

SINGLE SUPERVISED TREATMENT INTERRUPTION COUPLED WITH MYCOPHENOLATE MOFETIL THERAPY INDUCES CONTROL OF HIV 1 RNA REPLICATION IN PATIENTS TREATED WITH HAART SINCE PRIMARY HIV 1 INFECTION:102- WEEK FOLLOW UP

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INTRODUCTION

Primary HIV infection (PHI) is characterised by an heightened state of immune activation that is accompanied by the dissemination of the virus in the host. Events occurring during PHI, and the mutual interactions between the virus and the host, determine the course and the pattern of disease progression. Treatment of PHI with antiretroviral therapy (ART) improves both immune preservation and immune reconstitution, and might affect the course of disease progression. However, limits associated with ART, including drug adherence, drug toxicity, and drug resistance, have to be taken into account evaluating the risk/benefit ratio for the patient. Structured treatment interruptions (STI) have been tested as a mean to reduce exposure to ART, thus decreasing the impact of ART-associated caveats. In patients treated at the time of PHI, repeated cycles of STI have induced some extent of virus control in absence of ART, though not persisting over long-term follow-up. Mycophenolate mofetil (MMF) reduces the pool of dividing and activated CD4⁺ T cells, contributing to control virus replication in patients with chronic HIV infection. In this study, the impact of coupling MMF with a single supervised treatment interruption (sSTI) on the overall need of ART in patients treated at the time PHI has been evaluated.

STUDY DESIGN

In a prospective controlled open label non randomised study carried out at the San Raffaele Scientific Institute (Milan, Italy) and the Centre Hospitalier Universitaire Vaudois (Lausanne, Switzerland), 15 patients treated since PHI with ART have been enrolled. All patients had achieved optimal and persistent viral suppression, for at least 2 years before enrolment. At entry, patients added MMF (500 mg bid) 15 days before stopping ART; after ART interruption (at week 0), MMF was continued for 24 weeks. In case viral load (VL) exceeded 100K copies/ml on two consecutive measurements, ART was restarted. As controls, 6 well-matched patients for sex, age, PHI characteristics, and extent of VL suppression before enrolment, were included to undergo sSTI without taking MMF. Plasma viral load was measured with NasaB Organon assay (limit of detection: 80 copies/ml).

RATIONALE FOR THE USE OF MMF

MMF is the ester derivative of mycophenolic acid (MPA). It selectively inhibits the *de novo* synthesis of purines from ribose phosphate in T and B lymphocytes by inhibiting the inosine monophosphate dehydrogenase and guanylate synthetase. It suppresses HIV replication *in vitro* and enhances the antiviral activity of guanosine reverse transcriptase inhibitors (Fig. 1). A pilot study demonstrated that, along with the anti-HIV virological effect, MMF also induces apoptosis and cell death in a large proportion of activated CD4⁺ T cells suggesting an inhibitory capacity by immunological mechanisms (Chapuis et al. Nature Medicine 2000). Thus, the rationale to add MMF is to shut down immune activation induced by ART interruption, reducing the pool of dividing and activated CD4⁺ T cells that support virus production.

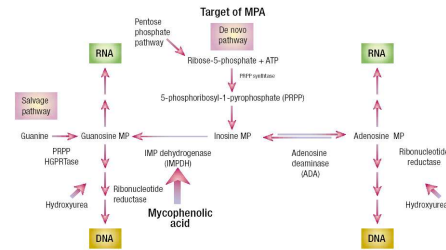


Figure 1 : Mechanism of inhibition of purine synthesis by MMF

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RESULTS

Patients in the MMF group (n=15) and in the control group (n=6) had well-matched baseline demographic and clinical characteristics. Patients who received MMF had been on continuous ART for 4.9±0.8 years (mean±SD), maintaining VL below the limit of detection for 3.6±0.7 years (mean±SD). In controls, these values are 2.7±0.2 and 2.3 ± 0.1 years (mean±SD), respectively. The mean follow-up is 24 months in both groups.

