

ORIGINAL ARTICLE

The prevalence and risk of immune restoration disease in HIV-infected patients treated with highly active antiretroviral therapy

DJ Jevtović,[1] D Salemović,[1] J Ranin,[1] I Pešić,[1] S Žerjav[1] and O Djurković-Djaković[2]

[1]*Institute for Infectious & Tropical Diseases, Clinical Centre of Serbia, Belgrade, and*[2]*Institute for Medical Research, Belgrade, Serbia & Montenegro*

Background

It is becoming increasingly clear that, during successful highly active antiretroviral therapy (HAART), a proportion of treated patients develop opportunistic infections (OIs), referred to in this setting as immune restoration disease (IRD). We examined the risk of developing IRD in HAART-treated HIV-infected patients.

Methods

A retrospective study of a cohort including all 389 patients treated with HAART between 1 January 1998 and 31 May 2004 in our HIV unit was performed to evaluate the occurrence of and risk factors for IRD during HAART. Baseline and follow-up values of CD4 T-cell counts and plasma viral loads (pVLs) were compared to assess the success of HAART.

Results

During successful HAART (significant increase in CD4 T-cell counts and decrease in pVL), at least one IRD episode occurred in 65 patients (16.7%). The median time to IRD was 4.6 months (range 2–12 months). IRDs included dermatomal herpes zoster (26 patients), pulmonary tuberculosis (four patients), tuberculous exudative pericarditis (two patients), tuberculous lymphadenitis (two patients), cerebral toxoplasmosis (one patient), progressive multifocal leucoencephalopathy (PML) (one patient), inflamed molluscum (one patient), inflamed *Candida albicans* angular cheilitis (three patients), genital herpes simplex (two patients), tinea corporis (two patients), cytomegalovirus (CMV) retinitis (two patients), CMV vitritis (one patient) and hepatitis B (three patients) or C (fifteen patients). A baseline CD4 T-cell count below 100 cells/μL was shown to be the single predictor [odds ratio (OR) 2.5, 95% confidence interval (CI) 0.9–6.4] of IRD, while a CD4 T-cell count increase to >400 cells/μL, but not undetectable pVL, was a negative predictor of IRD (OR 0.3, 95% CI 0.1–0.8).

Conclusions

To avoid IRD in advanced patients, HAART should be initiated before the CD4 T-cell count falls below 100 cells/μL.

Keywords: HAART, HIV, immune restoration disease

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Introduction

The major advance in HIV disease treatment coincided with the introduction of highly active antiretroviral therapy (HAART) in 1996. HAART protocols comprised two nucleoside reverse transcriptase inhibitors (NRTIs) and an HIV protease inhibitor (PI), a rather complicated regimen, but potent enough for complete and prolonged cessation of viral replication to allow reconstitution of the immune system. It has even been possible to achieve immune recovery in terminally ill patients. An overall reduction in late-stage complications of HIV infection, including death, dramatically decreased the number of hospital admissions, and an impressive improvement in the quality of life became obvious.

Correspondence: Dr Olgica Djurković-Djaković, Institute for Medical Research, Dr. Subotića 4, PO Box 102, 11000 Belgrade, Serbia and Montenegro. E-mail: olgicadj@imi.bg.ac.yu

However, although many patients continue to derive substantial benefit from HAART after 5–6 years of treatment, we are now facing the other side of the medal. Cumulative long-term toxicity and the problem of the development of HIV resistance to all drug classes are threatening to jeopardize the treatment benefits. In addition, over the past few years there have been growing numbers of cases of opportunistic infections (OIs) in patients on HAART. The common denominator in all these cases was paradoxical symptomatic deterioration of presumably pre-existing subclinical infections that became symptomatic after the recovery of the immune response and the consequent inflammatory response to certain pathogens [1,2]. In this setting, numerous authors described conditions including dermatomal herpes zoster, tuberculous lymphadenitis, inflamed molluscum, inflamed *Candida albicans* angular cheilitis, genital herpes, tinea corporis, hepatitis B or C virus (HBV or HCV) infection, and even *Toxoplasma gondii* encephalitis, as well as cryptococcal meningitis and progressive multifocal leucoencephalopathy (PML) [1–11], most commonly referred to as immune restoration disease (IRD). While the distinction between immunodeficiency-related OIs and IRD is not clear, it is becoming accepted that the appearance of clinical OIs at a time of restored immune functions should be classified as IRD [12].

The majority of HIV-infected patients in Serbia have advanced immunodeficiency on presentation. Even these deeply immunosuppressed patients may achieve a good virological and immunological response while on HAART, as well as clinically apparent restoration of the immune function. However, immune restoration may be associated with the development of OIs, some of which may be AIDS-defining and life-threatening [1–5]. These conditions are referred to as IRD. We examined the risks of developing OI/IRD in our patients during successful HAART.

