Effect of the TKI Dasatinib in SAMHD1, HIV Reservoir and Senescence in ART-Treated PWH (BCN04-DASA)

385

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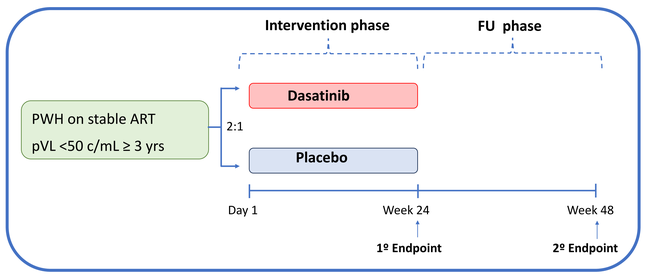
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BACKGROUND

- Dasatinib (DASA) has been proposed as an HIV-1 latency promoter in "block and lock" strategies and as a senolytic drug, but clinical data in people with HIV (PWH) are scarce.
- BCN04-DASA trial (NCT05780073) evaluated the safety and effect of low-dose DASA on the antiviral protein SAMHD1, its primary target, and on HIV-1 reactivation capacity, viral persistence and markers of inflammation and senescence in PWH.

METHODS

- Phase II, single-center, randomized, double-blind, placebo-controlled trial in 60 ART-suppressed PWH who were randomized 2:1 to oral DASA 70 mg QD or placebo for 24 weeks.



- **Primary endpoints:** safety and changes from baseline in phosphorylated (inactive) SAMHD1 (pSAMHD1) expression in activated CD4+ T cells (Flow cytometry).
- **Secondary endpoints:** changes in HIV-1 reactivation in activated CD4+ T cells (intracellular p24, Flow cytometry), total and intact proviral HIV-1 DNA and cell-associated RNA (caRNA) in CD4+ T cells (ddPCR); usHIV-1 RNA in plasma, and changes in soluble inflammatory and senescence-associated secretory phenotype (SASP) markers (Luminex).
- **Exploratory endpoints:** Dasatinib pharmacokinetics, phosphorylation of tyrosin kinase Lck in CD4+ T cells.

RESULTS

Table 1. Baseline characteristics of participants

	Dasatinib n=39	Placebo n=21
Age, years	43 (39 – 54)	50 (37 – 55)
Sex at birth, n (%)		
Male	36 (92.3)	20 (95.2)
Transmission group, n (%)		
MSM	32 (82.1)	18 (85.7)
Time since HIV diagnosis, years	11 (7 – 17)	10 (8 – 12)
Time on ART, years	10 (7 – 15)	9 (8 – 12)
ART at baseline, n (%)		
INSTI-based	38 (97.4)	20 (95.2)
Time since undetectable pVL, years	11 (7 – 14)	9 (8 – 12)
Nadir CD4⁺ T cell count, cells/mm³	320 (198 – 440)	286 (248 – 584)
CD4⁺ T cell count at baseline, cells/mm³	678 (564 – 777)	856 (639 – 1,027)
CD4/CD8 at baseline	1.2 (0.9 – 1.3)	1.2 (0.8 – 1.3)

Data are expressed as median (IQR) except when noted.

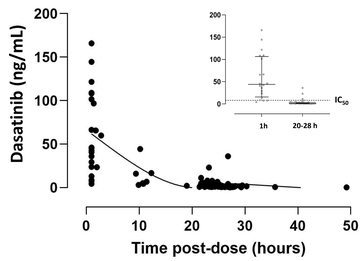
Table 2. Treatment with DASA (70mg QD) was associated with drug-related adverse events.

Adverse events during the intervention phase	Dasatinib n=39	Placebo n=21
AE	39 (100)	17 (81)
Grade 3-4	5 (13)	1 (5)
DRAE	20 (51)	0 (0)
Grade 3-4	0 (0)	0 (0)
DRAEs >5% in Dasatinib arm		
Headache	10 (26)	0 (0)
Diarrhoea	4 (10)	0 (0)
Fatigue	4 (10)	0 (0)
Dyspepsia	3 (8)	0 (0)
Dermatitis acneiforme	3 (8)	0 (0)
Nausea	3 (8)	0 (0)
Dizziness	2 (5)	0 (0)
Face oedema	2 (5)	0 (0)
Myalgia	2 (5)	0 (0)
Vomiting	2 (5)	0 (0)
SAE	4 (10)[a]	0 (0)
Drug-related SAE	0 (0)	0 (0)
Discontinued due to an AE	6 (15)	0 (0)
Discontinued due to a DRAE	5 (13)	0 (0)
Headache	3 (8)	0 (0)
Dyspepsia/Diarrhea	1 (3)	0 (0)
Facial edema	1 (3)	0 (0)

Data are expressed as n (%).

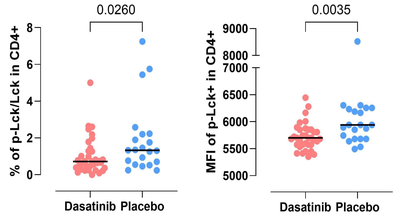
AE, adverse event; DRAE, drug-related adverse event; SAE: serious adverse event.
[a]*Urinary sepsis (Grade 4); Infectious enterocolitis (Grade 3).*

Figure 1. DASA concentrations in plasma were within in the expected range.



