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Four-year outcome of a PI and NRTI-sparing salvage regimen: maraviroc, raltegravir, etravirine

Silvia Nozza[1], Laura Galli[1], Alba Bigoloni[1], Nicola Gianotti[1], Vincenzo Spagnuolo[1], Alessia Carbone[1,2], Stefania Chiappetta[1,2], Marco Ripa[2], Giuseppe Tambussi[1], Adriano Lazzarin[1,2], Antonella Castagna[1]

[1]Department of Infectious Diseases, San Raffaele Scientific Institute, Milan, Italy;
[2]Università Vita-Salute San Raffaele, Milan, Italy

SUMMARY

Aim of this study was to report the 204-week efficacy and safety results of a novel PI- and NRTI-sparing regimen for salvage therapy including maraviroc, raltegravir, etravirine in 28 failing HIV-infected patients with R5-tropic virus. The trend of laboratory parameters was tested by ANOVA for repeated measures and Greenhouse-Geisser probabilities were reported. Results were described as median (Q1-Q3) values. Twenty-six (93%) out of 28 patients completed 204 weeks of treatment. Virological success (HIV-RNA<50 copies/mL) at week 204 was 96%. CD4+ counts significantly increased [244 (158-213) cells/mm^3, p<0.0001] from baseline [247 (68-355) cells/mm^3] as well as CD4+ percentage. Four serious adverse events (1 death due to Hodgkins's lymphoma, 1 anal cancer, 1 Hodgkins's lymphoma, 1 recurrence of mycobacterial spondylodiscitis) were observed; three events led to transitory discontinuation of the antiretroviral therapy due to drug-drug interaction. BMI (p<0.0001) and waist circumference (p<0.0001) significantly increased over 204 weeks. An amelioration was also observed in relation to haemoglobin (p=0.0006), platelets (p<0.0001), white blood cell (p=0.013), neutrophils (p=0.301), lymphocytes (p=0.207) and creatinine (p<0.0001). In highly treatment-experienced patients the maraviroc, raltegravir and etravirine combination is associated with a good long-term efficacy and safety profile.

KEY WORDS: Maraviroc, Raltegravir, Etravirine.

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INTRODUCTION

New antiretroviral combinations have achieved a high rate of virological response in patients harbouring multidrug-resistant HIV-1 viruses. The ANRS 139 TRIO trial reported that 88% of patients reached HIVRNA<50 copies/mL at 96 weeks of salvage treatment with raltegravir, etravirine and darunavir/ritonavir (Yazdanpanah 2009, Fagard 2012).
We recently published data on the 96-week outcome of a novel PI and NRTIs-sparing regimen including maraviroc, raltegravir, etravirine for salvage therapy in a small sample of 28 HIV-infected patients harbouring an R5-tropic virus: at week 96, 92% had HIVRNA<50 copies/ml and a CD4 increase of 211 (114-302) cells/mm^3 (Nozza 2010, Nozza 2011).
There are no long-term data on the immunovirological efficacy and safety of novel salvage regimens. The aim of this study was to evaluate the long-term efficacy and safety (204 weeks) of a novel PI and NRTI-sparing salvage regimen with maraviroc, raltegravir and etravirine.

Corresponding author
Silvia Nozza
Department of Infectious Diseases
San Raffaele Scientific Institute
Via Stamira d'Ancona, 20
20127 Milan, Italy
E-mail: silvia.nozza@hsr.it

PATIENTS AND METHODS

Twenty-eight triple-class experienced HIV-1-infected patients, failing a standard HAART regimen, attending the Department of Infectious Diseases of the San Raffaele Scientific Institute in Milan, Italy, were co-screened for entry

into the raltegravir (MK0518-023), maraviroc (A4001050) and etravirine (TMC125-C214) expanded access programmes after giving their written informed consent (Nozza 2010, Nozza 2011). A regimen with raltegravir, maraviroc and etravirine was planned for those with R5-tropic HIV-1, with resistance or previous failures to NRTIs (NNRTIs), NRTIs and PIs. At each visit (baseline, week 4, 12 and every 12 weeks until week 204), they underwent a physical examination, recording adverse events and fasting blood collection for haematological, biochemistry, immunological and virological analyses. HIV-1genotyping for resistance to protease and reverse transcriptase inhibitors, integrase and fusion inhibitors as well as HIV-1 co-receptor tropism test were performed at screening and at virological failure, if it occurred (defined as two consecutive values of HIV RNA >50 copies/mL).

