DISCORDANT IMMUNOLOGICAL AND VIROLOGICAL RESPONSE TO HAART THERAPY IN HIV-INFECTED PATIENTS

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The goals of highly active antiretroviral therapy (HAART - administration of 2 INRT/NNRT + 1 - 2IP) are the reduction of plasma HIV - RNA levels, the immune reconstitution - increasing the number of CD4 cells and a favorable clinical outcome.

The thesis consists of two main parts: a general part and personal contributions. The general part presents discussions about immunity in HIV infection, the highly active antiretroviral treatment (HAART) and the monitoring of this therapy.

The second part comprises two studies. The first study is a retrospective, clinical observational study, performed in the Infectious Diseases Clinic in Tg. Mures. One lot of study was formed by 144 HIV infected patients, 7-42 years old, under HAART (2 INRT + 1 - 2 IP), with CD4 cell count and HIV RNA plasma level determination in the Molecular Biology Laboratory of the Infectious Diseases Clinic in Tg. Mures. The CD4 cell count was assessed by flow cytometry (Becton Dickinson), the virus load was measured with the use of commercial quantitative PCR technique (LCx HIV-RNA Quantitative –Abbott and COBAS AMPLICOR HIV -1 MONITOR Test, v1.5).

On the basis of immunological and virological responses, patients were classified into four groups: complete response (CD4 cell increase and plasma HIV - RNA level decrease –I+V+), complete nonresponse (CD4 cell decrease and plasma HIV - RNA increase –I-V-), immunological response only (CD4 cell increase with plasma HIV - RNA level increase-I+V+) and virological response only (plasma HIV - RNA level decrease without CD4 cell level increase-I-V+).

The objective of this study is:

- to evaluate the frequency and possible predictive factors of discordant immunological and virological response: the age of patients, the total number of administered ARV, the number of INRT, INNRT and IP administered, the duration of treatment in months and the frequency of resistance mutations.
• Find characteristics of and compare both ARV naïve and pretreated groups;
• Find characteristics of both children and adults groups;

We observed a wide range of CD4 cell/plasma HIV-RNA levels; 38.19% of patients had complete response with increase in CD4 cell count and decrease in viral plasma load, 30.55% had discordant virological response, 9.72% had discordant immunological response and 22.9% had non-response.

The discordant immunological response was the most frequent in the children with initially elevated CD4 cell counts. At the end of the study, the patients of this group had relatively low numbers of CD4 cells and a prolonged ARV treatment with a decreased number of administered INRT.

The patients from the discordant virological response group had an initial low number of CD4 cells which was elevated at the end of the study, a decreased number of administered ARV, IP and elevated number of administered INRT. The initial viral load was the most elevated in this group with the most important decrease within the four studied lots.

The complete response group had the most elevated increase in CD4 cells by the end of the study, shortened-time ARV therapy, reduced numbers of administered ARV, INRT and IP.

The complete non-response group had an initially elevated number of CD4 cells, which were finally reduced. The viral load had initially reduced values which were extremely elevated at the end of the study. The number of total administered ARV is the most elevated in this group, with an elevated number of administered INRT, and the longest duration of treatment.

The importance of discordant responses is much discussed in medicine but in many cases they are considered non-response. Although during the study there have been inconveniences related to modified therapeutic regimens, to antiretroviral drugs that have been used, or to low compliance in some cases, on the basis of statistical differences that we observed between the discordant response and non-response groups, we considered that the two types of discordant response to antiretroviral therapy represent two different ways of disease evolution and not non-responses.

The second study tries to determine the frequency of resistance mutations in patients treated in Mures Regional Center of HIV Infection.

We included 24 patients with HIV infection in our study. The resistance testing was performed by viral genotyping in the Laboratory of Molecular Diagnosis of Infectious Diseases Institute.
“Prof. Matei Bals”, Bucharest. We also followed the age, the gender, the provenience of patients and the number of modifications in Cd4 and CD8 lymphocytes and viral load before and after the testing.

We observed an increase in number of CD4, CD8 lymphocytes, in the CD4/CD8 ratio and a decrease in viral load. The most frequent mutations of resistance were: M148V, M41L, T215Y, D67N, K70R, Y181C, K103N in the RT gene and L10I, I54V, L10V, K20R, M36I, V82A in the PR gene. We observed a great number of cases of resistance/intermediate sensitivity for the following drugs: IDV, RTV, DLV, EFV, NVP, AYT, ABC, NFV, ddC and SQV.