Poster #237

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Lopinavir/ritonavir Pre-Registrational Usage in France (ATU): A 2000 to 2001 Insight into the Therapeutic Trends and Outcomes in HIV Treatment-Experienced Patients

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BACKGROUND

Lopinavir/ritonavir (LPV/r, Kaletra™, formerly known as ABT-378/r), is a recently approved protease inhibitor for the treatment of HIV-1 infection in the United States and in Europe.

Lopinavir, co-formulated with a low dose of ritonavir, takes advantage of the P450 cytochrome inhibitor properties of ritonavir. Lopinavir is exquisitely sensitive to pharmacokinetic enhancement by ritonavir, resulting in substantially increased LPV drug exposure. The mean LPV ratio of C_{trough} (protein binding adjusted) to EC_{50} (Inhibitory Quotient or IQ) for wild-type virus is >75 (at 400/100 mg BID dose), potentially providing a pharmacological barrier to the emergence of viral resistance and superior antiviral activity, contributing to durability.

Prior to marketing authorization a program was developed to provide patients who were failing currently available therapeutic options access to potentially life-saving medications. This program, the Expanded Access Program (EAP) was initially carried out as a clinical trial. In France the EAP had been switched through agreement with the Drug Agency to an "ATU" program ("Autorisation Temporaire d'Utilisation", Provisional Authorization for Use) between March 2000 and April 2001.

METHODS

Selection criteria, initially restricted to patients with CD_4 < 200 cells/mm³ and viral load >4 log_{10} copies/mL, were modified to authorize the use of LPV/r in a broader PI-experienced population.

At baseline, demographics, medical history, virology (HIV-RNA), immunology (CD_4), prior and current antiretroviral medications and genotype were collected. Follow-up data was provided on a voluntary basis for HIV-RNA, CD_4 and Serious Adverse Events.

The overall enrollment in this cohort was 3,819 patients. Patients excluded from this analysis included 193 patients previously enrolled in the Expanded Access Program (EAP) and 179 patients with "Nominative ATU status." "Nominative ATU status" was granted for patients who did not fulfill the selection criteria of the ATU, i.e., children.

Number (N) refers to number of subjects for whom specific data was available.

RESULTS

Summary of Baseline Demographic and Disease Characteristics

A total of 3,447 patients were included in this summary. The mean baseline HIV RNA and CD_4 count for these patients were 4.66 log_{10} copies/mL and 202 cells/mm³, respectively.

One hundred fifty-two new opportunistic infections occurred in 135/1,846 (7.3%) patients for whom information was available during the three-month period prior to initiation of LPV/r therapy. Additionally, 51.3% of these patients for whom information was available had experienced at least one CDC Class C (AIDS-defining) event.

Demographic and disease characteristics are presented in Table 1.

Table 1. Baseline Demographic and Disease Characteristics

Gender		**CD_4 Count (cells/mm³)**	
Male	79.5%	<50	21.4%
Age (N = 1805)		[50 – 150[	24.5%
Mean	42 years	[150 – 300[	30.0%
Median	40 years	≥300	24.1%
CDC Classification (N = 3279)		Mean	202
Asymptomatic (Stage A)	16.8%	Median	165
Symptomatic (Stage B)	31.9%	Standard Deviation	178
AIDS – Indicator (Stage C)	51.3%	Minimum	0
HIV Diagnosis Date (N = 2753)		Maximum	1193
<1990	40.8%	**HIV RNA (log_{10} copies/mL)**	
1990 –1994	41.4%	<5 log_{10} copies/mL	60.9%
≥1995	17.8%	≥5 log_{10} copies/mL	39.1%
		Mean	4.66
		Median	4.78
		Standard Deviation	0.92
		Minimum	0.70
		Maximum	7.05

Figure 1. Baseline Patient Population by Age (N = 1805)

50% of patients were ≥40 years with the single most highly represented group being 35-40 years of age (30%).

Figure 2. Baseline Patient and Population by CDC Stage (N = 2465)

N.S. = Not stated
Stage A = >500
Stage B = 200-500
Stage C = <200

Clinical Category	CDC Category Cat.1	Cat. 2	Cat. 3	N.S.
Stage A	51	123	175	203
Stage B	29	192	501	323
Stage C	60	124	1210	288
Total	2465			

Approximately 84% of patients have suffered an AIDS-defining condition (CDC 1993).

