ARE INTEGRASE INHIBITORS A RISK FACTOR FOR IRIS IN THE ANRS 146 OPTIMAL TRIAL ?

Poster 495

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BACKGROUND

At CROI 2017, two observational studies based on retrospective assessment of IRIS occurring within 6 to 12 months after first antiretroviral treatment (ART) initiation have reported an increased risk of IRIS with integrase inhibitor (II) based regimen.
We evaluated this association in the context of the ANRS 146 trial, an European, multicenter, randomized, double-blind, phase III trial, in France, Spain and Italy, in ART-naïve HIV1-infected adults with CD4+ count<200/µL or an AIDS defining event. IRIS was a component of the composite primary endpoint prospectively validated by an event review committee.

METHODS

Study population

Inclusion criteria
- Confirmed HIV-1 infection
- Adult patients (age >18 years)
- CD4+ T lymphocytes <200/mm3 and/or AIDS-defining-illness
- Antiretroviral naïve patients

Non-inclusion criteria
- Current pregnancy, lack of contraceptive method, breast-feeding
- Current active tuberculosis (either suspected or diagnosed)
- Ongoing malignancies except cutaneous Kaposi's sarcoma (Patients with a previous cancer considered as cured for at least 6 months could be included in the study)
- Current or previous severe cardiac failure, chronic respiratory disease, renal or liver insufficiency; any life-threatening organ failure
- Cognitive impairment, psychiatric disorders, severe depressive affects, inappropriate behavior
- Use of cytostatic drugs, immunosuppressive agents, steroids
- Current or previous, during the last three months, use of immunomodulatory agents (G-CSF, IL-2, GM-CSF, interferons, pentoxifylline)
- Hypersensitivity to peanut and /or soy products

Design

- HIV-1 infected patients with an AIDS-defining event and/or CD4 counts ≤ 200 cells/mm³

1:1 randomization, double-blind

- ARV according to the recommended regimen in most commonly used guidelines + **MARAVIROC**
- ARV according to the recommended regimen in most commonly used guidelines + **Placebo**

- International: France, Spain and Italy,
- Follow-up to week 72

- Primary endpoint: Occurrence of a severe morbidity (AIDS, other HIV related diseases, serious non-AIDS events, IRIS and death)

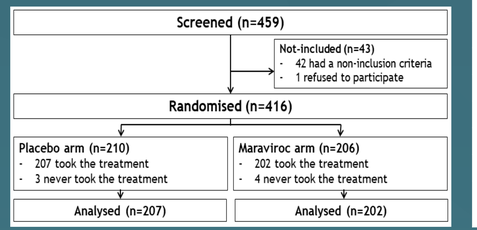
IRIS was defined as two major criteria (A.B) or major criterion A plus two minor criteria (French AIDS 2004, revised by Meintjes, Lancet ID 2008)

Major criteria
- A= atypical presentation of OI or tumours in patients responding to ART
- B= decrease in plasma HIV RNA of at least one log/mL

Minor criteria
- Increase in CD4 count after starting ART
- Increase in an immune response to the relevant pathogen
- Spontaneous resolution of the disease without specific antimicrobial therapy or tumour chemotherapy with continuation of ART

We compared the risk of IRIS using Kaplan-Meier estimates and multivariable Cox proportional-hazards models.

Study Flowchart



RESULTS

Between October 2011 and November 2014, 409 patients were included. Sixty-two individuals initiated with II (55 with raltegravir) and 347 did not (PI/r=283, NNRTI=64). Overall, 28 documented IRIS occurred, 26 within the first six months.

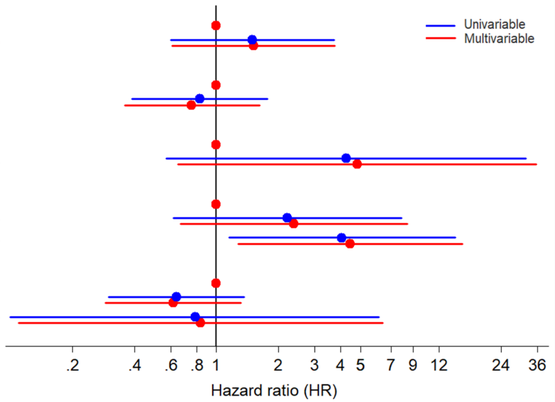
IRIS	II (n=6)	no II (n=22)
Adenopathy	0	1
CMV	1	1
Cryptococcal infection	0	2
Folliculitis	0	4
Herpes zooster	1	0
Histoplasmosis	1	0
Kaposi sarcoma	2	5
Mycobacterial infection	0	1
PCP	1	4
PML	0	1
Vasculitis	0	2
VZV infection	0	1

