Treatment with tyrosine kinase inhibitors makes PBMCs from patients with chronic myeloid leukemia less susceptible to HIV-1 infection: control of CD4+ T cell activation to control HIV-1 replication

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CONCLUSIONS

• PBMCs from CML patients on chronic treatment with TKIs showed resistance to SAMHD1 phosphorylation and proviral integration after activation with PHA/IL-2.
• Dasatinib was the most potent against HIV-1 replication, closely followed by ponatinib. Dasatinib showed the best therapeutic index.
• Treatment with both TKIs interfered with CD4+ T cell activation and proliferation induced by several physiological stimuli, impeding HIV-1 replication.
• Dasatinib could reduce the number of infected cells, and therefore control the reservoir size, by blocking the homeostatic proliferation.

BACKGROUND

• Tyrosine kinase inhibitors (TKIs) are currently used for treating chronic myeloid leukemia (CML).
• Imatinib is very selective against the chimeric fusion protein BCR-ABL responsible for causing CML. Second generation nilotinib, dasatinib and bosutinib are 20-, 100- and 200-fold more potent than imatinib against BCR-ABL, respectively. Third generation ponatinib has been approved for CML patients resistant to other TKIs.
• TKIs, and particularly dasatinib, provide an interesting antiretroviral tool due to a direct effect through the inhibition of SAMHD1 phosphorylation and consequently, of proviral integration, and through the inhibition of the clonal expansion of the infected cells due to its cytostatic effect.
• We have proposed that the use of TKI together with ART can decrease the replenishment of reservoirs through the enhancement of SAMHD1 activity and decreased CD4 activation.
Coiras et al., Expert Opin Drug Saf. 2017;16(5):547-559

OBJECTIVE

To determine which TKI could be the better choice to be used as adjuvant of antiretroviral treatment against HIV-1 infection

MATERIAL & METHODS

• PBMCs isolated from 42 CML patients on treatment with imatinib, nilotinib, dasatinib, bosutinib or ponatinib.
• PBMCs isolated from 44 healthy controls.
• All patients were treated for >2 years with usual TKI dose; they showed no HIV-1 infection, normal lymphocyte count, clinical and hematological remission, and no toxicity related to the current TKI

RESULTS

1 IC50 for inhibiting HIV-1 replication was calculated in vitro for each TKI

2 PBMCs from CML patients showed lower SAMHD1 phosphorylation after PHA/IL-2 treatment for 5 days (p<0.0001 for dasatinib; p<0.01 for bosutinib).

3 Ex vivo infection of PBMCs from CML patients showed that proviral integration was inhibited after treatment with all TKIs, being dasatinib the most significant (p<0.01).

4 TKIs interfered differently with CD4+ T cell proliferation induced by several stimuli (PHA/IL-2, anti-CD3/CD28/IL-2, IL-2 or IL-7), being dasatinib and ponatinib able to interfere with CD4+ T cell activation in all cases.

CD4+ T cells from healthy donors were treated with different stimuli and incubated with CFSE to analyze the generations produced during proliferation.