Increased risk of IRIS-associated tuberculosis in HIV-infected patients receiving Integrase Inhibitors

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Médecine et Maladies Infectieuses

"Titre" Augmentation du risque de syndrome de restauration immunitaire chez les patients co-infectés VIH-tuberculose sous inhibiteurs d'intégrase. "Titre secondaire" Increased risk of IRIS-associated tuberculosis in HIV infected patients receiving Integrase Inhibitors

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Abstract:	Contexte: Le traitement par inhibiteurs d'intégrase (INSTI) est recommandé en première intention chez infectés par le VIH-1 naïfs. La tuberculose est associée à un sur-risque de syndrome de restauration immunitaire (SRI) induit par les anti-rétroviraux. Il existe peu de données quant au sur-risque spécifique des INSTI dans cette situation. Méthode: Tous les patients co-infectés par le VIH et la tuberculose, et suivis dans le service de maladie infectieuse de la Pitié Salpêtrière entre 1997 et 2017 ont été évalués. Ceux présentant les critères de SRI (paradoxale et maladie) dans les 6 mois suivant l'introduction du traitement anti-rétroviral ont été inclus. Nous avons évalué l'incidence de SRI associé à la tuberculose selon le régime anti-rétroviral. Résultats: Cinquante-cinq patients ont été inclus: 21 recevaient un régime anti-rétroviral comportant des INSTI et 34 un régime sans INSTI. À l'exception du régime antirétroviral, les deux groupes étaient comparables (taux initial médian CD4 = 85 / mm3). Le pourcentage global de SRI était de 34% (19/55), avec 52% de SRI sous INSTI et 23% sans INSTI (p = 0,04). En régression logistique multivariée, nous avons observé un sur-risque de SRI sous INSTI avec un OR à 3,33 [IC 95%, 1,01-11,1] (p = 0,05). Il n'y avait pas de différence de sévérité des SRI entre les deux groupes. Conclusions: Les inhibiteurs d'intégrase pourraient être associés à un sur-risque de SRI associé à la tuberculose. Des études prospectives sont nécessaires pour déterminer quel est le schéma thérapeutique optimal chez les patients co-infectés TB-VIH.

ART containing integrase inhibitors could be associated with a higher incidence of TB-associated IRIS. Prospective studies are needed to better characterized the risk of IRIS-TB and determine which is the optimal ART regimen in TB-HIV coinfected patients.

Background:

Tuberculosis is associated with a risk of immune reconstitution inflammatory syndrome (IRIS) after ART initiation.

Methods:

Data from all patients with newly diagnosed tuberculosis disease and uncontrolled HIV infection from 1997 to 2017 in a French center were retrospectively collected. We evaluated the incidence of tuberculosis-IRIS in patients initiating ART with or without integrase inhibitors (INSTI).

Results:

Fifty-five patients were included: 21 receiving an INSTI regimen and 34 a non-INSTI regimen. Except ART regimen, the two groups were comparable (median CD4 of 85/mm^3). The overall percentage of IRIS was 34% (19/55), with respectively 52% IRIS in INSTI regimen and 23% in non INSTI regimen (p=0.04). In a multivariate logistic model, we observed an increased risk of IRIS in the INSTI regimen compared to the non-INSTI with an OR at 3.33 [95% CI, 1.01-11.1] (p=0.05).

Conclusions:

ART containing integrase inhibitors could be associated with a higher incidence of TB-IRIS.

SHORT COMMUNICATION

Increased risk of IRIS-associated tuberculosis in HIV infected patients receiving Integrase Inhibitors

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Introduction

HIV-associated tuberculosis (TB) is common with an estimation of 900.000 cases including 300.000 deaths annually.[1] Antiretroviral therapy (ART) is essential to reduce morbidity-mortality of HIV-infected patients. However, ART initiation can lead to tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) with a prevalence of 4 to 54%[2]. TB-IRIS is an immunopathological reaction characterized by recurrent and inflammatory complications of TB in a patient already on TB treatment after starting ART (paradoxical TB-IRIS), or a new diagnosis of TB after starting ART (unmasking TB-IRIS).[3, 4] TB-IRIS is a serious reaction leading to hospitalization in 25% of cases, and IRIS-attributable death in about 2%.[2, 4] The major risk factors associated with the development of TB-IRIS are a shorter duration between TB treatment initiation and ART initiation, disseminated-TB, lower CD4 cell counts, higher viral load (VL) at ART introduction, the degree and kinetics of VL decrease and CD4 cell count increase after the start of ART.[2, 5]

