Integrase Inhibitors are an Independent Risk Factor for IRIS: an ATHENA-Cohort Study

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Hypothesis

Use of integrase inhibitor (INI) containing combination antiretroviral therapy (cART) is an independent risk factor for immune reconstitution inflammatory syndrome (IRIS) in HIV-1 late presenters.

Introduction

Treatment with INI-containing cART is recommended as first choice by treatment-guidelines for cART-naive HIV-1 infected patients.

The use of INI-containing cART results in a faster HIV-RNA decline and CD4-T-lymphocyte recovery than use of PI- or NNRTI-containing cART.

HIV-RNA-decline and CD4-T-lymphocyte recovery are associated with IRIS.

HIV-1 late presenters with CD4-T-lymphocytes < 200 cells/mm^3 are at particular risk for IRIS.

IRIS is a pathological inflammatory response against antigens of opportunistic infections (OI).

Phase III studies include very few late-presenters. In particular the subset of patients with an active OI is excluded from these trials. Therefore, little is known about the incidence of IRIS in patients treated with INI-containing cART.

Methods

Design:
Multicenter retrospective observational study in the Dutch ATHENA-cohort.

Inclusion criteria:
1. Initiation of cART ≥ 24-03-2009 (date of registration of raltegravir in the Netherlands) AND
2. CD4-T-lymphocytes ≤ 200 cells/mm^3 before initiation of cART

As it was impossible to evaluate the entire ATHENA population that fulfilled criterium 1 and 2, we required patients to also fulfill at least 1 of the following 2 criteria. This limited the study population to those patients at highest risk for IRIS:
1. An OI diagnosed prior or after initiation of cART AND/OR
2. Use of corticosteroids ≤ 12 months after initiation of cART

Finally, to allow for the evaluation of IRIS as a possible cause of mortality, all patients fulfilling inclusion criterium 1 and 2, who died within 12 months after initiation of cART, were included and their patients files were reviewed as well.

2 definitions for IRIS were used:
$IRIS_{FRENCH}$ = IRIS according to French et al (French et al, AIDS 2004).
An atypical presentation of an OI or tumor in a patient responding to cART AND a documented decline in HIV-RNA OR increase in CD4 count.

$IRIS_{CLINICAL}$ = IRIS according to clinician.
IRIS as most likely diagnosis in the patient file OR IRIS in the differential diagnosis with initiation of treatment for IRIS (e.g. corticosteroids).

Every patient and IRIS endpoint was counted only once: As we considered $IRIS_{FRENCH}$ to be more specific than $IRIS_{CLINICAL}$, patients with IRIS according to both definitions were counted as $IRIS_{FRENCH}$.

Primary endpoint:
Incidence of $IRIS_{FRENCH+CLINICAL}$ and $IRIS_{FRENCH}$ in INI versus non-INI users.

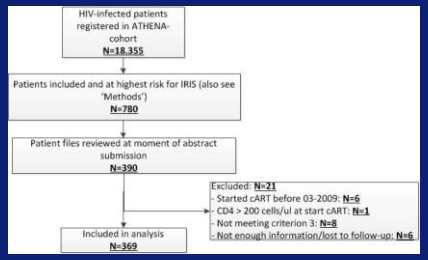
Secondary endpoints:
Use of steroids for IRIS, hospital (re)admission after cART-initiation and death within 12 months after cART-initiation.

Statistical analysis: Cox regression analysis
Outcome: time to diagnosis of IRIS
Exposure of main interest: use of INI
Censoring: switch from NNRTI/PI to or away from INI
Controlling for potential confounders
Interactions of INI use with other significant predictors of IRIS

Potential confounders included in the analysis were:
Demographic (e.g. gender, age, ethnicity)
Immunological and virological (e.g. CD4-T-cell nadir, HIV-RNA-zenith)
cART (e.g. time between diagnosis OI and cART initiation)
OI characteristics (e.g. type of OI, use of corticosteroids as part of OI treatment)

Results

Inclusion of patients:



Study population:

