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Cartesian coordinate analysis of viral burden and CD4 + cell count in HIV disease: implications for clinical trial design and analysis

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Abstract

HIV-1 infection represents a dynamic interaction between the rapid turnover of virus, CD4 + cell proliferation and clearance. HIV-1 disease progression is assessed, in part, by the inverse relationship between virus burden and CD4 + cell count. However, there is enormous individual subject variability between virus burden in the peripheral blood and CD4 + cell count with subsequent disease progression, suggesting that there must be virologic and immunologic modifiers of the inverse relationship between virus load and CD4 + cell count. To investigate these modifiers, we have used a Cartesian coordinate plot analysis to describe the inverse relationship between viral burden and the peripheral blood CD4 + cell count. Subjects from several clinical studies with CD4 + cell counts ranging from < 50 to > 600 cells/μL and varying viral burdens were studied. The analysis described the effect of various virologic and immunologic modifiers on this inverse relationship, for example, viral resistance, viral phenotype and the effect of very low CD4 + cell counts, and specifically addressed individual subject variation in assessing the association between the viral and immunologic parameters that define disease progression and response to antiretroviral therapy. As such, the Cartesian coordinate plot analysis method provides one approach to investigating the individual subject response to antiretroviral therapy.

Keywords: Viral burden; CD4 + cell; Cartesian coordinate plot; Individual therapy response; Virologic response modifier; Immunologic response modifier; Clinical trial design

1. Introduction

Although the inverse relationship between viral burden and CD4 + cell count is established, only recently has the dynamic interaction between viral

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replication and CD4+ cell decline been described (Ho et al., 1995; Wei et al., 1995). As such, there is a need to apply this information to the analysis of data obtained from clinical trials of antiretroviral therapies. Others have described the diversity of HIV-1 and the relationship to immunologic containment (de Boer and Boerlijst, 1994) and the development of drug resistance (Coffin, 1995). However, there has not been an integrated analysis that includes the dynamic steady state relationship between viral replication and CD4+ cell loss, which includes both virologic and immunologic factors that may modify this dynamic state.

2. Materials and methods

We analyzed data from four AIDS Clinical Trials Group protocols (ACTG 229, 194, 143 and 116B/117) and a natural history study conducted at the University of Washington (Cavert et al., 1995; Fiscus et al., 1995; Hooper et al., 1994a; Hooper et al., 1994b; Paxton et al., 1995). Measures of CD4+ cell count and virus burden (quantitative microculture and plasma HIV-1 RNA) were $\log_{10}$ transformed and the relative changes in these measures were used for the analysis.

3. Results

The total number of CD4+ cells at a given point in time describes the relationship between CD4+ cell number, CD4-proliferation, virus burden and virologic response modifiers (de Boer and Boerlijst, 1994). This relationship is described by equation (1) which is the basis for our Cartesian coordinate plot analysis. This equation is predicated on the inverse correlation between the CD4+ cell count and the virus burden (Schnittman et al., 1990) and assumes that change in one correlates inversely with change in the other (Fiscus et al., 1995; Ho et al., 1995; Wei et al., 1995). The total number of CD4+ cells at a given point in time [CD4(T)] is proportional to the difference between the CD4-positive cell proliferation [CD4(P)] less the death of the cells associated with the multiplicative effect of viral burden [CD4(L)] and virologic response modifiers (V). Both CD4(P) and (V) are dimensionless but weighted for the degree of proliferation or modification that reflects the relative hazard of disease progression.

Equation 1: $CD4(T) = CD4(P) - [CD4(L) \cdot (V)]$

When log transformed, equation (1) describes a four-quadrant coordinate plot in which antiviral activity is defined independently of pathogenesis; i.e. the influence of change in log virus load (x-axis) is defined relative to the change in log CD4-positive cell count (y-axis) (Fig. 1).

Quadrants A ($x-$, $y+$) and D ($x+$, $y-$) define the effect of a change in virus load on the change in CD4-cell count; quadrants B ($x+$, $y+$) and C ($x-$, $y-$) respectively define the nullifying effect of either (i) decreased or increased virologic response modifiers or (ii) increased or decreased CD4-proliferation on the change in virus load. The antiretroviral response is best assessed at higher viral loads in the diagonal AD while the influence of pathogenetic (e.g. viral phenotype or immunologic) or other factors on this response is assess by the diagonal BC.