Treatment with integrase strand transfer inhibitors (INSTI) is recommended as first regimen by treatment-guidelines for ART naive HIV-1 infected.[6-8] Pre-marketing phase III studies assessing INSTI efficiency included very few late-presenters (patients with CD4<200/mm^3 or opportunistic infections (OI))[7, 8], patients at the highest risk for developing TB-IRIS. As few data about INSTI-associated TB-IRIS are available, we report a cohort of TB-HIV co-infected patients, comparing IRIS characteristics according to the ART regimen.

Methods

Database:

We retrospectively collected data from patients followed for HIV and TB between 1997 and 2017 in the computerized and anonymous medical file of the Department of Infectious Diseases of Pitié Salpêtrière hospital in Paris (Nadis).[9]

Study population:

All patients with concomitant *Mycobacterium tuberculosis* infection and uncontrolled HIV infection (naive or without current treatment) were included. We excluded HIV-2 and atypical mycobacteria infections in order to ensure overall homogeneity. The data used fulfilled the confidentiality criteria of the "Commission Nationale de l'Informatique et des Libertés" (CNIL 2085894), and were extracted from medical informatics charts named NADIS, with signed patient consent, authorizing exploitation of data.

Diagnostic criteria:

TB diagnosis was established on bacteriological samples or according to a set of arguments: clinical and radiological presentations, differential diagnosis exclusion and improvement under specific treatment.

Criteria for TB-IRIS diagnosis were based on the consensus definitions from The International Network for the Study of HIV-associated IRIS (INSHI) of paradoxical and unmasking TB-IRIS[3, 4]. IRIS not related to TB was excluded.

The diagnosis of IRIS, according to INSHI criteria, was made by two independent observers unblinded.

Follow-up:

We recorded the clinical, biological (VL, CD4 cell count), and radiological data up to 6 months after ART initiation, issued from systematic follow-up consultations (2 or 3 visits within 6 months) and hospitalizations in severe cases.

Analysis:

Between-group characteristics were analyzed using either exact Fisher test (binary variables) or Kruskall-Wallis test (continuous variables). A multivariate logistic model (including age at TB, higher VL, lower CD4 count, ART timing of introduction, ART regimen) was used to

determine risk factors for IRIS. Quantitative variables were expressed as median, minimal, maximal while qualitative variables were expressed as a percentage.

Results

Of all TB infected patients followed in our Center from 1997 to 2017, 82 were eligible and screened, and we enrolled 55 HIV-1 TB patients who met the inclusion criteria (Figure 1): 21 in INSTI group 1 and 34 in non-INSTI group 2. Apart from ART regimen, the epidemiological, clinical, and biological characteristics of the two groups were not different. (Table 1) Only one cerebral-tuberculosis received pre-emptive corticosteroids.

At baseline, median viral load and CD4 cell count were 5.44 Log_{10} copies/ml [2.3-6.74] and 89/mm^3 [2-391] respectively. HIV infection was previously known in 43% and 29% of patients respectively in INSTI and non-INSTI groups (treatment discontinuation in 9/9 in INSTI, 11/13 in non-INSTI group).

ART treatment was introduced within a median of 2 weeks (-3 to 8 weeks) after anti-tuberculosis treatment (mainly consists of a quadritherapy based on rifampin/rifabutin, isoniazid, ethambutol, pyrazinamide) and this lag-time was not significantly different between groups (p = 0.18).

The overall percentage of IRIS was 34% (19/55), with respectively 52% IRIS in INSTI regimen and 23% in non-INSTI regimen, which was significantly different (p=0.04). In both groups, median time for IRIS occurrence after ART initiation was about 3 weeks, with a median viral load decrease of 2.51 log_{10} copies/ml (INSTI = 2.7 log_{10} copies/ml ; non-INSTI = 2.0 log_{10} copies/ml) and a median increase in CD4 count of 47/mm^3 (INSTI = 63/mm^3 ; non-INSTI = 31/mm^3). There were too few data to statistically prove the faster downward trend in VL and the faster rise of CD4 driven by INSTI.

