Erasmus MC
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Integrase inhibitor use is an independent risk factor for immune reconstitution inflammatory syndrome (IRIS) in HIV-1 late presenters in the Dutch ATHENA cohort

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Introduction

- Treatment with integrase inhibitor (INI)-containing combination antiretroviral therapy (cART) is recommended as first choice by treatment-guidelines for cART-naive HIV-1 infected patients[1].

- INI versus protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTI)[2-4]:
  - Faster HIV-RNA decline
  - Enhanced CD4 T-cell recovery

1. https://aidsinfo.nih.gov, guideline for use of antiretroviral agents in HIV-1 infected adults and adolescents, v.14-07-2016
2. Rockstroh, JAIDS 2013
3. Sax, Lancet 2012
4. Clotet, Lancet 2014

Introduction

- CD4-T-cell recovery and HIV-RNA decline associated with IRIS[1].
  - HIV-1 late presenters: CD4-T-cells < 200 cells/mm^3
- IRIS is a pathological inflammatory response against antigens [2].
  - Opportunistic infections (OI)
- Consequences of IRIS:
  - (Re)hospitalization
  - Use of corticosteroids and other immunomodulating agents
  - Death

1. *Grant, PLoS ONE 2010*
2. *Chang, Curr HIV/AIDS Rep 2014*

Hypothesis

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

Methods

- Multicenter retrospective observational study: ATHENA cohort.
- Standardized data collection with CRF.
- Selection of HIV-1 infected adults with highest risk for IRIS:
  - Initiation of cART after 24-03-2009 AND
  - CD4-T-cells < 200 cells/mm^3 at initiation of cART AND
  - An OI prior or after start cART OR
  - Use of corticosteroids < 12 months after start cART OR
  - Death < 12 months after start cART

Methods

- How to define IRIS?

1. ‘French IRIS’ = IRIS defined by French et al[1]:

Major criteria
A. Atypical presentation of ‘opportunistic infections or tumours’ in patients responding to antiretroviral therapy (ART). Localised disease, eg. lymph nodes, liver, spleen Exaggerated inflammatory reaction, eg. Severe fever, with exclusion of other causes Painful lesions Atypical inflammatory response in affected tissues, eg. Granulomas, suppuration, necrosis Perivascular lymphocytic inflammatory cell infiltrate Progression of organ dysfunction or enlargement of pre-existing lesions after definite clinical improvement with pathogen-specific therapy prior to the commencement of ART and exclusion of treatment toxicity and new diagnoses, eg. Development or enlargement of cerebral space occupying lesions after treatment for cerebral cryptococcosis or toxoplasmosis Progressive pneumonitis or the development of organizing pneumonia after treatment for pulmonary MTB or PCP New onset or worsening of uveitis/vitritis after the resolution of CMV retinitis Fever and cytopenia after treatment for disseminated MAC Enlargement of Kaposi’s sarcoma lesions and subsequent resolution or partial regression without commencement of radiotherapy, systemic chemotherapy or intralesional therapy B. Decrease in plasma HIV RNA level by >1 $\log_{10}$ copies/mL
Minor criteria
Increased blood CD4 T-cell count after ART. Increase in an immune response specific to the relevant pathogen, eg. DTH response to mycobacterial antigens Spontaneous resolution of disease without specific antimicrobial therapy or tumour chemotherapy with continuation of anti-retroviral therapy

Confirmed IRIS = A + B or A + 2x minor

Probable IRIS = A + 1x minor

1. *French, AIDS 2004*

Methods

- How to define IRIS?

1. ‘French IRIS’ = IRIS defined by French et al[1].

2. ‘Clinical IRIS’ = IRIS defined by a broader clinical definition:
   - IRIS as most likely diagnosis in patient file OR
   - IRIS in differential diagnosis AND treatment for IRIS was initiated

- French IRIS:
  - French conf./prob. YES
  - Clinical YES or NO

- Clinical IRIS:
  - French conf./prob. NO
  - Clinical YES

1. *French, AIDS 2004*

Methods

- Exemplary case IRIS

- M54, MSM
- Admission with PJP and newly diagnosed HIV infection
- HIV-RNA 5 $\log_{10}$ c/ml, CD4 T-lymphocytes 25 cells/mm^3

- Treatment PJP: cotrimoxazole 3 x 1920 mg/day for 14 days
    - Improvement of clinical performance and chest X-ray
- Start cART 3 weeks after initiation of treatment OI

- 4 weeks later: recurrence of fever, dyspnea, coughing
- No microbial agent found in cultures, chest X-ray: deterioration
- HIV-RNA 2 $\log_{10}$ c/ml, CD4 T-lymphocytes 189 cells/mm^3

Methods

- *Primary endpoint:*
  - Incidence of IRIS in INI versus non-INI
    - Both ‘French IRIS’ and ‘Clinical IRIS’
    - Univariate and multivariate analysis
    - Odds ratio (OR) and Hazard ratio (HR)
    - Cox regression analysis

Methods

- Cox regression:
  - Outcome: time to diagnosis of IRIS
  - Exposure of main interest: use of INI
  - Sensoring: after switch to or away from INI
  - Controlling for potential confounders
  - Interactions of INI use with other significant predictors of IRIS
- Potential confounders:
  - gender, age, ethnicity, mode of HIV acquisition, calendar year
  - baseline CD4, CD4/8-ratio and pVL
  - type of cART-regimen (NNRTI vs PI-based)
  - # and type (CM, TB/MAC, CMV, PJP, toxo, PML, KS) of AIDS-events
  - time between start of antimicrobial therapy and start of cART
  - use of steroids for OI treatment.

Results

Results

- Baseline characteristics

	INI (N=69)	n-INI (N=300)
Sex, male (%)	51 (75)	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/ul	36	30
Mode of transmission, (%)		
HSX	33 (49)	119 (40)
MSM	22 (32)	111 (37)
Unknown	6 (9)	36 (12)
Other	7 (10)	35 (11)
Region of origin, (%)		
NL	34 (50)	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)

Results

- 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

Results

Incidences of both types of IRIS in INI versus n-INI:

	INI (N=69)
French IRIS, N *(%)*	13 *(19)*
Clinical IRIS, N *(%)*	13 *(19)*
Total, N *(%)*	26 *(38)*

OR_{INI} 3.25, 95%CI 1.83-5.80

Results

Cox regression analysis:

	IRIS French + clin. 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

No other investigated parameters were significant predictors of IRIS.

No interactions between use of INI and any of the other parameters.

Conclusion and discussion

- INI use in HIV-1 late presenters is an independent risk factor for IRIS.

- For more definitive conclusions:
  - Increase sample size
  - Cohort study: confirmation by other studies needed.

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

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Questions

Methods - Pilot studies

1. Goal: determine the sensitivity of the cut-off value 100 cells/mm^3

   - Population: 100 – 200 cells/mm^3
   - EMC IRIS: 0% | AMC IRIS: 7.6%
   - Outcome: CD4 T-cell count ≤ 200 cells/mm^3 at start cART

2. Goal: determine the sensitivity of inclusion criterium corticosteroids

   - Population: 0 – 200 cells/mm^3
   - EMC: not treated with corticosteroids: 60%
   - Outcome: besides ‘use of steroids’ also ‘OI present before or after start cART’ as inclusion criterion