Baracitinib, ruxolitinib, dasatinib block HIV replication, activation, reactivation

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Background

HIV-induced activation/inflammation is associated with HIV persistence/ reactivation, and is a predictor of morbidity in HIV-infected individuals. HIV-induced activation of myeloid cells promotes trafficking of infected cells to the CNS, and is associated with HIV-induced neurocognitive impairments and HIV-associated dementia. Jak-STAT pathway and tyrosine kinases are activated in macrophages and lymphocytes upon HIV-1 infection, representing attractive cellular targets. As ruxolitinib and baracitinib are Jak1/2 inhibitors either FDA approved or in late phase 3 clinical investigation for myelofibrosis or arthritis respectively, and dasatinib is FDA approved for myeloid malignancies, we evaluated their ability to block 1) HIV replication in primary human macrophages, 2) HIV-induced activation in primary human monocytes and macrophages, and 3) reactivation of latent HIV in T cells.

Methods

Macrophages were treated with various concentrations of ruxolitinib, baracitinib, or dasatinib for 2hr prior to infection (HIV-1_{bal}). Cells were maintained for 6 days before viral quantification (p24-ELISA). Macrophages or monocytes were treated with various concentrations of drug prior to infection (HIV-1_{bal}) and maintained for 3 or 6 days before quantification of HLA-DR, CD163, CCR5 (macrophages), or CD14/CD16 (monocytes). Macrophages and monocytes were treated with various concentrations of drug for 6 days and stained with Near-IR live/dead dye and quantified by FACS. J-lat latent T cells were treated with various concentrations of drug plus TNF-alpha and reactivation was quantified by GFP reporter 24 hr post induction.

Results

Antiviral potency and toxicity of baracitinib, ruxolitinib, and dasatinib in primary human macrophages

Compound	Anti-HIV-1 EC_{50} in acutely infected human macrophages (μM)	Anti-HIV-1 EC_{90} in acutely infected human macrophages (μM)	IC_{50} in primary human macrophages (μM)
Baracitinib	0.3 ± 0.4	3.0 ± 0.6	> 50
Ruxolitinib	0.3 ± 0.1	3.1 ± 1.8	> 50
Dasatinib	0.001 ± 0.007	0.04 ± 0.07	36.4 ± 5.2
AZT	0.01 ± 0.02	0.07 ± 0.12	> 50

Table 1. Antiviral potency and toxicity of baracitinib, ruxolitinib, and dasatinib in primary human lymphocytes and macrophages. Ruxolitinib, baracitinib, and dasatinib were not cytotoxic (>50 μM for ruxolitinib/baracitinib; ~ 20 μM) in primary human macrophages, and antiviral potency ranging from 0.001-0.3μM in macrophages. As expected, AZT control demonstrated submicromolar antiviral potency. Data are mean and standard deviations calculated from at least 4 independent experiments, with pooled cells from four donors and duplicates in each experiment.

Inhibition of reactivation of latent HIV-1 in J-lat latent T cell model

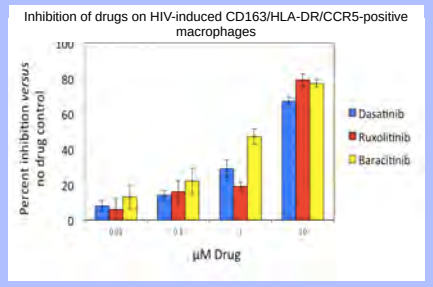
Compound	Inhibition of reactivation of latent HIV-1 in J-lat T cells (IC_{50}, μM)
Baracitinib	4.1 ± 0.1
Ruxolitinib	2.5 ± 0.7
Dasatinib	3.6 ± 0.6
AZT	> 100

Table 2. Baracitinib, ruxolitinib, and dasatinib inhibit reactivation of latent HIV-1 in the J-lat T cell model. Dasatinib, ruxolitinib, and baracitinib are low micromolar inhibitors of reactivation of latent HIV-1 in J-lat T cells. As expected, AZT did not inhibit reactivation. Data are mean and standard deviations from at least three independent experiments.

Results

Inhibition of HIV-induced activation in primary human monocytes and macrophages

A.



B.

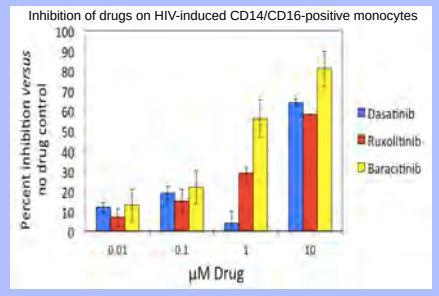


Figure 1. Baracitinib, ruxolitinib, and dasatinib inhibited HIV-induced activation in primary human macrophages (A) and monocytes (B). Dasatinib, ruxolitinib, and baracitinib confered a dose dependent inhibition of activation markers that were upregulated by HIV-1 infection in primary human macrophages (A) and monocytes (B). Data are mean and standard deviations from at least three independent experiments.

Conclusions

Ruxolitinib, baracitinib, and dasatinib inhibited:

1) HIV replication in macrophages

2) reactivation of latent HIV-1 (T-cells)

3) HIV-induced activation markers (monocytes/ macrophages).

These events are linked to trafficking of infected cells to the CNS, disease progression, and neurocognitive dysfunction. Selectively blocking Jak-STAT or tyrosine kinase signaling could reverse or prevent HIV-mediated immune activation both systemically and within the brain/CNS.

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