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EDITORIAL

Potential role of tyrosine kinase inhibitors during primary HIV-1 infection

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1. Introduction

Acute/recent infection represents approximately 20–25% of new HIV diagnoses in European countries. However, they disproportionally contribute to transmission because patients frequently have extremely high viral loads and are often unaware of the diagnosis [1]. Additionally, essential virological and immunological processes take place during this phase, including massive activation and destruction of CD4 + T cells and the establishment of viral reservoirs (VR). VR represents the burden of the integrated virus in the entire organism and makes HIV-1 infection currently incurable [2]. This period is a unique opportunity for therapeutic interventions but, unfortunately, even long periods of effective antiretroviral therapy (ART) cannot completely offset CD4 + T cell depletion or significantly decrease VR [3].

These processes occur extremely early after infection, and ART alone, even initiated weeks after infection, cannot completely block VR establishment, although the earlier ART is initiated, the lower the VR size [4–6]. Indeed, approximately 10% of patients initiating ART during primary infection and later interrupting it show control of viral replication and have become known as 'post-treatment controllers' [7]. This proportion is much higher than the spontaneous rate of complete control of viral replication without ART, achieved in less than 1% of patients (known as 'elite controllers') [8].

ART regimens recommended by current guidelines include an integrase strand transfer inhibitor (InSTI) associated to two nucleoside reverse transcriptase inhibitors (NRTI) [9,10]. InSTIs have the capacity to rapidly decrease HIV-1 viral load, but, by the time undetectability is achieved, VR is completely established. So far, no adjunctive therapy to ART has shown to be effective in further reducing VR, or blocking its development.

For all the foregoing, new strategies are needed to promptly diagnose HIV infection and initiate ART earlier, which may decrease VR size; to potentiate the limitation of VR establishment induced by early ART and/or to directly impede their establishment by additional mechanisms.

2. Tyrosine kinase inhibitors and HIV-1

The family of tyrosine kinase inhibitors (TKI) is a group of small molecules directed against the activation of tyrosine kinases from the Src family. These drugs are used for the treatment of chronic myeloid leukemia (CML) and include imatinib, dasatinib, nilotinib, bosutinib, and ponatinib [11]. They are used chronically in CML patients and have modified the natural evolution of this disease significantly reducing morbidity and mortality. They show different patterns of tyrosine kinase inhibition, which is responsible for their different adverse event profiles. In some selected cases, treatment can be interrupted and a drug-free remission observed. An immunological mechanism induced by the chronic administration of TKIs has been suggested in these patients [12].

Some of the kinases inhibited by this family of drugs are also essential for the activation of CD4 + T cells, the major target of HIV-1. Massive CD4 + T cell activation during HIV-1 acute infection is mostly responsible for viral spread, the establishment of VR and the destruction of CD4 + T cells. In 2014, Pogliaghi *et al.* reported the reduction of HIV replication induced by dasatinib *in vitro* and suggested that this was mediated by the inhibition of activation and proliferation [13]. More recently, it has been shown that dasatinib is able to inhibit SAMHD1 phosphorylation in CD4 + T cells [14]. SAMHD1 is a cellular factor that acts as an innate antiviral restriction factor, and whose phosphorylation (that leads to inactivation) is induced by HIV. Thus, TKIs may preserve the antiviral activity against HIV of this innate factor. Finally, their antimitotic properties may reduce the clonal expansion of infected cells carrying HIV provirus, decreasing the replenishment of VR.

Taking all this together, TKIs may act against HIV-1 by several mechanisms: the inhibition of the massive activation and, consequently, of VR establishment and CD4 + T cell depletion; the reduction of the clonal expansion of infected cells; and a direct antiviral effect through the inhibition of SAMHD1 phosphorylation. Finally, an indirect immunological effect may occur, similar to that described in CML patients who are on drug-free remissions.