Statistical analysis was performed on 26 of the 28 patients who started the antiretroviral regimen: as they were regularly followed up to week 204, a per-protocol analysis was performed. Results were described as median (Q1-Q3) values or frequency (%), as appropriate. Trend of laboratory parameters was tested by ANOVA for repeated measures and Greenhouse-Geisser probabilities were calculated to detect significant variations during follow-up.

RESULTS

All the 26 patients who reached 96 weeks of follow-up remained in the study and were followed-up until week 204.

Twenty-four of 26 (93%) of patients enrolled were males, 6 (21%) were intravenous drug users, and 8 (29%) were co-infected with hepatitis C virus (HCV). At baseline, they were 43.9 (42-49.4) years old and had 16.6 (14-20.2) years since their first HIV positive test, 14 (12-16.7) years of cART exposure, 74 (28-195) cells/mm^3 of nadir CD4+ count, 254 (76-399) cells/mm^3 of CD4+count, 13.6% (8.1%-19.6%) of CD4%, 0.21 (0.12-0.36) of CD4+/CD8+ ratio and 4.16 (3.85-5.08) $\log_{10}$ copies/mL of plasma HIV-RNA load. Sixteen patients (57%) had been previously diagnosed with a Centre for Disease Control and Prevention category C HIV-related illness.

Twenty-six of 28 (92%) enrolled patients completed 204 weeks of the study treatment; 2/28 (7%) patients discontinued for safety reasons: 1 patient died at week 72 and 1 patient stopped antiretroviral therapy at week 72 for AST and ALT increase due to alcohol abuse. Both patients had undetectable viral load at the time of treatment interruption.

At week 204, 25/26 (96%, 95%CI: 80%-100%) enrolled patients had HIVRNA <50 copies /mL (Fig. 1, panel A); 10/26 (39%, 95%CI: 20%-59%) had HIVRNA below 1 copies/ml detected by an ultrasensitive method. No other virological failures were reported after 96 weeks.

Overall, the median (IQR) CD4+ cell count rose from 247 (68-355) cells/mm^3 at baseline to 505 (419-505) cells/mm^3 at week 204 with a median increase of 244 (158-213) cells/mm^3 by week 204 ($p<0.0001$) (Fig. 1, panel B). A similar trend was observed in relation to CD4% (Tab. 1; p for trend over time: $P<0.0001$) and CD4+/CD8+ ratio (Tab. 1; p for trend over time: $p<0.0001$).

We observed 4 serious adverse events (15%) during the first 96 weeks, no other events occurred after this time. In three patients the antiretroviral therapy was suspended along with the administration of cytostatic drugs (for anal cancer and Hodgkins's lymphoma) or rifampin (for mycobacterial spondylodiscitis). Patients re-started the same regimen after completion of specific therapies, reaching undetectable viral load after 12 weeks of treatment.

Table 1 shows the trend of all the laboratory parameters considered during follow-up. There was a significant increase in body mass index ($p<0.0001$) and waist circumference ($p<0.0001$) during 204 weeks. We also observed an improvement of the haematological profile, with a significant increase in haemoglobin (p for trend over time: $p=0.0006$), platelets ($p<0.0001$), white blood cells ($p=0.013$) and a non-significant increase in lymphocytes ($p=0.207$) and neutrophils ($p=0.301$).

No significant changes were detected in relation to AST ($p=0.104$), ALT ($p=0.300$) and GGT ($p=0.480$).

No significant changes were observed with respect to the lipid parameters, although they generally improved [HDL-cholesterol: $p=0.061$; triglycerides: $p=0.197$; total cholesterol: $p=0.142$; LDL-cholesterol: $p=0.566$]. Although median

