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Raltegravir in Children and Adolescents : The French Expanded Access Program.

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Summary

***Objective*:** to describe tolerance and efficacy of Raltegravir (RAL) in patients aged less than 18 years who were treated in France during the RAL expanded access program (RAL-ATU).
***Design*:** Retrospective analysis of the outcome of the 23 consecutive adolescents with a multidrug- resistant HIV1 treated in France with RAL-ATU from Dec 2006 to Dec 2007.
***Results*:** 21 patients were treated because of active replication (mean HIV-1 RNA level of 5 log10 copies/ml) and 2, with viral control, switched from T20 to RAL. In these 23 heavily pre-treated patients infected since birth, RAL was combined with other antiretroviral drugs including 2 drugs also delivered via expanded access: Etravirine (ETR) for 16 patients, Darunavir (DRV) for 17 and both drugs for 13. Median follow-up on treatment including RAL was 12 months (9-21 months). Except for one patient who stopped treatment at 3 weeks because of headache, no moderate-to-severe clinical side effects were noted. No grade 3 or 4 laboratory abnormalities occurred. Mean CD4 cell counts significantly increased after 9 months of RAL-containing treatment from 191 cells/ml to 523 (p<0.001, 22 patients). At the last follow-up, viral load was < 400 copies/ml in 18 patients and < 50 copies/ml in 13. A trend in favor of a superior virologic response was observed for patients receiving a regimen including RAL, ETR and DRV compared to those under other RAL containing regimens (-3.7 versus -2.67 log10, p=0.076, Mann Withney test).
***Conclusions*:** In the first French adolescents treated with RAL, combined with ETR and/or DRV in 20 cases, a potent antiretroviral effect was observed despite very long periods of viral replication on previous ARV therapies and large spectra of resistance.

Introduction

For a sizeable number of HIV adolescents infected since birth, who had developed highly drug- resistant HIV, there is a major need for potent new antiretroviral treatments. Raltegravir, the first licensed inhibitor of HIV-1 integrase has shown a significant antiretroviral activity and a good safety profile in treatment experienced adults.

During one year, from 12/2006 to 12/2007, date of RAL commercialization in France, a total of 23 consecutive adolescents aged less than 18 years were treated with RAL on compassionate grounds via a nominative temporary use authorization (Autorisation Temporaire d'Utilisation -ATU), a regulatory statement granted by the French health authority before market drug commercialization. RAL was most often used in combination with 2 other antiretroviral drugs also delivered via expanded access: Darunavir for 17 adolescents, Etravirine for 16 patients and both drugs for 13 patients.

We described characteristics of the patients and we retrospectively analyzed RAL containing-treatment outcome for these 23 adolescents.

Characteristics of the patients at the start of RAL

The 23 patients (17 males , 6 females) treated with RAL-ATU, have been HIV-1 infected since birth. They had **median age** and **duration of previous ARV therapy** of **15.5 yrs** (range 12-17) and **13 yrs** (10-17). Their median weight was 48 kg (range 28-72). A history of **AIDS** was recorded for 17 patients and 22 were or have been **immune class3**. CD4 cells number ranged from 5 to 484 (median: **194 cells/ml**). All patients were heavily pretreated and 22 had genotype-documented triple-class oral drug resistance: median number of drugs received was **6** (range 5-7) and **4** (range 2-7) for **NRTI** and **PI**. All patients except one had received 1 or 2 NNRTI drugs. Enfuvirtide has been previously used in 13 patients.

21 of the patients were treated via RAL -ATU because of active replication of multidrug resistant virus (median HIV-1 RNA level of **5 log 10 copies/ml** range 3.34 to 6.1) but 2 patients had viral control on treatment including enfuvirtide and switched to RAL because of injection-site reactions. **10** adolescents had **never** experienced an **undetectable VL** during their previous ARV treatment history.

Methods

TREATMENT AND REGULATORY PROCEDURES: RAL (400 mg bid) was administered in combination with 2 to 5 other antiretroviral drugs selected by each clinician. With the aim of optimizing ARV drugs introduced with RAL, ETV was used in 16 patients, DRV in 17 and both in 13. During all the study period, RAL and ETR were administered via the **regulatory procedure of ATU** after the agreement of French health authority experts, based on information provided about patient's characteristics and genotypes. DRV/r was also prescribed via ATU until its commercialization.

VIROLOGIC METHODS : Genotypic resistance tests were performed on sites. Mutations associated with HIV-1 drug resistance were analyzed using the ANRS 2007 interpretation algorithm (v.16). Genotypic sensitivity score (**GSS**) at the start of RAL was retrospectively determined (*CT and ML C*) and indicated the total number of fully active prescribed drugs. Historical genotypes which have documented NNRTI resistance were taken into account.