Figure 3. Distribution of Baseline CD_4 Cell Count for Patients Initiating Kaletra Therapy (N = 3415)

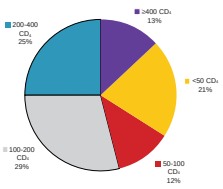
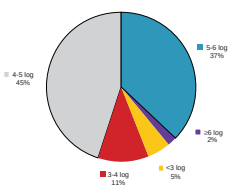
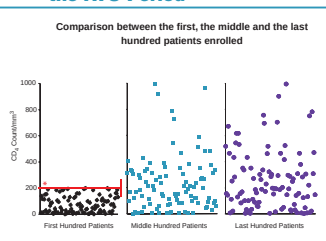


Figure 4. Distribution of Baseline Viral Load for Patients Initiating Kaletra Therapy (N = 3412)



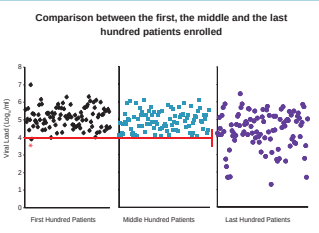
The majority of patients initiating therapy with Kaletra had baseline CD_4 <200 cells/mm³ (62%) and approximately one third had a viral load greater than 5.0 logs.

Figure 5. Trend in Baseline CD_4 Count During the ATU Period



* Reflects initial entry criteria

Figure 6. Trend in Baseline Viral Load During the ATU Period



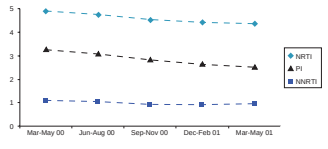
* Reflects initial entry criteria

As the selection criteria became less restrictive, the mean baseline status of the patient population shifted to healthier patients, as reflected by Figures 5 and 6.

- Median CD_4 count was 64, 180, and 192 for the first, middle and last hundred patients, respectively, in Figure 5.
- Median viral load was 5.15, 4.85, and 4.55 log_{10}/mL for the first, middle and last hundred patients, respectively, in Figure 6.

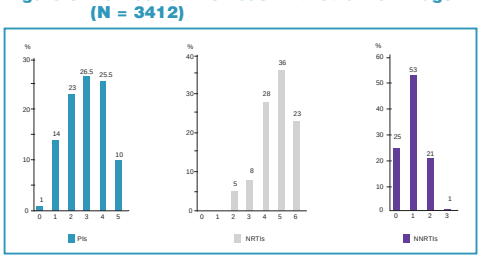
Prior Antiretroviral Experience

Figure 7. Mean Number of Antiretrovirals Used Prior to Initiating Kaletra Therapy



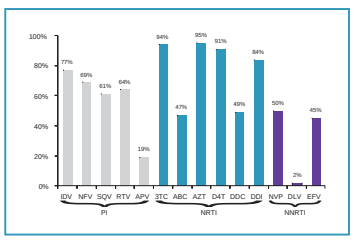
- Figure 7 demonstrates the mean number of prior NRTIs, PIs and NNRTIs used prior to the ATU experience.

Figure 8. Number of Previous Antiretroviral Drugs (N = 3412)



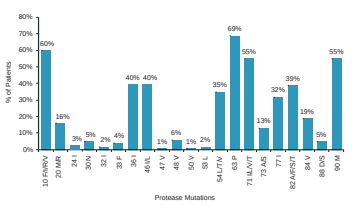
- Prior ARV therapy is provided in Figure 8.

Figure 9. Previous Antiretroviral Treatments (N = 3412)



- The majority of patients were previously treated with at least 3 PIs (62%), at least 5 NRTIs (59%), and at least 1 NNRTI (75%). Treatment experience with individual antiretrovirals is provided in Figures 8 and 9.

