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Abacavir and cardiovascular risk in HIV-infected patients: does T-lymphocyte hyperactivation exert a pathogenic role?

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Purpose of the study

The association between abacavir exposure and cardiovascular disease (CVD) in HIV-infected patients is currently intensely debated. Recently, the D:A:D Study Group described increased myocardial infarction risk in patients with current/recent abacavir exposure, while repository data from GlaxoSmithKline clinical trials failed to find any association. Given the association between lymphocyte hyperactivation and CVD, and the major role of T-cell hyperactivation in HIV/AIDS, the purpose of our study was to investigate T-cell immunephenotype and proinflammatory cytokines kinetics in HIV-infected patients receiving abacavir-containing regimens.

Methods

Peripheral T-cell immunephenotype and proinflammatory cytokines were evaluated in 11 HIV-infected patients starting on an abacavir-containing HAART at baseline, 3 and 6 months. In particular, the following subpopulations were quantified by flow cytometry: CD38+CD8+, CD95+CD4+ and CD8+, CD127+CD8+. IL-6 and TNF-alpha plasma levels were quantified by ELISA. During abacavir treatment, all the patients underwent ultrasonography of carotid and femoral vessels to evaluate intima-media thickness (IMT).

Summary of results

Major results are shown in Table 1. We observed a significant rise in activated CD38+CD8+ ($p < 0.01$), and a reduction in CD95+CD4+ and CD8+ ($p < 0.01$), suggesting CD95 internalization on apoptosis-committed T-cells. A non-significant contraction of central memory CD127+CD8+ was shown, with no changes in plasma IL-6 and TNF-alpha ($p > 0.05$). Interestingly, during abacavir treatment all patients displayed carotid/femoral thickening involving at least one site.

Conclusion

While significantly reconstituting total CD4+, abacavir resulted in significant expansion of activated/senescent/pro-apoptotic T-cell subsets associated to vascular damage. Analogously to other drug-toxicity models, a specific interference of abacavir with purine signaling pathways might be speculated, leading to impairment of lymphocyte activation. By suggesting T-lymphocye hyperactivation as relevant in the pathogenesis of abacavir-related CVD, these data, albeit preliminary, advocate thorough assessment of possible immunologic biomarkers of abacavir-related cardiovascular damage.

Table 1:

Characteristic (n = 12)	T0	T3	T6
Age, years	50 (33–67)	NA	NA
Current smoking, n	3/12	NA	NA
Male/Female, n	9/3	NA	NA
Current CD4 cells/μL	312 (91–1650)	348 (132–1664)	476 (234–1908)
Current CD4 %	25 (7–55)	24 (11–52)	26 (21–53)
CD38+CD8+ %	1 (0–47)	1 (1–4)	2 (1–3)
CD38+CD8+ n	21 (0–42)	23 (10–69)	33 (12–46)
CD95+CD4+ %	2 (1–9)	1 (0–4)	1 (1–1)
CD95+CD4+ n	26 (12–270)	21 (0–42)	19 (12–36)
CD95+CD8+ %	2 (1–10)	2 (1–6)	1 (1–2)
CD95+CD8+ n	31 (17–130)	30 (14–63)	22 (13–36)
CD127+CD8+ %	14 (9–24)	13 (5–28)	12 (5–25)
CD127+CD8+ n	269 (78–480)	208 (65–588)	218 (75–580)
TNF-alpha, pg/ml	2.7 (0.9–5.1)	ND	2.6 (1.7–8.9)
IL-6, pg/ml	1.4 (0–6.5)	ND	1.4 (0.5–3)
Total cholesterol, mg/dL	225 (154–301)	246 (159–339)	241 (186–366)
LDL cholesterol, mg/dL	133 (76–401)	50 (82–505)	53 (32–74)
Tryglicerides, mg/dL	136 (90–571)	169 (36–923)	227 (132–1137)
Homocysteinemia, mg/dL	12 (4.6–23.5)	ND	11 (3.4–17.4)
IMT, mm right carotid	ND	ND	0.99 (0.79–1.49)
IMT, mm left carotid	ND	ND	0.99 (0.82–1.61)
IMT, mm right femoral	ND	ND	0.96 (0.83–1.24)
IMT, mm left femoral	ND	ND	1.01 (0.92–1.75)
Current HIV-RNA, Log10/mL	1,77 (1,77–4,3)	1,77 (1,77–2.4)	1,77 (1,77–3.9)