Poster #238

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Collection of Drug Adverse Events in Pre-Registrational Access Programs: What Relevance Compared to Controlled Studies? Analysis of the French ATU Cohort for Kaletra®

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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 European Union and in the US.

Lopinavir/ritonavir was prescribed to patients in France with medical need in a pre-registrational expanded access program (ATU). This cohort included 3819 moderately immunosuppressed patients with extensive treatment experience, and was active from March 2000 until April 2001. At baseline, complete information on clinical and therapeutic histories was collected, as well as a list of different drugs to be used in combination with lopinavir/ritonavir in the program. The recommended lopinavir/ritonavir dosage was the standard 3 capsules BID. The declaration of the Adverse Events (AE) was made on a voluntary basis (pharmacovigilance). The definitions of Serious Adverse Events (SAE) were provided to the physicians, as well as declaration forms. Quarterly safety reports were provided to the French Drug Agency. This poster summarizes the adverse events that occurred in more than 0.2% of the study population.

METHODS

Data were mainly collected on the ATU Case Report Forms (Protocole d'Utilisation Therapeutique) distributed to attending physicians at the time of patient enrollment.

- Adverse Event Collection Form
- Treatment Discontinuation Form when safety reasons or product inefficacy was mentioned
- Follow-up Form when adverse events were noted

Adverse events seriousness criteria, as defined in the International Conference on Harmonisation (ICH) Guidelines, are summarized as follows:

Mild: The adverse event is transient and easily tolerated by the patient.

Moderate: The adverse event causes the patient discomfort and interrupts the patient's normal activities.

Severe: The adverse event causes considerable interference with the patient's normal activities, and it may be incapacitating or life-threatening.

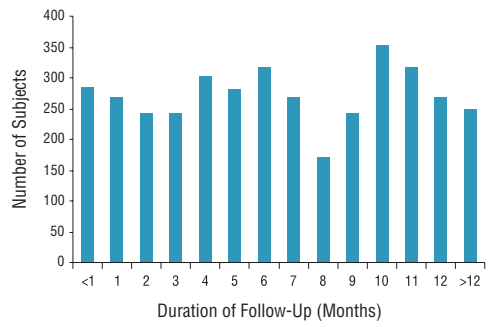
Of the 3819 patients that participated, the majority (79.5%) were male with a mean age of 42 years. Additionally, 51.3% of these patients had previously experienced at least one CDC Class C (AIDS-defining) event. Baseline demographic and disease characteristics are presented in Table 1.

Table 1. Baseline Demographic and Disease Characteristics

Gender		**CD_4 Count (cells/mm³)**	
Male	79.5%	<50	21.4%
Age (N=1805)		50 – 149	24.5%
Mean	42 years	150 – 299	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
		Maximum	1193
HIV Diagnosis Date (N=2753)		**HIV RNA (log_{10} copies/mL)**	
<1990	40.8%	<5 log_{10} copies/mL	60.9%
1990 – 1994	41.4%	≥5 log_{10} copies/mL	39.1%
≥1995	17.8%	Mean	4.66
		Median	4.78
		Standard Deviation	0.92
		Minimum	0.70
		Maximum	7.05

The first patient initiated lopinavir/ritonavir therapy in the ATU program on March 23, 2000. As of April 16, 2001, the mean duration of follow-up for patients with confirmed lopinavir/ritonavir dosing was 7.16 months. The duration of follow-up for subjects who have initiated dosing with lopinavir/ritonavir in the ATU program is summarized in Figure 1.

Figure 1. Summary of Duration of Follow-Up



RESULTS

Reporting of Adverse Events

During the time period from March 2000 to April 2001, 356 cases describing 836 adverse events were reported. Since several adverse events may be described in one report, the number of AEs (n = 836) is higher than the number of reports (n = 356). The number of reports and adverse events according to their seriousness and expectedness is presented in Table 2. Expectedness was determined using the French ATU SPC (Summary of Product Characteristics).

Table 2. Adverse Events and Reports by Seriousness

	Serious	Non-Serious
Patients Reporting Adverse Events	120	236
Adverse Events	241	595

Seriousness Criteria

Seriousness criteria for adverse events reported during the ATU are summarized in Table 3, ordered by decreasing seriousness. When several seriousness criteria were noted in the same report, the most severe criterion was taken into account.