4. Discussion

There are several advantages to the Cartesian coordinate plot for analyzing the CD4+ cell response to antiretroviral therapy. First, it offers a simplified graphical approach to understand the proportional distribution of individual patient data between different response quadrants for several different clinical studies. Patients are distinguished by their distribution into one of four possible outcomes despite small sample sizes, thus allowing for a simple categorical analysis. Second, it identifies the optimal therapeutic response profile (i.e. quadrant A) for each patient regardless of the influence of either virologic response modifiers or type of therapy. Third, it allows for data analysis of antiviral activity without a full understanding of the potentially complex interac-

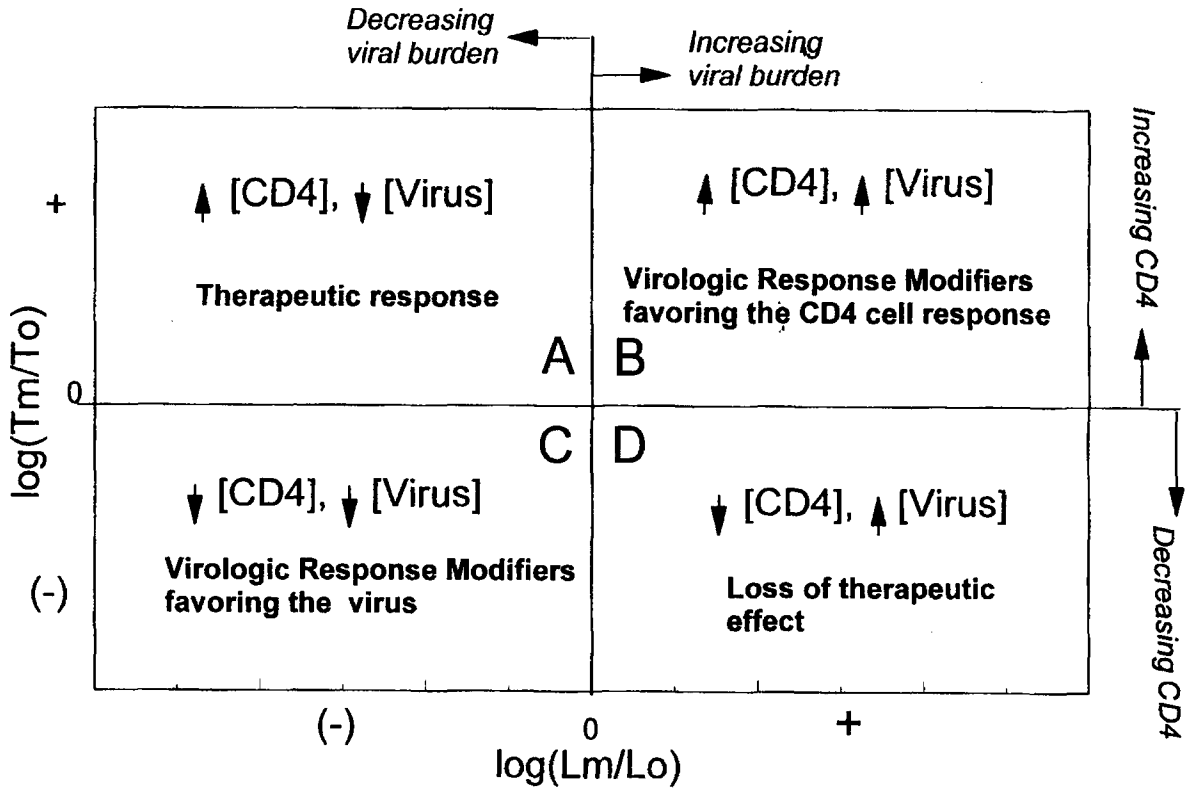

Fig. 1. Schematic of equation (1) showing the relationship between relative change in CD4-positive cell count and HIV-1 burden, and effect of virologic response modifiers and CD4-proliferation rate on the assessment of antiretroviral response. The x-axis represents the relative log change in measurement of virus burden between two time points [log (L_m/L_o)]; the y-axis represents the relative log change in measurement of CD4 + cell count between the same two time points [log (T_m/T_o)]. Quadrants A, B, C and D catalogue the predicted outcomes between the change in virus burden and CD4 + cell count for subjects receiving antiretroviral therapy. In quadrants A and D, change in virus burden and neither virulence nor CD4-proliferation is the predominant factor driving the inverse change in CD4-positive cell count; in quadrants B and C, viral response modifiers or CD4-proliferation or both, rather than the change in virus burden, influence the change in CD4-positive cell count. A positive response to antiretroviral therapy, as defined by both a decrease in the viral burden and an increase in the CD4 + cell count, is indicated by a shift from quadrant D to A while a negative response is indicated by a shift from quadrant A to D.

tions between the various virologic and immunologic factors that define HIV-1 disease; e.g. the shift between quadrants D and A without regard to the influence of quadrants B and C. Fourth, it defines the pathogenetic contribution of virologic response modifiers without a full understanding of their individual contributions.

In summary, the Cartesian coordinate plot categorizes the results of natural history studies, the effect of antiretroviral therapy, the differential effect of therapies, the effect of a virologic response modifiers (such as syncytium-inducing phenotype or antiretroviral drug resistance), and the effect of lower-limit CD4-cell and viral thresholds. As such, this analysis method has a potential application to the design of clinical trials and the individualized patient management of antiretroviral therapy.

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