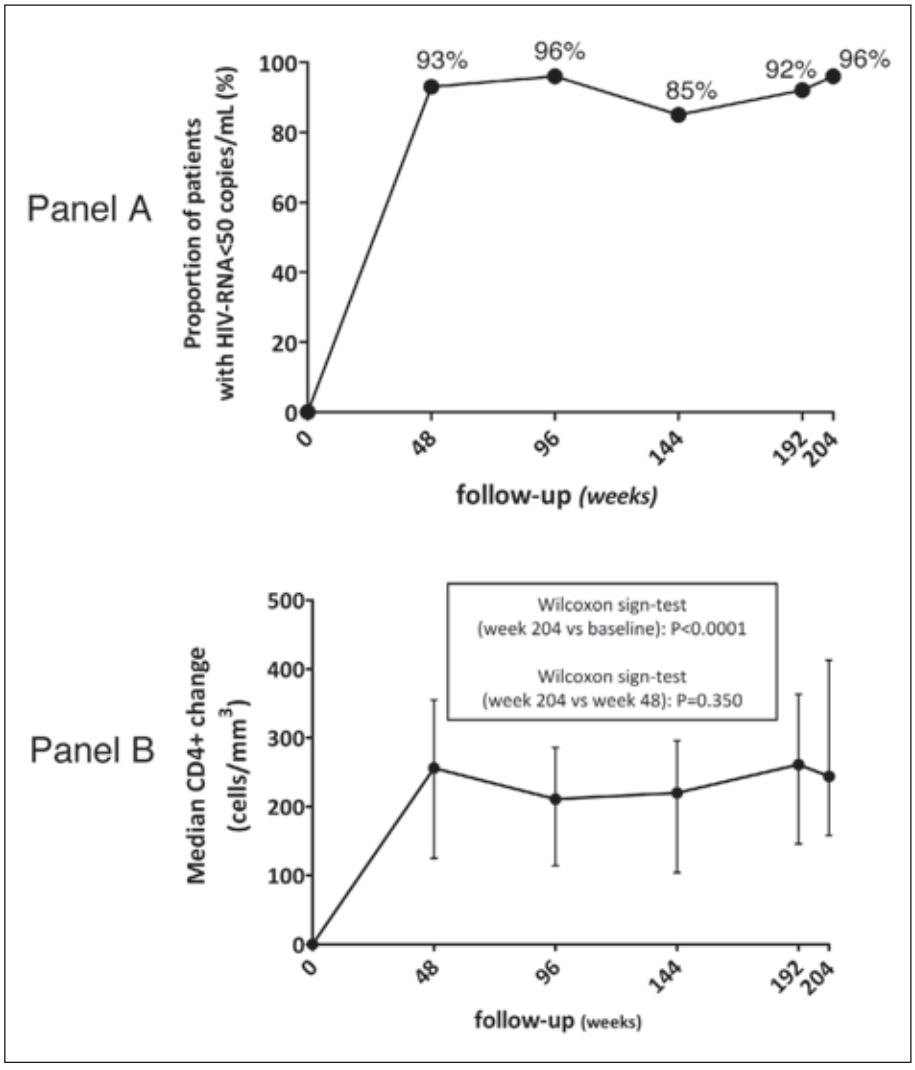

FIGURE 1

fasting glucose and insulin did not vary significantly during follow-up, 4 patients (15%) developed diabetes mellitus. There was a significant decrease in plasma creatinine levels ($p<0.0001$) and no decrease in uricemia ($p=0.152$). CPK levels did not show significant variations over time ($p=0.269$).

DISCUSSION

Current treatment guidelines suggest the use of antiretroviral agents in new drug classes to achieve maximal virological suppression in failing patients (Panel of Antiretroviral Guidelines for Adults and Adolescents, 2012). Data on the long-term efficacy of new drug classes are available (Gatell JM 2010, Katlama C 2010, Hardy WD 2010), but there are few data on new combinations.

An antiretroviral regimen containing new antiretroviral drugs such as raltegravir, etravirine, darunavir/ritonavir (Yazdanpanah 2009, Fagard 2012) or maraviroc, raltegravir, etravirine (Nozza 2010, Nozza 2011), or maraviroc, raltegravir, darunavir/ritonavir (Patterson 2012) has been reported to have 48-96 weeks' virological efficacy as high as those observed in antiretroviral naïve patients.

Our results confirm the high virological efficacy of maraviroc, raltegravir and etravirine at week 204. This new antiretroviral combi-

TABLE 1 - *Main findings in 26 multidrug resistant, failing HIV-infected patients, receiving raltegravir, maraviroc and etravirine. Results described as median (Q1-Q3) values.*