Methods

Patients

A retrospective study of all 389 HIV-positive patients treated with HAART at the HIV/AIDS Department of the Institute of Infectious and Tropical Diseases in Belgrade between 1 January 1998 and 31 May 2004 was conducted. The patient series consisted of 39.7% females and 60.3% males. The mean age was 41 ± 10 years (range 16–78 years). All patients were diagnosed according to the 1993 revised CDC HIV classification system and expanded AIDS surveillance definition for adolescents and adults.

Over half (55.3%) of the patients were pretreated with monotherapy or dual regimens. HAART regimens were defined as combinations of two or three NRTIs, with one or two PIs (in 64% of all patients), or one nonnucleoside reverse transcriptase inhibitor (NNRTI). Dual *Pneumoeystis carinii* pneumonia (PCP) and toxoplasmosis primary prophylaxis was withdrawn after patients achieved a sustained immune response (CD4 cell count $>$ 200 cells/μL).

After commencing HAART, clinical evaluation was performed at least once every 2 months.

Herpes zoster, inflamed molluscum, tinea corporis, genital herpes, and angulus infectiosus were all diagnosed by skin or mouth examination. For cerebral toxoplasmosis and PML, clinical and neuroradiological presentations were the clue to the diagnosis. *T. gondii* serology was routinely performed. However, virological confirmation for PML, such as cerebrospinal fluid JC virus (JCV) immunoglobulin M (IgM) antibodies or PCR for JCV, was not available. Cryptococcal menigitis was diagnosed according to the clinical presentation and CSF findings, including Indian ink stain and CSF culture. Tuberculosis was diagnosed on the basis of clinical, radiographic and microbiological confirmation. In patients who suffered coinfection of HIV with HBV or HCV, the aggravation of hepatitis was defined as an increase in alanine aminotransferase (ALT) activity of at least 5-fold above the upper limit of the reference range. Cytomegalovirus (CMV) retinitis relapse and vitritis were diagnosed according to typical symptoms and fundoscopy findings.

Laboratory methods

CD4 cell counts and viral loads were measured on peripheral blood samples drawn at baseline (immediately before HAART initiation) and every 4–6 months during follow-up. CD4 T-cell counts were quantified by flow cytometry. Plasma HIV-1 RNA loads were measured by a quantitative reverse transcriptase PCR (Ultrasensitive assay version 1.5, Roche Molecular Systems, Branchburg, NJ, USA), which has a lower limit of detection of 50 copies/mL (1.7 $\log_{10}$).

Statistics

All analyses were performed using an electronic database organized with the SPSS (version 11.5) statistical package (SPSS Inc., Chicago, IL, USA). CD4 cell count and plasma viral load means were compared by one-way analysis of variance (ANOVA). The level of significance was 0.05. The association between IRD development and variables such as basic and follow-up CD4 cell counts and plasma viral loads, as well as other possibly related variables, was

assessed using univariate and step-wise multivariate regression models, and the Cox regression model. Results are presented as odds ratios (ORs) with 95% confidence intervals (95% CIs).

Results

Baseline characteristics

Of the total of 389 patients, 87.3% had AIDS (CDC stages A3–C3) before HAART was initiated. The baseline CD4 cell count was below 100 cells/μL in 61.8% of patients, with a mean of 108.2 ± 92.8 cells/μL (range 0–450 cells/μL). The median plasma viral load was 4.6 log copies/mL before treatment.

Treatment effects

After a mean duration of treatment of 34.7 ± 24.4 months, the mean CD4 cell count in the whole patient series was 375 ± 240 cells/μL, while 37.2% of patients reached a value of above 400 cells/μL. In 76.8% of patients, the viral load fell below 50 copies/mL (1.7 log). However, the most desirable response to treatment, considered to be a rise in the CD4 cell count of $\geq$400 cells/μL, along with a plasma viral load of below 50 copies/mL, occurred in 44.6% of patients.