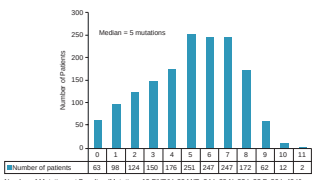
Figure 10. Prevalence of PI Mutations at Baseline (1604 genotypes)



Baseline Genotype

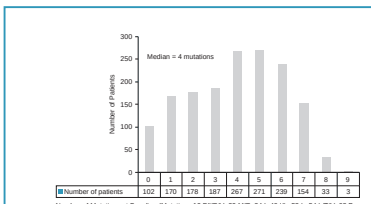
- HIV RNA sequence was performed in this heavily ARV-experienced patient population according to the French guidelines (Rapport Delfraissy 2000) and were provided, when available, on a voluntary basis.
- The prevalence of multiple baseline PI mutations associated with cross resistance within the PI class was high (Figure 10). The majority of isolates contained one or more primary mutations[1] at positions 82, 84 and 90, as well as secondary mutations at positions 10, 46, 54 and 71.

Figure 11. Number of PI-Associated Mutations at Baseline (1604 patients)



- Within this population, the number of PI associated mutations ranged from 0 to 11, with a median of 5 mutations (Figure 11).

Figure 12. Number of Mutations from LPV Mutation Score Present at Baseline (1604 patients)



- The baseline median LPV mutation score (number of mutations associated with reduced susceptibility to LPV) was 4 (Figure 12).
- Approximately half of the patients (777/1604, 48%) had a baseline LPV mutation score of 4-6 mutations (Figure 12).

Concomitant Antiretroviral Therapy

Figure 13. Description of LPV/r-Containing Regimens (N = 1828)

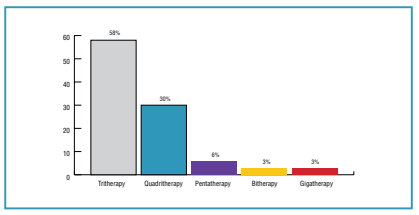
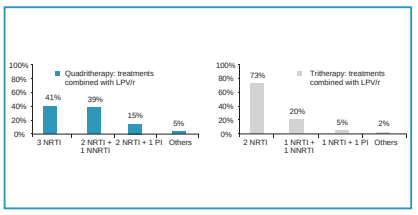
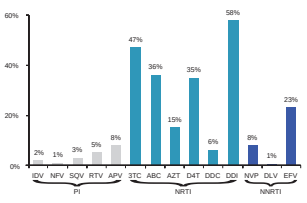


Figure 14. Description of LPV/r-Containing Regimens (N = 1828)



- Concomitant ARVs in the LPV/r-containing regimens for the study population are provided in Figure 13 and 14. The majority of patients (58%) received two additional drugs.
- A sizeable minority of patients (30%) received three additional drugs, consisting mainly of either three NRTIs (41%) or two NRTIs and one NNRTI (39%). Nine percent of patients received more than three concomitant ARVs. Concomitant use of another PI was uncommon in this population.

Figure 15. Associated Antiretroviral Treatments (N = 1828)



- The most commonly coadministered drugs were ddI, 3TC, ABC and d4T.

CONCLUSIONS

With 50% of patients in the >40 years of age group, a benefit of HAART therapy and its relation to the aging of the HIV population is suggested. This was further documented by comparing these results to the period of protease inhibitor introduction, where the most highly represented group (Norvir ATU experience, 1996) was 30-35 years of age (28%).

The ATU patient profile is that of highly antiretroviral experienced HIV-infected patients with an advanced stage of the disease. Prior antiretroviral experience for these patients typically included at least 3 PIs, 5 NRTIs and 1 NNRTI.

Patients enrolled into the ATU (2000 to 2001) were mainly treated with a three or four drug regimen that included lopinavir/ritonavir as the lone protease inhibitor in the regimen.

The median baseline LPV score of 4 suggested a potential benefit of Kaletra for enrolled patients and is consistent with other reports relating lopinavir mutation score and response (oral presentation #525 Retrovirus 2001 and poster #236 ECCATH 2001).

REFERENCE

1. Hirsch, MS, et al. Antiretroviral drug resistance testing in adults with HIV infection: Implications for Clinical Management. International AIDS Society - USA Panel. *JAMA* 1998; 279;1984-94

ACKNOWLEDGMENTS

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