In a multivariate logistic model, we observed an increased risk of IRIS in the INSTI regimen compared to the non-INSTI with an OR at 3.33 [95% CI, 1.01-11.1] (p = 0.05). However, there was no significant difference in terms of hospitalization rate, and IRIS-related corticosteroid use (respectively 4 hospitalizations and 5 corticosteroid introductions in each group). The only death occurred in a patient with cerebral tuberculosis treated, two weeks after anti-tuberculosis and corticosteroids, with INSTI. This patient had an initial CD4 count of 104/mm^3.

Few secondary OI have been reported in each group: one toxoplasmosis and two CMV plasma replications in group 1, and 4 CMV plasma replications in group 2.

Discussion

ART containing integrase inhibitors seemed to be associated with a higher incidence of TB-IRIS compared to non-INSTI regimen. Overall incidence of IRIS (34%) in our patients is within the rates found in similar series with HIV-TB co-infected late-presenters.[2]

Since INSTI are more promptly efficient on VL than other class of ART, it seems logical that a treatment based on INSTI could increase the rate of IRIS, especially in a population at high risk of IRIS. However the data reported so far are weak and contradictory. [10-16]

Several observational studies have reported an association between ART containing integrase inhibitors and all-cause of IRIS.[10-12] A retrospective monocentric study including 417 HIV infected patients treated with ART, with 92 OI (only 8 cases of tuberculosis) at diagnosis, identified 45 cases of IRIS, and found, in multivariate analysis, INSTI use (OR 2.89; 95% CI 1.26-6.64; p=0.012) as an independent risk factor of IRIS.[10] The ATHENA cohort in the Netherlands, including 369 HIV treatment-naïve patients with CD4 $\leq$ 200/mm^3 and concomitant OI (of which 51 mycobacterial infections unspecified about the type), found in a regression model that INSTI use was independently associated with any form of IRIS (HR

2.6, 95% CI 1.3-5.1, p=0.004), and *Mycobacterium avium* complex-related IRIS (HR 2.46, 95% CI 1.04-5.84, p=0.041). However, there was no precise information about TB-IRIS, probably related to the low number of cases.[11] Lastly, in a large prospective multicentric cohort including 2,287 HIV infected patients (398 in INSTI group, compared to non-INSTI treatment) with an average rate of pre-ART CD4+ T cell count of 83/mm^3, IRIS requiring hospitalization occurred in 41 patients, respectively in 3% (12/398) and 1.5% (29/1889, p=0.05). Generalized linear modelisation showed that all-cause IRIS was associated with INSTI use (OR 1.96 (1.07-3.43). TB-IRIS was recorded in 12 cases, without difference between groups (5 cases under INSTI) keeping in mind the small number of cases.[12]

At the opposite, in an open-label trial including 153 HIV/TB co-infected patients randomized in 3 groups of either raltegravir (400 mg or 800 mg/day) or efavirenz, there were few (5%) and equally distributed IRIS between the 3 groups (respectively 2, 4 and 3). Nevertheless, the mean initial CD4 count was > 100/mm^3 (140/mm^3) and the delay between TB treatment and ART initiation was 5.7 weeks, potentially explaining the lower risk of IRIS.[13] Moreover, a recent meta-analysis addressing dolutegravir use did not find an association with IRIS but all the analyzed randomized trials excluded late-presenters.[14] Finally, the REALITY trial randomized 1,805 naïve patients with CD4<100/mm^3 to standard ART (2NRTI+NNRTI) + raltegravir (n=902) vs standard ART alone (n=903) and enhanced prophylaxis versus standard prophylaxis. This study did not find any difference in the incidence of all-cause IRIS (TB, cryptococcosis, Kaposi, viral hepatitis, CMV and unknown pathogen) between the 2 groups, including for TB-IRIS (which occurred in 53 (5.9%) vs 54 (6.0%) respectively (p=1.00)). This study did not differentiate new TB diagnosis during follow-up from unmasking IRIS (196 cases). In addition, endpoints were predominantly clinically defined, as microbiological and other diagnostic facilities were limited in most centers, the validity of the IRIS diagnosis seems therefore relative in regards to the international validated criteria.[15, 16]

