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Transparency declarations

None to declare.

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Low frequency of skin reactions in a cohort of patients on raltegravir

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Sir,

In the last 25 years, highly active antiretroviral therapy has been continuously improving the life expectation and quality of HIV-infected people. As new drugs were more effective and adverse events less frequent and severe, HIV infection turned into a chronic disease. Recently licensed drugs, such as raltegravir and darunavir, are characterized by high efficacy and tolerability. However, on 2 November 2011, updates to the Isentress (raltegravir) package insert were approved by the FDA to include a new warning, subsequent to the post-marketing experience.[1] Severe, potentially life-threatening and fatal skin reactions have been reported during raltegravir treatment.

Several classes of antiretroviral drugs have been associated with cutaneous adverse events, in particular non-nucleoside reverse transcriptase inhibitors and protease inhibitors.[2] Some of these events may lead to treatment discontinuation; their early detection is clinically relevant in order to prevent severe reactions.

In the literature, information about raltegravir and skin reactions is still scanty. A recent paper[3] stating the efficacy and safety of raltegravir in association with etravirine and darunavir/ritonavir reported one case of recurrent epidermal necrolysis leading to raltegravir discontinuation, out of 100 multiexperienced patients (1.0%). Antiretroviral drugs associated with adverse cutaneous reactions were reviewed by Borrás-Blasco *et al*.,[4] who reported that in Phase II and III studies raltegravir was mainly associated with skin rash of mild to moderate intensity, not leading to discontinuation. Long-term safety data from clinical trials[5] showed that rash frequency during raltegravir treatment was higher compared with placebo, but lower in comparison with efavirenz.

To add information on this issue, we report the results from the SCOLTA (Surveillance COhort Long-term Toxicity Antiretrovirals) project. This is an online reporting system for adverse reactions to antiretroviral drugs, designed by the CISAI (Coordinamento Italiano per lo Studio Allergia e Infezione da HIV; Italian Coordination for the Study of Allergy and HIV Infection) group. It originated as a pharmacovigilance system for newly introduced drugs and as a sentinel scheme for unexpected or late adverse reactions arising during any antiretroviral treatment. It works through the internet site www.cisai.info and currently involves 18 Italian infectious disease centres. Cohorts of patients are established for each new drug as it comes onto the market, and these patients are followed

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Table 1. Demographic and clinical baseline characteristics of 448 patients enrolled in the raltegravir cohort

	N, mean or median	%, SD or IQR
Age (years)	45.8	9.2
Sex		
male	300	67.0
female	148	33.0
HIV transmission category		
IVDU	164	36.6
sexual	241	53.8
other or unknown	43	9.6
CDC stage		
A	135	30.1
B	139	31.0
C	174	38.8
CD4 count (cells/μL)[a]		
<200	126	28.4
200–499	199	44.9
≥500	118	26.6
HIV viral load at study entry <50 copies/mL	175	39.1
HCV positive	173	38.6
Lipodystrophy	179	40.0
Previous antiretroviral therapy (years)	10.4	5.6
Concomitant treatment		
NRTI alone	82	18.3
PI	312	69.6
NNRTI	74	16.5
other drugs	69	15.4
Total cholesterol (mg/dL)	187	59
HDL cholesterol (mg/dL)	42	15
Triglycerides (mg/dL)	153	108–233
Glucose (mg/dL)	94	31
Observation period (months)	23	13–30
Reason for discontinuation		
death	9	2.0
virological failure	13	2.9
adverse events	15	3.3
STI	3	0.7
simplification	4	0.9
lost to follow-up	17	3.8
other	21	4.7

IVDU, intravenous drug use; HCV, hepatitis C virus; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; HDL, high density lipoprotein; STI, structured treatment interruption.
[a]Five patients had missing information on CD4 count at enrolment.

prospectively. Data collection and follow-up procedures for the cohorts have been described previously.[6] In 2006 we started to collect information on patients taking raltegravir. Subjects were followed up every 6 months, including information about blood lipids, liver function and immunological examinations. Grade 3–4 adverse events that occurred at any time were recorded; any grade event leading to drug discontinuation was also reported.

As of January 2012, 469 patients on raltegravir treatment had been enrolled in this study (67% males, mean age 46 years, 7.0% naive, 40% stage C); 448 (95.5%) had at least one follow-up and the median observation time was 23 months. Table 1 summarizes the main features of these patients.

Among these patients six skin adverse reactions were reported (three cases of diffuse itching and three cases of cutaneous rash); two (one itching and one rash) led to drug discontinuation, but none was life-threatening. Nine patients died during the study, for reasons unrelated to skin adverse reactions.

In this sample there were 816 person-years of observation; the incidence of adverse skin reactions was 0.73/100 person-years (95% CI, 0.15–1.32). The frequency of drug discontinuation related to skin reactions was 0.4%.

To our knowledge, at present this study includes the largest series of patients treated with raltegravir and prospectively followed aside from clinical trials. In conclusion, we found that raltegravir-treated patients observed in a real-life setting showed a low frequency of severe skin reactions.

Ethics

This multicentre research was approved by the local Ethics Committees. Patients starting a newly introduced drug are asked to give written informed consent to the use of data.