	INI (N=69)	n-INI (N=300)
Male sex, N (%)	51 (74)	250 (83)
Age, median	43	43
Year of HIV-diagnosis, median	2011	2011
HIV-RNA at HIV-diagnosis, median c/ml	446.694	257.040
CD4-T-lymphocytes at HIV-diagnosis, median cells/mm^3	36	30
Mode of transmission, N (%)		
HSX	33 (48)	119 (40)
MSM	22 (32)	111 (37)
Unknown	6 (9)	36 (12)
Other	7 (10)	35 (12)
Region of origin, N (%)		
NL	34 (49)	180 (60)
Europe	8 (12)	21 (7)
Africa	11 (16)	40 (13)
South America and Caribbean	8 (12)	39 (13)
Other	7 (10)	23 (8)

INI = Integrase Inhibitorm HSX = HeteroSexual, MSM = Men having Sex with Men, NL = Netherlands.

Diagnosed Opportunistic Infections:

	INI (N=101 in 69 pts)	n-INI (N=423 in 300 pts)
Pneumocystis jirovecii pneumonia	26	141
Candidiasis	21	122
Mycobacterial infections	19	32
Kaposi's sarcoma	6	32
Cerebral toxoplasmosis	4	23
CMV	5	20
Cryptococcosis	1	7
Other	19	46

INI = Integrase Inhibitor, CMV = CytoMegaloVirus.

Use of steroids, (re)hospitalization and death after start cART:

	INI (N=69)	n-INI (N=300)	P-value
Initiation of steroids for IRIS, N (%)	16 (23)	40 (13)	0.035
Hospital (re)admission after cART-initiation, N (%)	39 (57)	136 (45)	0.072
Death within 12 months after cART-initiation*, N (%)	9 (13)	31 (10)	0.465

** of 3 patients, the exact date of death was not available.*

Incidences of both forms of IRIS:

	INI (N=69)	n-INI (N=300)	Total (N=369)
Type IRIS			
$IRIS_{FRENCH}$, N(%)	13 (19)	27 (9)	40 (11)
$IRIS_{CLINICAL}$, N(%)	13 (19)	20 (7)	33 (9)
Total, N (%)	26 (38)	47 (16)	73 (20)

Cox regression analysis:

	$IRIS_{FRENCH+CLINICAL}$ HR (95% CI), p-value	$IRIS_{FRENCH}$ HR (95% CI), p-value
Use of INI	2.69 (1.63-4.44), 0.0001	2.62 (1.35-5.10), 0.0045
Female gender	1.64 (0.97-2.78), 0.067	-
Diagnosed with CM	3.71 (1.55-8.88), 0.0033	11.6 (4.77-28.3), <0.0001
Diagnosed with MAC	2.46 (1.04-5.84), 0.041	-
Diagnosed with CMV	2.25 (1.06-4.79), 0.035	4.23 (1.84-9.74), 0.0007

INI = integrase Inhibitor, CM = Cryptococcal Meningitis, MAC = Mycobacterium Avium Complex, CMV = CytoMegalo Virus.

OR $IRIS_{FRENCH}$: 2.35 (95% CI 1.14 – 4.83)
OR $IRIS_{CLINICAL}$: 3.25 (95% CI 1.53 – 6.91)
OR $IRIS_{TOTAL}$: 3.25 (95% CI 1.83 – 5.80)

None of the following patient characteristics were associated with an increased HR for IRIS: gender, age, ethnicity, mode of HIV acquisition, calendar year, baseline CD4-T-lymphocytes, CD4/CD8-ratio, HIV-RNA-zenith, type of cART-regimen, number and type of OI-events (CM, TBC/MAC, CMV, pneumocystis jirovecii pneumonia, toxoplasmosis, progressive multifocal leucoencephalopathy, kaposi's sarcoma), time between start treatment OI and start cART, use of steroids for OI treatment.

No interaction was observed between the use of INI and any of the other characteristics that were significantly associated with the presence of IRIS.

Conclusions

Use of INI containing cART in HIV-1 late presenters is an independent risk factor for IRIS.

If confirmed by others, the use of INI as initial cART in HIV-1 late presenters may have to be revisited.