Smoothed line represents a LOWESS fit to show trend

Figure 2. At week 24, DASA decreased phosphorylation of tyrosine kinase Lck in CD4+.



Lines represent medians and dots represent individual data.
Mann-Whitney test was applied.

Figure 3. Ex vivo activation and intracellular detection of pSAMHD1 and p24 in CD4+ T cells.

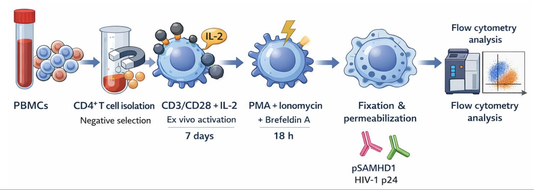
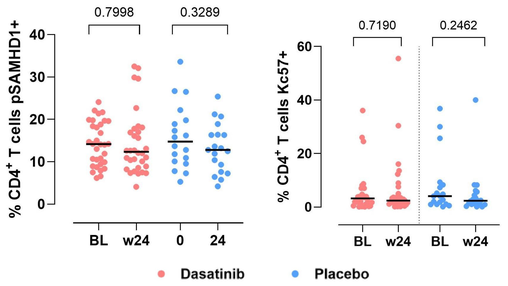
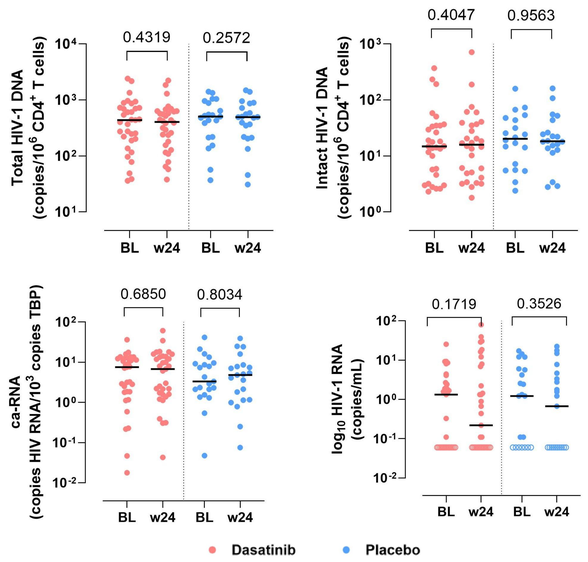


Figure 4. pSAMHD1 and HIV-reactivation in activated in CD4+ T cells remained unchanged.



Lines represent medians and dots represent individual data.
Wilcoxon rank test was applied.

Figure 5. No changes in HIV-1 reservoir parameters during the study.

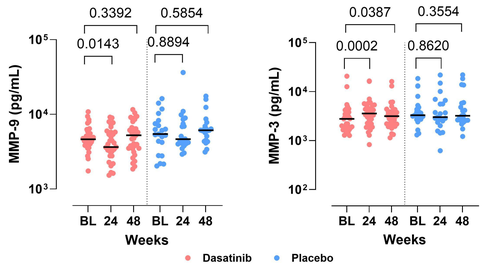


Lines represent medians and dots represent individual data (open dots represent values <LLOQ).
Wilcoxon rank test was applied.

Figure 6. Most soluble inflammatory and SASP markers remained unchanged.

Immune axis	Soluble markers
Inflammatory / SASP	IL-1β, IL-6, IL-8, TNF-α, IL-18, IL-17A, IL-12/IL-23p40, GM-CSF, IL-1RA, IL-10, MMP-3, MMP-9
Homeostatic / Lymphopoietic	IL-2, sIL-2R, IL-7, IL-15, IL-4, IL-5, IL-13
Monocyte–Macrophage Activation & Microbial Translocation	sCD14, sCD163
Interferon / Chemokine Axis	IFN-α, IFN-γ, IP-10 (CXCL10), MIG (CXCL9), CXCL13, CCL21, MCP-1 (CCL2), MIP-1α (CCL3), MIP-1β (CCL4), RANTES (CCL5), CXCL1, CCL11
Endothelial / Coagulation & Angiogenesis	D-dimer, VEGF-A

Figure 7. DASA decreased MMP-9 (tissue degradation) while increased MMP-3 (tissue remodeling).



Lines represent medians and dots represent individual data.
Wilcoxon rank test was applied (not adjusted for multiple comparisons).

CONCLUSIONS:

- Low-dose DASA (70 mg QD for 24 weeks) achieved expected concentrations in plasma and inhibited phosphorylation of tyrosine kinase Lck. However, no changes were observed in SAMHD1 activity, HIV-1 reactivation, or viral reservoir measures in ART-suppressed PWH, and treatment was associated with some drug-related discontinuations.
- The low dose and/or limited duration of DASA exposure may have been insufficient to modulate these pathways. However, these data provide clinical evidence to refine block-and-lock strategies.
- Decrease in MMP-9 together with increase in MMP-3 suggests effects on tissue remodeling consistent with senescent-cell clearance, supporting further investigation of dasatinib as a senolytic agent.

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