. Other authors show that in general group of similar patients' virologic response is enough to protect patients against oportunistic diseases[3]. Our patient developed opportunistic disease – toxoplasmosis of central nervous system within first two months of the ARV treatment that could have been related to immunologic reconstitution inflammatory syndrome (IRIS). But during consecutive two years no other opportunistic diseases were observed in spite of CD4 count under 200 cells/uL. In spite of very low viremia (under 1000 copies/uL) immunologic response was not satisfying in our patient as it was observed in groups of similar patients [1, 2]. It was fluctuating between 100 and 200 cells/uL and only in two separate tests CD4 cells count exceeded 200 cells/uL. The consecutive decisions to change therapy regimens and to intensify therapy did not cause any significant improvement. That could be caused by prolonged secondary prophylaxis of toxoplasmosis with clindamycin that can influence cytochrome P450 activity and ARV drugs levels. It could also been suspected that the patient was infected with drug resistant virus but such thesis cannot be confirmed because of lack of genotyping tests.

Taking under consideration the whole patients history when new protease inhibitor – darunavir became available on Polish market it was decided to introduce it into the treatment. Darunavir is a nonpeptidic protease inhibitor recently approved for the treatment of antiretroviral therapy-experienced patients [3]. It has potent in vitro activity against viral isolates that are resistant to previously available protease inhibitors. In clinical trials, it has shown virologic and immunologic responses superior to comparator-based regimens. The potential of the drug was good enough to achieve goal of the treatment in our patient undetectable viremia. First tests after darunavir treatment was started did not show marked improvement of CD4 cells count but improvement is anticipated in further analyses.

Conclusions

Patients with persistent low level viremia during HAART cause a lot of problems in daily practice and there are no general rules available how to treat them. Newly registered ARV drugs, like Darunavir in our case, may help to achieve therapy goal – undetectable viremia in such patients.

Our case shows that genotyping tests should be performed before the start of ARV therapy. Availability of result of such test in our patient would have been very helpful when change of therapy had been considered but unfortunately genotypic tests were not included into routine practice when patients therapy begun.

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