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ULB UNIVERSITÉ LIBRE DE BRUXELLES

Foscarnet in salvage-therapy of multi-drug experienced HIV-1 infected patients: a Belgian case series.

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Study design and objectives

Foscarnet (= Foscavir) is a pyrophosphate analogue which binds reversibly near the pyrophosphate-binding site of the HIV retrotranscriptase, resulting in the interruption of viral DNA elongation.
In CHU Saint-Pierre, it has been used as part of a salvage therapy in multi-drug-experienced HIV-1 patients in virological failure.
The salvage-therapy protocol consisted of two phases :
1. Induction : administration of IV Foscarnet AND numerous oral antiretroviral drugs (+/- subcutaneous Enfuvirtide, T20)
2. Maintenance : Foscarnet was stopped whereas the antiretroviral (ARV) treatment on discharge from hospital included the best possible combination of oral ARV drugs (+/- subcutaneous T20).

The objectives of our retrospective observational study :
❑ Evaluation of **efficacy** : effect on CD4⁺ T-cell count, plasmatic viral load (pVL), and survival
❑ Evaluation of **tolerability**

Patients and methods

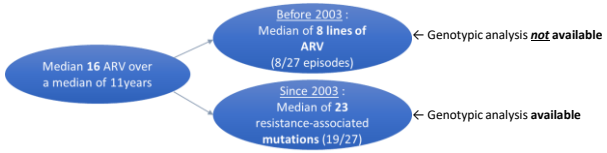
Inclusion criteria
❑ Adult HIV-1 infected patients on antiretroviral (ARV) drugs for ≥ 6months
❑ Virological failure (viral load > 200 copies/mL)
❑ History of numerous lines of ARV drugs
❑ Treated with a Foscarnet-based salvage-therapy

If a genotype analysis had been carried out before the Foscarnet induction protocol :
❑ A cumulative resistance profile was determined, according to all major and minor resistance-associated mutations known so far
❑ A Genotypic Susceptibility Score (GSS) was calculated for each treatment combination before and after the induction protocol
➢ According to Rega rules, KU Leuven, last version (v10.0 in 2017)
➢ Resistance development is expected when GSS is <2 in therapy-experienced patients with limited treatment options

Baseline population characteristics

Between 1997 and 2019, 27 episodes of administration of Foscarnet as an induction agent in the salvage-therapy protocol were found, in 13 patients :
❑ ratio M/F : 9/4
❑ ethnicity : 8 caucasian, 5 african
❑ **median age : 38 years old** (min 25 - max 56)
❑ HIV transmission : 6 heterosexual, 5 MSM (men having sex with men), 2 perinatal
❑ **92% had a history of ≥1 AIDS-defining-event**

Median viral load : 5.14 log_{10} copies/mL (IQR 25-75: 5-5.69)
Median CD4⁺ T-cell count : 20/mm³ (IQR 25-75: 7-121)



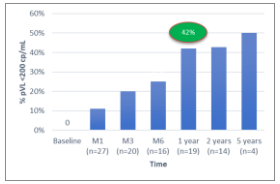
Study drugs

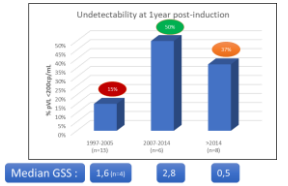
In-hospital **induction phase of salvage-therapy** consisted of :
➢ Intravenous Foscarnet
➢ A median of **5 ARV** drugs included in the « best possible therapy »
❑ including T20 in 67% episodes (18/27), mostly in IV
❑ T20 was already administered as part of the failing regimen upon hospital admission in 7/18 episodes (subcutaneously before the induction protocol, and switched to intravenous administration during the induction protocol)
❑ 5/18 episodes were harbouring a virus which was proved to be resistant to T20
After the induction phase, when returning home, the **maintenance therapy** included
➢ The best possible oral ARV therapy (if T20 was included, it was switched to subcutaneous administration)
➢ For the 18/27 episodes in which a genotypic analysis had been carried out (and so GSS calculation was possible), the **recommended GSS treshold ≥2** was achieved in ***only 33%*** (6/18) of maintenance ARV combinations at hospital discharge.

Immunological and virological results

Up to 2-years-follow-up, the increase in CD4⁺ T-cell count from baseline was <100/mm³ in all episodes.
Viral load at one month from induction phase (M1) showed a **median reduction of 2.34 log_{10} cp/mL** (IQR25-75: -2.71 to -1.69) .
81% episodes had a viral load reduction of ≥ 1log_{10} cp/mL.

The proportion of **undetectability** (viral load <200 copies/mL) at **one year post-induction** phase was :
- achieved in **42%** of episodes.
- **greater** in the subgroup of episodes happening **after the introduction of first-generation integrase inhibitors** on the market (≥2007).





N.B. in the subgroup of episodes happening after 2014, 5/8 episodes belonged to one patient whose HIV was dolutegravir-resistant.

Long-term outcome and tolerability

54% survival rate at 4 years follow-up, despite patients being multi-drug experienced **and** very immunocompromised.

There were significant side effects in 66% (18/27) episodes, leading to premature discontinuation in 6 episodes (22%), 5 of which resolved rapidly after Foscarnet discontinuation.

Side effect	n episodes	n patients	Premature FOS discontinuation
Electrolyte disturbances (Ca^{2+}, K^+, Mg^{2+}, PO^{4-})	13	6	No
Acute renal failure	7	5	Yes (n=2/7)
Proteinuria	3	2	No
Genital ulcers	2	1	Yes (n=2/2)
Injection site phlebitis	1	1	No
Gastro-intestinal toxicity	1	1	Yes (n=1)
Anemia	1	1	No
Fanconi syndrome	1	1	No
Myocarditis (leading to intensive care admission)	1	1	Yes (n=1)

Acute renal failure is defined by a creatinine increase of ≥0.3mg/dL from baseline.

Conclusions

1) Despite the current extensive antiretroviral (ARV) options, **HIV-1 multidrug cross-resistance remains a serious concern** in heavily ARV-experienced and immunocompromised patients in virological failure.
2) Future access to new ARV or classes of ARV drugs may be different in high versus low-and-middle income countries. **Foscarnet may be considered relatively affordable in middle-income countries in comparison to Ibalizumab, Fostemsavir, and Lenacapavir.** Moreover, a generic version of Foscarnet exists since March 2021.
3) Foscarnet-based salvage-therapy may be **a valuable alternative when no other therapeutic option is left** as it may help to gain survival time, and may be used as a standby option while waiting for access to new ARV classes.
4) **Long-term efficacy depends on the activity of the maintenance « best possible ARV therapy » and the patient adherence.**

Study limitations	Study strenghts
Small cohort	Largest series to date, longest follow-up
Retrospective and observational study	Intravenous use of T20 during induction
Data collection spans over 23years	Efficacy persist even if repeated

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