So far, *in vitro* and *ex vivo* results suggest that dasatinib is the most potent anti-HIV drug among the TKI family [14] in CD4T cells, without cell toxicity. Consequently, this drug should be chosen to be tested in pilot clinical trials. From a therapeutic and anti-infective perspective, the optimal situation would be the earliest possible HIV diagnosis (ideally when only RNA or P24 Ag are detectable) [15], and an

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immediate initiation of ART together with a short course of dasatinib during 8 to 12 weeks, when VR establishment in the organism occurs. With current InSTI-based ARV regimens, most patients have undetectable VL after 8–12 weeks of ART, and this short duration may decrease the risk of drug-related toxicity observed when dasatinib is used chronically. Moreover, *in vitro* and *ex vivo* studies suggest that low concentrations of the drug may achieve the anti-HIV effect. Thus, dasatinib doses might be lower than those used in CML. Finally, an intermittent administration may be considered during follow-up, if an immunological effect similar to that of drug-free remission CML patients is observed [12]. The main limitations for such a clinical trial are the difficulties observed in detecting HIV-infected patients at such early stages of infection.

Dasatinib pharmacokinetics (PK) have been studied in healthy volunteers and cancer patients, but remain unknown in HIV-infected individuals, although no significant differences should be expected. Another concern is dasatinib penetration into different body compartments, since HIV VR may develop in tissues and organs where the drug may not reach sufficient concentrations, such as the central nervous system (CNS). The PK of dasatinib in body compartments, and particularly the CNS, is poorly studied. In the limited number of available cases, cerebrospinal fluid (CSF) concentrations of dasatinib seem to be low (around 2% of plasma AUC) [16], but the same drug has also been successfully used to treat acute lymphoblastic leukemia with meningeal involvement[17] and is also under evaluation for other CNS neoplasms, such as malignant gliomas [16], suggesting that the antineoplastic effect could be achieved even with low CSF concentrations. Whether this could be extrapolated to HIV is unknown.

Initial clinical studies in HIV-positive patients should be focused on toxicity, and carefully selected patients (e.g. high CD4 + T cell count, no active coinfections) should be included; it would be improbable to observe a significant decrease in VR in short treatment periods and in small trials. Since the target of dasatinib is a cellular factor (SAMHD1), no risk of development of resistance or cross resistance with ART should be expected. If increased toxicity is excluded by initial trials, then efficacy of dasatinib should be evaluated by measuring markers, such as total and integrated DNA in CD4 + T cells and particularly in memory cells, to assess changes in the VR. Besides, the study of CD4 + T cell activation parameters and inflammatory markers would provide new data about the potential benefit of dasatinib through decreased immune activation. It would be unethical to delay ART initiation in acute/recently infected patients, since ART limits VR establishment, but in chronic patients who have already established VR, a pilot trial administrating a short period of dasatinib monotherapy for 2–4 weeks before ART initiation may also allow to safely test the intrinsic anti-HIV activity *in vivo* of dasatinib.

Considering the pharmacological profile of dasatinib, which is mostly metabolized by cytochrome P450 3A4 (CYP3A4) [18,19], ARV regimens containing cobicistat or ritonavir – both potent inhibitors of CYP3A4 – should be avoided, since they could increase dasatinib levels and potentiate toxicity [20]; conversely, most NNRTIs might reduce dasatinib concentrations due to their inductor effect, offsetting the anti-HIV effect. Among current recommended regimens, concomitant use with the InSTIs raltegravir or dolutegravir would not be contraindicated and should not increase adverse events since no drug–drug interactions with dasatinib are expected. Elvitegravir-based regimens should also be avoided since cobicistat is also required to boost elvitegravir. The current recommended NRTIs included in initial ART regimens [9,10] do not have potential serious drug–drug interactions with dasatinib. At any rate, toxicity should be carefully monitored, particularly bone marrow toxicity, pleural effusion and infectious complications – all reported with dasatinib –, but, in short periods of administration and in low doses, these complications would probably be infrequent. Nevertheless, in initial pilot studies with a small number of patients, serious adverse events would not be expected, although they may appear later in larger studies. Finally, economical issues should be considered. TKI are, in general, onerous drugs. However, the patent protection of dasatinib, which is the most promising antiretroviral TKI, is due to expire in 2020. It will probably take that long to conduct pilot studies and, should they give favorable results, larger studies, and clinical use.

In conclusion, TKIs currently used for treating CML, and particularly dasatinib, are interesting drugs to be added to the current ART arsenal. Dasatinib could be an attractive potential adjuvant of ART to treat HIV infection, particularly during primary infection. It may decrease VR and increase the proportion of patients becoming post-treatment controllers or ideal candidates for eradication trials. Immunological strategies to reduce VR are necessary, and TKIs, particularly dasatinib, merit further research.

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Declaration of interest

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