Untangling the Immunological Implications of Nadir on CD4+ Cell Recovery during Suppressive Highly Active Antiretroviral Therapy

To the Editor—Moore et al. [1] recently described a significant difference in CD4+ cell recovery following HIV RNA suppression among patients receiving HAART according to nadir CD4+ cell count, with individuals whose nadir CD4+ cell counts were <200 cells/μL not achieving a protective CD4+ cell count.

A lack of CD4+ cell rescue despite complete HAART-driven viremia suppression represents an everyday dilemma for HIV/AIDS clinicians [2]. Invariably, CD4+ cell count nadir proved to be a major and reliable determinant of suboptimal CD4+ cell recovery and clinical outcome [1–8]. However, the mere quantification of CD4+ cell count nadir fails to qualitatively estimate the ultimate immunological mechanism(s) hindering CD4+ cell rescue. Only by detailing the immunological holes in nadir-driven T cell homeostasis will it be possible to devise the most efficacious treatment approach.

By limiting immune recovery assessment to total CD4+ cell count in a large patient cohort, Moore et al. [1], although gaining statistical power, miss an insight into the immunological role of CD4+ cell count nadir. On the contrary, we feel that stringently focused studies are needed that address the time course of specific immune pathways by nadir CD4+ cell count strata. It would be interesting to know whether the authors have found distinct dynamics in immunophenotype and other immunologic parameters according to CD4+ cell count ranges.

Given their major regulatory role in T cell homeostasis, common γ-chain cytokines, including IL-2, IL-7, IL-15, and IL-21 [9], might be ideal markers of the direction of immune recovery. Thus, although Moore et al. [1] recommend HAART initiation at a CD4+ cell count >350 cells/μL for the most robust immune recovery, we advocate a broad immunologic investigation of regulatory cytokine networks to obtain an indication of pretherapy immune damage and CD4+ cell rescue potential, as well as possible clinical relapses.

As an example of the exploitation of γ-chain cytokine kinetics, we would like to share our experience with the IL-7 and IL-7R system [10] in a cohort of 18 antiretroviral-naive, HIV-positive patients with advanced infection (nadir CD4+ cell count <150 cells/μL) whom we observed prospectively for the first 12 months of HAART. These patients displayed different virological and immunological responses to HAART: 12 patients had concordant responses (HIV RNA level, ≤50 copies/mL; CD4+ cell count, ≥200 cells/μL), and 6 patients had discordant responses (HIV RNA level, ≥50 copies/mL; CD4+ cell count, ≤200 cells/μL). Despite having a higher median baseline plasma IL-7 level than that for patients with concordant responses, patients with discordant responses had a tendency toward reduced CD4+ cell count and lower IL-7Rα availability, which, by indicating free IL-7 mainly resulting from receptor down-modulation rather than compensatory production, also rules out a functional potential on T cell homeostasis. In fact, during HAART, despite a progressive reduction in IL-7, only patients with discordant responses displayed a substantial increase in CD4+ cell and IL-7Rα expression. These findings, by clearly pointing to opposite IL-7 and IL-7R dynamics, also indicate that a lack of IL-7 and IL-7R regulatory control over CD4+ cell homeostasis could be the basis of discordant responses, which cautions against IL-7–based treatment.

In conclusion, it is time to investigate the early integration of classic quantitative determinations of CD4+ cell count nadir proposed by Moore et al. [1] with additional qualitative measures of CD4+ cell count nadir–associated immune imbalances. The effort should be to highlight the immunological role of CD4+ cell count nadir, not only as a quantitative reflection of T cell depletion, but mainly as evidence of more-complex T cell qualitative impairment. The intriguing hypothesis that a lack of IL-7– and IL-7R–mediated regulatory function is behind discordant responses in antiretroviral-naive patients with advanced infection clearly indicates the complexity of the immunopathogenetic mechanisms of CD4+ cell immune recovery. The possibility of monitoring major T cell homeostasis regulators, such as γ-chain cytokines, by possibly disclosing upstream breakdown offers the appealing prospect of targeted immune interventions.

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Laurenza Ferraris,1 Giusi Maria Bellisti,2 Valentina Pegorer,2 Camilla Tincati,2 Luca Meroni,1 Massimo Galli,1 Antonella d’Arminio Monforte,2 Andrea Gori,3 and Giulia Marchetti2

1Department of Clinical Sciences, “Luigi Sacco” Hospital, and 2Department of Medicine, Surgery and Dentistry, Clinic of Infectious Diseases, “San Paolo” Hospital, University of Milan, Milan, and 3Division of Infectious Diseases, “San Gerardo” Hospital, Monza, Italy

References


Interstrain Antigenic Variability of Mumps Viruses

To the Editor—We would like to congratulate Peltola et al. [1] on their excellent review. As the authors emphasize, protection from clinical disease is not perfect, even after 2 doses of mumps component vaccine; both primary and secondary vaccine failure were discussed as potential reasons. Another possibility for lack of protection after mumps vaccination (and wild-type virus infection) is the existence of heterologous mumps viruses that may escape immune protection because of interstrain antigenic variability [2, 3]. Here, we report 3 such laboratory-confirmed cases of symptomatic mumps virus infection in patients with documented pre-existing immunity.

The first case occurred in a 12-year-old girl who had received 2 mumps vaccinations (with Jeryl-Lynn vaccine strain in both July 1990 and April 1997) and presented with a lymphadenitis colli. At that time, antimumps IgG antibodies were determined in a serum specimen (IgG antibody concentration, 1400 IU/mL; IgM antibody negative). Two weeks later, bilateral parotid swelling appeared; a second ELISA performed in the same laboratory revealed a 17-fold increase in antimumps IgG antibody concentration to 24,000 IU/mL (IgM antibody negative).

The second case occurred in a 9-year-old boy who had received 2 documented mumps vaccinations (with Rubini vaccine strain in July 1995 and with Jeryl-Lynn vaccine strain in March 2000) and presented with acute bilateral parotid swelling; his antimumps IgG antibody concentration was 2900 IU/mL (IgM antibody negative). Four weeks later, convalescent-phase serologic examination revealed a