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Transparency declarations

None to declare.

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In HIV-infected patients, some differential alterations of CD4 and CD8 T cell homeostasis may not be restored by ≥7 years of highly active antiretroviral therapy, in spite of good CD4 T cell repopulation

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Keywords: immune reconstitution, antiviral, HAART

Sir,

We read with interest the recent manuscript by Méndez-Lagares *et al*.[1] describing significant alterations in T cell homeostasis in patients on highly active antiretroviral therapy (HAART) showing low-level CD4 T cell repopulation, despite long-lasting and persistent viral replication control. In particular, notable reductions of circulating naive CD4 T cells with increased expression of markers for activation, senescence and proliferation were found in comparison with patients with satisfactory CD4 T cell repopulation. These results agree with their proposed model of immune impairment in patients with low-level CD4 T cell repopulation,[2] suggesting intrinsic thymus failure and specific features of premature immune senescence.

Our laboratory is actively working on a custom eight-colour flow-cytometry assay (BD LyoTube 8-color CD4 and CD8 bundle, BD Biosciences, San Jose, CA, USA), which is able to analyse differentiation, activation and senescence in CD4 and CD8 T cells (CD4 Lyotube: CD95 FITC/CCR7 PE/CD3 PerCP-Cy 5.5/CD25 PE-Cy7/CD127 Alexa Fluor 647/CD45 APC-H7/CD4 AmCyan/CD45RA V450; clones DX2/150503/SK7/2A3/HIL-7R-M-21/2D1/SK3/HI100, respectively; and CD8 Lyotube: CD38 FITC/CCR7 PE/CD3 PerCP-Cy 5.5/CD69 PE-Cy7/CD127 Alexa Fluor 647/CD45 APC-H7/CD8 AmCyan/CD45RA V450; clones HB7/150503/SK7/L78/HIL-7R-M-21/2D1/SK1/HI100, respectively). Stained and lysed whole blood was analysed on an FACS-Canto II flow cytometer using FACS-Diva v.6.1.3 software (BD Biosciences). This test, performed on whole blood on a semi-routine scale, proved useful to analyse T cell homeostasis in HIV-infected persons in a protocol approved by the Institute's Ethics Committee. In particular, this approach allowed us to verify that naive CD4 T cell frequency was lower in patients unable to reach CD4 reconstitution than in HIV patients reaching CD4 reconstitution [7.4% (IQR: 1.2–20.0) versus 33.1% (IQR: 27.9–43.9), $P<0.0001$],[3] confirming the results of Méndez-Lagares *et al*.[1]

In order to evaluate how HAART impacts on CD4 and CD8 T cell homeostasis, residual samples from 10 untreated HIV-infected persons were analysed by this assay before starting treatment and after 6 months of treatment. After 6 months of treatment, all patients fulfilled immune reconstitution criteria [CD4 cells/mm^3: 530 (IQR: 467–834)] and obtained viral load control [plasma viral load: undetectable (<40 copies/mL)]. Thirty-two seronegative healthy donors (HDs) were used as controls.

Table 1 summarizes the immunological parameters that are found to be affected by HIV infection: these include CD95 expression on CD4 T cells, Treg frequency and CD8 activation markers. Many of these factors are positively modulated by 6 months of successful HAART, gradually approaching, but not reaching, the level found in HDs: CD4+, CD4CM+CD95+, Treg, CD8EM+CD127+ and CD8+CD69+. Others are completely restored, as in HDs: CD8+CD38+, CD8EM+CD38+, CD8TEMRA+CD38+, CD8TEMRA+CD127+ and CD8CM+CD69+. Notably, two CD8 T cell subsets (CD8CM+ and CD8TEMRA+) seem negatively affected by HAART, increasing the difference with respect to HDs. Finally, many immunological markers are not affected at all by HAART (Table 1, last column). Thus, the short-term control of HIV replication seems able to allow a reduction of CD8 T cell activation and of CD4 apoptosis, but fails to completely restore CD4 and CD8 T cell homeostasis.

Moreover, in order to ascertain if long-term HAART may be effective in fully restoring CD4 and CD8 T cell homeostasis, residual samples from 18 HIV-infected patients treated with HAART for 7–10 years, with recovered CD4 counts [CD4 cells/mm^3: 910 (IQR: 685–1074)] and with a controlled viral load [plasma viral load: undetectable (<40 copies/mL)], were also analysed. Notably, many parameters that were not restored after 6 months of HAART were found fully normalized after long-term HAART. Nevertheless, as shown in Table 2, some markers (CD4+CD95+, CD4CM+CD95+, CD8+, CD8NA+, CD8+CD127+, CD8NA+CD127+ and CD8EM+CD127+) remained significantly altered, despite long-term immunological and virological treatment response. These observations suggest immune homeostasis damage inflicted by HIV infection in the active replication phase that cannot be recovered by (apparently) successful HAART.

As markers of treatment efficacy, HIV-RNA plasma levels and CD4 T cell count are routinely used; in particular, the CD4 count itself plays a major role, since counts below the 200 cells/mm^3 threshold have been associated with a worse prognosis, and therefore has been adopted in international guidelines to guide and evaluate antiretroviral treatment decisions.[4] Despite its

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