Subgroup of OI/IRD patients

Clinical findings

At least one IRD episode occurred in 65 patients (16.7%). The median time on HAART to IRD was 4.6 months, with a range of 2–12 months. These included episodes of dermatomal herpes zoster (26 patients), pulmonary tuberculosis (four patients), tuberculous exudative pericarditis (two patients), tuberculous lymphadenitis (two patients), cerebral toxoplasmosis (one patient), PML (one patient), inflamed molluscum (one patient), inflamed *C. albicans* angular cheilitis (three patients), genital herpes simplex (two patients), tinea corporis (two patients), CMV retinitis (two patients), CMV vitritis (one patient) and HBV (three patients) or HCV (fifteen patients) infection. In the patients with tuberculosis, cerebral toxoplasmosis and cryptococcosis as manifestations of IRD, symptoms and signs occurred after early initiation of HAART, before withdrawal of antimicrobial therapy. In the case of inflamed molluscum, aggravation of skin lesions also occurred soon after HAART initiation. Genital herpes, angular cheilitis, and herpes zoster and warts occurred *de novo*. Aggravation of hepatitis was associated with clinical disease in only two cases, both of HCV infection, of which one female patient with HCV-induced cirrhosis died of liver failure. In a patient who experienced immune recovery vitritis, the sight-threatening vitreomacular traction syndrome and detachment of the retina occurred, which did not resolve during 2 years of successful HAART.

Response to HAART: laboratory findings

In the subgroup of IRD patients, the mean CD4 cell count during HAART rose from 106 ± 104 to 337 ± 219 cells/μL. The median plasma viral load simultaneously decreased by >1 log copies/mL (from the initial 4.6 to 2.1 ± 0.8 $\log_{10}$ copies/mL), with 80% of patients reaching undetectable viraemia. However, the median CD4 count increase and the median plasma viral load decrease were similar to those in the non-IRD patients ($P = 0.6$ and $P = 0.7$, respectively).

IRD risk assessment

Multivariate logistic regression analysis showed that, of all the examined factors, including age over 40 years, gender, AIDS-related OIs prior to HAART, pretreatment with mono and/or dual antiretroviral regimens, and baseline CD4 count below 100 cells/μL, the latter was the only predictor of IRD (OR 2.5, 95% CI 0.9–6.4). However, the Cox regression model showed that achievement of a rise in the CD4 cell count to above 400 cells/μL, but not undetectable viraemia, was a negative predictor of IRD (OR 0.3, 95% CI 0.1–0.8).

IRD management

Anti-infective therapy was used to treat IRD when needed, to which all patients responded well, with the exception of one fatal case of HCV infection, as described above. During such treatment, HAART was temporarily withdrawn, mostly because of potential unfavourable drug–drug interactions. Corticosteroids or other anti-inflammatory drugs were not used to treat IRD. After IRD resolution, patients continued HAART successfully.

Discussion

Numerous studies have shown that HAART corrects many of the immune defects caused by HIV infection [12–14]. Restored pathogen-specific immune responses may result in regression or prevention of OIs [13–16]. However, the restoration of pathogen-specific immune responses may also cause inflammation of tissues infected by the pathogen, known as IRD [1–12]. Thus, the major question in the setting of HAART-treated HIV disease is whether a clinical OI is immunodeficiency-related or an IRD, because the appearance of OIs among HIV-infected patients on HAART always raises the concern of possible HAART failure. Attempts at solving this problem resulted in the first proposal of criteria for the diagnosis of IRD

[12], which include, in addition to precise clinical findings, success of HAART, where virological success is considered a major criterion and an increased blood CD4 cell count a minor criterion.

In our patient series, all 65 OI episodes fulfilled the above criteria for the clinical OI to be defined as IRD, as significant immunological and virological improvement was documented. Hence, the incidence of IRD in our series was 16.7%. This is in sharp contrast with the study of Michelet *et al.* [6], who reported that 68% of patients exhibited one or more disease episodes after successful HAART. One reason for the lower incidence in our study may be that our series included patients observed over a rather long period of over 6 years; at the beginning of this period (1998), the IRD syndrome was not well known, so some OIs as IRDs may have been overlooked because symptoms had not been searched for, while some infections of possible IRD origin had been considered HIV-related OIs. However, our results are not in disagreement with those of French *et al.* [3], who reported that 25% of HAART-treated patients developed IRD episodes after commencing HAART, all related to pre-existing subclinical infections with opportunistic pathogens. The IRD episodes were more common in patients with a baseline CD4 count of less than 50 cells/μL [3]. We also showed that a low baseline CD4 count represents a risk factor for IRD. These data indicate the need for earlier HAART initiation.

In conclusion, with the wide use of HAART in AIDS patients, the frequency of IRD may be expected to increase. IRD should particularly be considered during the first 12 months following HAART initiation. We showed that the likelihood of developing IRD was elevated in those who commenced HAART at an advanced stage of HIV disease and, conversely, extremely low in patients who achieved CD4 cell count rises to above 400 cells/μL. Thus, any effort to decrease the incidence of IRD should include HAART initiation before the disease has reached an advanced stage, i.e. before the CD4 cell counts have fallen below 100 cells/μL. In patients with OIs as a consequence of HIV-induced immunodeficiency, it seems wise to complete antimicrobial therapy before commencing HAART.

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