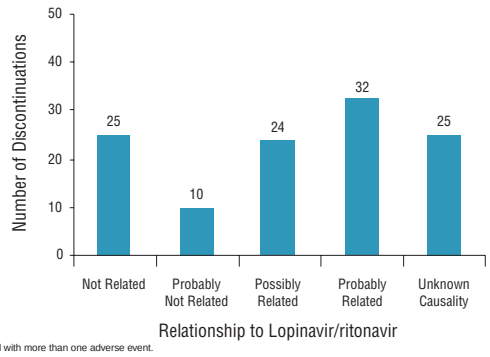
Table 3. Distribution of Seriousness Criteria

	Number of Patients (N=120)
Death	19
Life-threatening	8
Incapacity/Invalidity	3
Hospitalization or prolongation of hospitalization	49
Medically important event	41

Discontinuations Due to Adverse Events

These reports described 350 adverse events experienced by 107 patients. Discontinuations due to adverse events were primarily related to the digestive system. The relationship to lopinavir/ritonavir, as assessed by the investigator, is summarized in Figure 2.

Figure 2. Discontinuation Due to Adverse Events by Relationship to Lopinavir/ritonavir



Note: Patients could have discontinued with more than one adverse event.

Nature of Adverse Events

The most frequently reported adverse events were diarrhea, nausea, rash, hyperlipemia, abdominal pain, vomiting, asthenia, and fever. The majority of the adverse events were related to the digestive system or the body as a whole. Those adverse events reported in >0.20% of the patient population are summarized in Table 4.

Table 4. Adverse Events by Body System

	Number of AEs	Percent of Enrolled Patients (%)
Digestive System	271	7.10
Diarrhea	102	2.67
Nausea	46	1.20
Vomiting	30	0.79
Liver Damage	13	0.34
Anorexia	9	0.24
Flatulence	9	0.24
Other Digestive Systems AEs*	62	1.62
Body as a Whole	210	5.50
Abdominal Pain	33	0.86
Asthenia	26	0.68
Fever	19	0.50
Reaction Aggravation	16	0.42
Infection	12	0.31
No Drug Effect	11	0.29
Headache	10	0.26
Pain	10	0.26
Malaise	9	0.24
Reaction Unevaluable	9	0.24
Other Body as a Whole AEs*	55	1.44
Metabolic and Nutritional Disorders	116	3.04
Hyperlipemia	34	0.89
Hypercholesterolemia	14	0.37
Weight Decrease	9	0.24
Other Metabolic and Nutritional Disorders AEs*	59	1.54
Skin and Appendages	62	1.62
Rash, Rash Maculopapular, Rash Pustular, and Rash Vesiculubullous	35	0.92
Pruritis	14	0.37
Other Skin and Appendage AEs*	13	0.34
Nervous System	55	1.44
Vertigo	9	0.24
Other Nervous System AEs*	46	1.20
Other Body Systems	122	3.19

* No single event occurred in >0.2% of the patient population.

Adverse Events of Special Interest

- Hyperlipemia: Adverse events of hyperlipemia or hypercholesterolemia were reported for 36 (0.94%) patients enrolled in the ATU. Of these patients, 8 (22%) discontinued from the program.
- Diabetes: A total of 6 patients reported diabetes as an adverse event; medical history was available for 5. Of these, 3 were considered by the investigator to be probably not, or not related to study drug and the remaining two were reported as possibly or probably related to study drug.
- Pancreatitis: A total of 7 patients reported pancreatitis as an adverse event, 5 of which were considered by the investigator to be of possible, probable, or unknown relationship to study drug. All had alternative risk factors reported including ddI use (4) or alcohol use (1).
- Death: During the course of the program, 19 (0.50%) patients died; however, none of the deaths was considered related to study drug.

CONCLUSIONS

- The pharmacovigilance database analysis shows that the overall tolerance to lopinavir/ritonavir was good, even in these treatment-experienced patients.
- Adverse events in the ATU program were infrequent and rarely resulted in study interruption or discontinuation.
- Overall, the safety profile observed in the ATU program was comparable to that seen in Phase III clinical trials.

ACKNOWLEDGMENTS

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