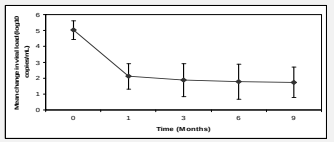
Clinical Results

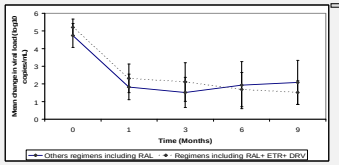
Follow-up data were obtained for 22 patients out 23, treatment containing RAL being discontinuated by one patient after 2 weeks. For the 22 remaining patients, the **median treatment duration** was **12 months** (9 -21 months). During this time, their **mean SD score for weight** increased significantly **from -0.82 SD** (-2.63 to +1.4) **to -0.46 SD** (-2.9 to +1.81) (**p=0.006**, wilcoxon test). No death or AIDS-defining clinical events occurred. A second patient permanently stopped RAL at 9 months because of virologic failure. At the time of analysis (Oct 2008) 21 patients remained under treatment including RAL.

Safety

Except for the patient who definitively stopped treatment at 2 weeks because of sleep disorders, nausea and headache, no clinical side effects were noted. **No laboratory abnormalities of grade 3 or 4 occurred**. One patient had initial anemia (grade 2) and another neutropenia (grade 1): both remained unchanged. Liver abnormalities were initially present in 3 patients and remained unchanged or improved subsequently. Mild increase in fasting triglyceride levels appeared in 3 patients/18 evaluated while in 3 others, previously treated with LPV, TG levels improved.

Virologic Response





Statistical analysis was restricted to the 20 patients treated with active viral replication, excluding the 2 patients switched from T20 to RAL: **VL significantly decreased** from a mean (SD) of **5.02** log10(0.59) at the **start** of RAL to **2.12** (0.8), **1.87** (1.02), **1.78** (1.1), and **1.74** (0.96) at **M1**, **M3**, **M6** and **M9** (p<0.001 using the non parametric Friedman test).

The difference in the VL decrease between the 12 patients receiving **RAL, ETR and DRV** versus the 8 receiving other regimens was near significant at M9 (-3.7 versus -2.67 log10, p=0.076, Mann Withney test)

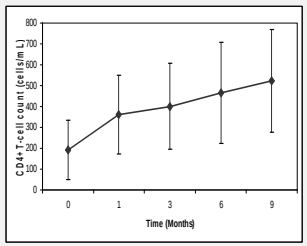
Virologic response	BL	M1	M3	M6	M9	M12
Number of patients < 50c/ml	**1/23**	**5/22**	**9/22**	**11/22**	**10/22**	**13/16**
Number of patients < 400c/ml	**2/23**	**16/22**	**19/22**	**18/22**	**18/22**	**14/16**

At the last f-up (9 to 21 months), 21 patients remained under treatment including RAL. 18 had VL < 400 c/ml and 13 <50 c/ml. Virologic failure (VL > 400 c/ml at 2 consecutive points after initial response) occurred in 4 patients and was clearly related to suboptimal adherence in 2. 6/10 patients who had never experienced VL <400 c/ml during their previous ARV treatment achieved and maintained VL <50 c/ml

Genotypic sensitivity score

Despite initial highly drug-resistant HIV, only one patient had a initial **GSS** of 1**,** RAL being the only fully active drug. The **use of ETR and DRV permitted addition of one active drug** for 13 of 16 adolescents and 11 of 17, respectively. Median GSS was 2 and did not differ between patients receiving the combination of RAL, ETR and DRV versus the others. The number of active PI was 0 or 1 for 14 patients.

Change in CD4 Cell count



Patients experienced a **regular and significant increase** in their CD4 cell counts over the treatment period (**p<0.001,** Friedman test). The mean CD4 cell counts (SD) increased from **191** (143) cells/ml at **baseline** to 361 (188), 401 (206), 466 (243), **523** (246), 530 (228) at M1, M3, M6, **M9** and M12, respectively.

Increase in CD4 cell count did not differ between the patients receiving ARV therapy containing RAL, ETR and DRV and the others at M1, M3, M6, M9.

Conclusions

All patients aged less than 18 years treated in France during the RAL expanded access for **highly drug-resistant HIV infection** were included in this report. With 1 year median follow-up under treatment:

-Virologic response was remarkable suggesting that most extensive treatment experienced but integrase inhibitor-naïve adolescents can achieve viral control when the salvage regimen also contains other active agents. Despite the small number of patients, **a trend in favor of a higher decrease in VL for patients receiving RAL+ETR+DRV** was observed with time, compared with those treated with other regimens.

-A high immunologic response was obtained among these immunosuppressed patients with a long past history of treatment failure and a median initial CD4 cells < 200 cells/ml.

-As in adult patients, **a good safety profile** of the different regimens including RAL was noted.

Durability of viral suppression in these heavily pre-treated adolescents should be assessed in the long term but would be optimized by the combined use of ETR and/or DRV with RAL.