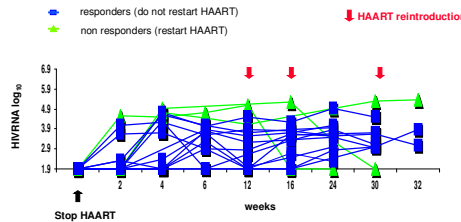


Figure 2: sSTI in patients treated with MMF

In the MMF group only 3 out of 15 patients (20%) restarted HAART and viral rebound >100 Kcopies happened between 12 and 24 weeks. After stopping HAART mean of individual highest rebounding viral load peak between weeks 2-12 was 3.9 ± 0.26 (mean±SD), in the 15 MMF patients versus 5.62 ± 0.21 (mean±SD), in the 6 controls (p=0.001).

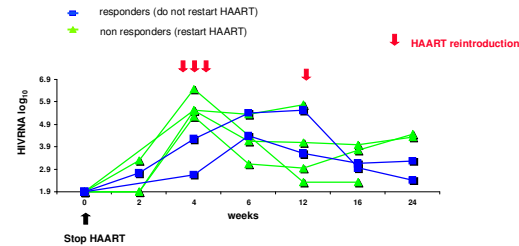


Figure 3: sSTI in patients without MMF

In the control group 4 out of 6 patients restarted HAART (66%) and higher viral rebound >100 Kcopies/ml occurred sooner than the MMF group within the first 12 weeks after sSTI (3 out of 4 patients restarted therapy at week 4). Of note also rebound viral slope were significantly higher in the controls than in MMF group (0.006 log₁₀ vs 0.007 log₁₀, p=0.006). In the remaining 2 patients of the control group, who did not restart HAART, although with viral load at long term < 10 Kcopies/ml, CD4 cell count substantially decreased at week 102 (-419 and -494 cells/μl).

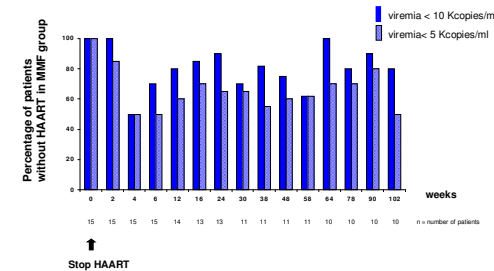


Figure 4: proportion of patients without HAART in MMF group with viremia below 10 and 5 Kcopies/ml

Following sSTI and MMF 80% of the patients maintained effective VL control over time, mostly < 5 K copies/ml, and of note 2 patients had stably VL below the detection limit.

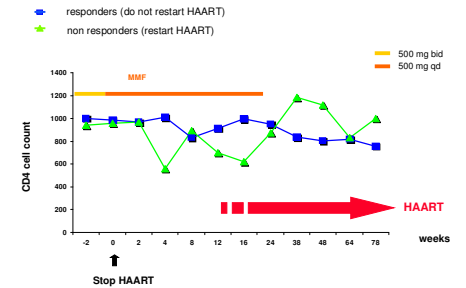


Figure 5: Mean CD4 cell count in MMF group

With the introduction of MMF we had a slightly decrease of CD4 cell count but during the all follow up in patients without HAART CD4 count remained high (at week 102: CD4 546 ± 74) (mean ± SD). In all patients MMF was safe and no side effects were experienced. In patients, where HAART was restarted, regained CD4 cell count very fast even at higher levels than the baseline.

CONCLUSIONS

In patients treated with HAART during PHI the combined use of single STI and 24 weeks-MMF leads to a remarkably lower VL rebound than observed in patients undergoing sSTI alone. In addition 80% of sSTI+MMF achieved a long term control of virus replication versus only 44% in the control group. A unique treatment interruption along with MMF is safe and induces a better outcome than that observed in multiple STI studies without concomitant use of MMF.

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