Participant baseline characteristics

	No II (n=347)	II (n=62)	Total (n=409)	P-value
Randomisation group				0.66
• PBO	174 (50.1%)	33 (53.2%)	207 (50.6%)	
• MVC	173 (49.9%)	29 (46.8%)	202 (49.4%)	
Age. years. median [range]	42 [21-74]	41 [22-68]	42 [21-74]	0.50
Male	292 (84.1%)	55 (88.7%)	347 (84.8%)	0.35
Sub-saharan-Africa	58 (16.7%)	3 (4.8%)	61 (14.9%)	0.12
Men who have sex with men	171 (49.3%)	34 (54.9%)	205 (50.1%)	0.70
Baseline HIV VL. (log10) (cp/mL)	5.4 [1.9-6.7]	5.3 [4.4-6.7]	5.4 [1.9-6.7]	0.40
• <100.000	89 (25.8%)	19 (30.6%)	108 (26.5%)	
• 100.000 -500.000	157 (45.5%)	29 (46.8%)	186 (45.7%)	
• >500.000	99 (28.7%)	14 (22.6%)	113 (27.8%)	
R5 Tropism at D0††	224 (66.1%)	43 (69.4%)	267 (66.6%)	0.61
CD4 cell count (/µL) at baseline	81.5 [0-615]	76 [3-229]	80 [0-615]	0.97
• <50/µL	134 (38.6%)	26 (41.9%)	160 (39.1%)	
• 50-200/µL	202 (58.2%)	34 (54. %)	236 (57.7%)	
• >200/µL	11 (3.2%)	2 (3.3%)	13 (3.2%)	
CD4/CD8 at baseline	0.11 [0-0.84]	0.10 [0.01-0.54]	0.11 [0-0.84]	0.67
• <0.10	148 (42.9%)	29 (47.5%)	177 (43.6%)	
• 0.10-0.30	163 (47.2%)	27 (44.3%)	190 (46.8%)	
• >0.30	34 (9.9%)	5 (8.2%)	39 (9.6%)	
AIDS Defining Events at screening	144 (41.5%)	26 (41.9%)	170 (41.6%)	0.95

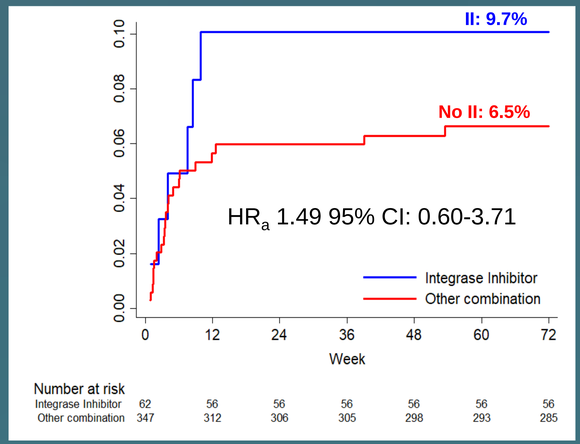
Impact of integrase inhibitor on the occurrence of IRIS

		N	Events	Incidence (p.-y.)	HR*
Integrase inhibitor	**No**	**347**	**22**	**5.22**	**1**
	Yes	**62**	**6**	**8.02**	**1.49**
Randomisation group	PBO	207	16	6.35	1
	MVC	202	12	4.91	0.83
Origin	African	61	1	1.34	1
	Other	348	27	6.40	4.26
HIV RNA at screening	<100,000	108	3	2.15	1
	100,000–500,000	186	12	5.31	2.20
	>500,000	113	13	10.14	4.06
CD4 cell count at screening	<50/µL	160	14	7.49	1
	50-200/µL	236	13	4.44	0.64
	>200/µL	13	1	6.00	0.79



*Multivariable: adjusted on treatment arm, origin, baseline CD4 count and VL

Probability of IRIS according to whether or not the ART regimen was including an II



CONCLUSION

Although a numerically higher rate of IRIS was observed with II, no significant association was evidenced between the risk of IRIS and initiating ART with an integrase inhibitor in individuals presenting at an advanced stage in the ANRS Optimal trial, where IRIS was a prospectively validated endpoint

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