Our study has several limitations mostly related to the observational, retrospective, open and monocentric characteristics. In addition, the small number of patients limits the multivariate analysis. However, our results are issued from the comparison of two groups of patients that prove homogenous and similar in terms of relevant characteristics and bring new data concerning the possible role of INSTI containing regimens in TB-IRIS development in HIV late presenters or uncontrolled patients. Prospective studies are needed to better characterize the risk factors for TB-IRIS in this patient population, to determine which might be the optimal care (ART regimen, pre-emptive corticosteroid therapy) to reduce occurrence of IRIS and avoid drug-drugs interactions.

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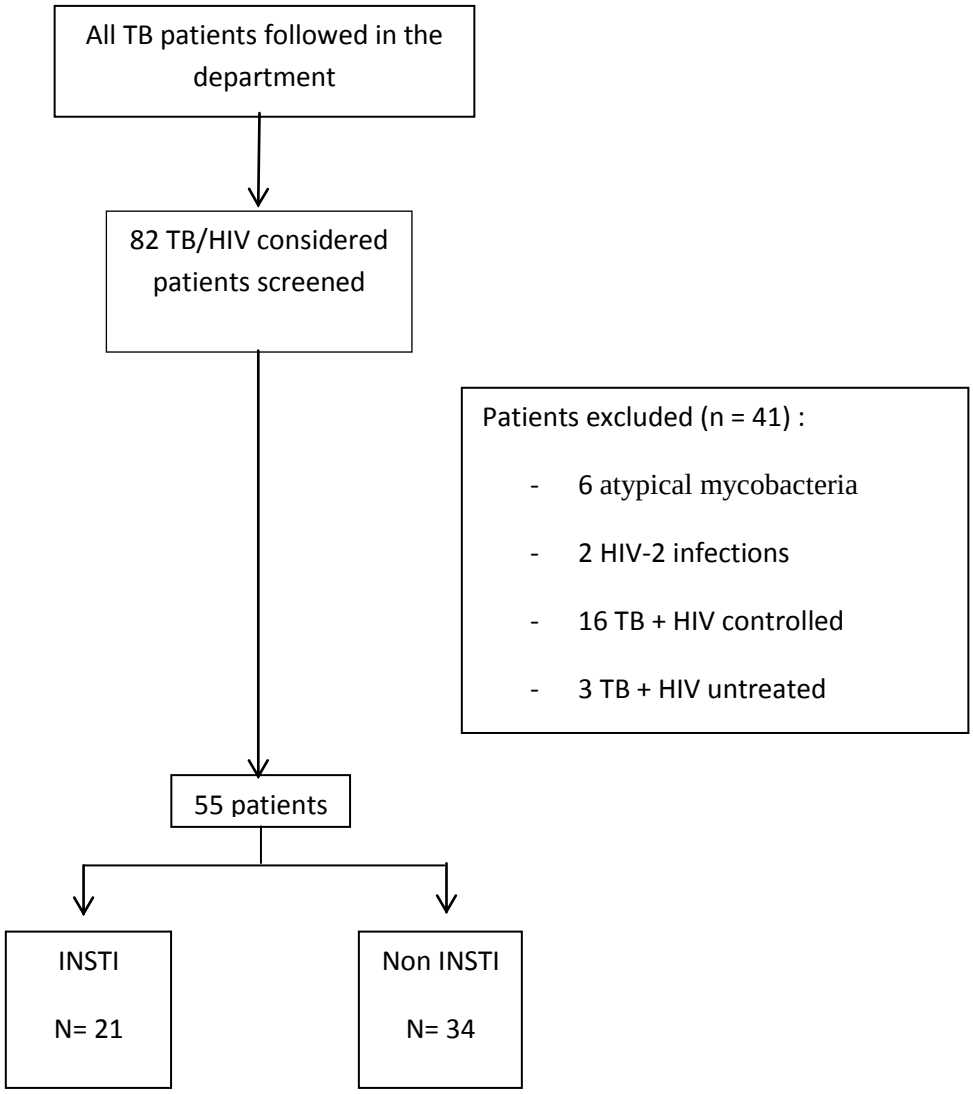
Figure

Figure 1: Flow chart



Table

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