Characteristic	*Baseline*	*Week 48*	*Week 96*	*Week 144*	*Week 192*	*Week 204*	*P-valuea*
CD4 (*cells/mm³*)	247 (68-355)	517 (403-616)	454 (282-538)	481 (371-664)	522 (384-610)	505 (419-705)	**<.0001**
CD4%	12.6 (8.1-19.5)	21.1 (14.5-25.3)	19.7 (14.1-26.2)	22.7 (16.1-26.7)	22.9 (16.7-27.3)	24.4 (18.6-29.4)	**<.0001**
CD4/CD8 ratio	0.21 (0.13-0.35)	0.45 (0.29-0.57)	0.44 (0.27-0.62)	0.56 (0.3-0.71)	0.6 (0.36-0.78)	0.6 (0.44-0.77)	**<.0001**
HIV-RNA (log_{10} *copies/mL*)	4.16 (3.85-5.05)	1.69 (1.69-1.69)	1.69 (1.69-1.69)	1.69 (1.69-1.69)	1.69 (1.69–1.69)	1.69 (1.69–1.69)	**<.0001**
Haemoglobin (*g/dl*)	13.6 (12.3-14.8)	15.1 (14.5-15.9)	15.3 (14.5-15.9)	15.1 (14.8-15.9)	15 (14.1-15.3)	14.9 (14.3-15.3)	**0.0006**
Platelet count ($10^9/mm^3$)	185 (152-207)	200 (184-241)	192 (177-220)	185 (164-225)	195 (170-229)	191 (165-227)	**<.0001**
White blood cells ($10^9/mm^3$)	5.1 (4.1-5.6)	6.3 (5.6-7.6)	6.2 (5.3-7.8)	6.3 (5.2-7.3)	6.5 (5-8.8)	6.8 (5.6-8.2)	**0.013**
PMN ($10^9/mm^3$)	2.4 (2-3.7)	3.6 (2.6-4.4)	3.2 (2.7-4.3)	3.1 (2.5-4.1)	3.5 (2.6-5.3)	3.3 (2.6-4.5)	0.301
Lymphocytes ($10^9/mm^3$)	1.8 (1.2-2.4)	2.2 (2.0-2.7)	2.3 (1.9-2.8)	2.3 (1.8-2.7)	2.3 (1.9-2.8)	2.3 (1.8-2.9)	0.207
Body mass index (kg/m^2)	23.8 (20.5-25.7)	23.8 (21.5-27.1)	24.2 (22.5-26.2)	24.2 (22.2-26.9)	24.2 (22.4-27.1)	24.6 (21.6-27.3)	**<.0001**
Waist circumference (*cm*)	86 (82-90)	90 (84-95)	92 (88-97)	92 (90-99)	93 (88-98)	93 (88-99)	**<.0001**
Total cholesterol (*mg/dL*)	114 (82-129)	107 (81-121)	104 (88-128)	115 (88-133)	116 (86-131)	121 (97-131)	0.142
HDL-cholesterol (*mg/dL*)	38.5 (34.5-45)	41 (38-47)	43 (39-54)	42 (38-47)	43 (36-50)	43 (35-52)	0.061
LDL-cholesterol (*mg/dL*)	114 (82-129)	109 (84-129)	108 (80-124)	110 (88-127)	116 (86-131)	104 (88-128)	0.566
Triglycerides (*mg/dL*)	134 (91-190)	99 (73-159)	96 (76-153)	108 (92-155)	103 (79-134)	117 (79-154)	0.197
Fasting glucose (*mg/dL*)	86 (75-90)	88 (79-97)	85 (78-97)	85 (79-93)	83 (77-94)	84 (78-97)	0.545
Fasting insulin (*U/L*)	10 (7-15)	12.2 (7-18)	13.2 (7.8-18.5)	12.7 (9.4-17.9)	9.9 (8.1-12.7)	10.7 (7.3-16.5)	0.251
CPK (*U/L*)	114 (69-160)	137 (84-225)	134 (98-217)	137 (91-218)	187 (108-259)	140 (118-224)	0.269
AST (*U/L*)	30 (25-49)	29 (20-35)	26 (20-38)	24 (18-34)	23 (15-33)	26 (20-38)	0.104
ALT (*U/L*)	26 (21-59)	40 (27-59)	44 (28-75)	34 (27-43)	33 (27-43)	38 (27-53)	0.300
GGT (*U/L*)	33 (20-97)	25 (20-52)	35 (28-65)	26 (19-59)	30 (21-37)	3 (20-53)	0.480
Creatinine (*mg/dL*)	0.97 (0.87-1.22)	0.88 (0.81-1.06)	0.88 (0.81-1.01)	0.87 (0.77-1)	0.83 (0.76-1)	0.8 (0.69-0.96)	**<.0001**
Uricemia (*mg/dL*)	5.44 (3.8-6.17)	6 (4.6-6.9)	5.9 (4.5-6.8)	5.3 (4.7-6.9)	5.85 (4.5-6.45)	5.4 (4.1-6.25)	0.152

[a]by ANOVA for repeated measures; Greenhouse-Geisser probability of trend over time.

nation showed a long-lasting response despite concerns over the low genetic barrier of such compounds and highly variable pharmacokinetic parameters (Calcagno 2011, Barrail-Tran 2010), highlighting that the main predictive factor for efficacy of these new combinations in experienced patients is the number of fully active drugs (Pichenot 2012). Our rate of virological failure (4%) was lower than that reported in other studies on multi-experienced patients (Charpentier 2010).

The increase in CD4+ cells in our patients (concentrated during the first 48 weeks) was maintained over 204 weeks and no patient dropped below 200 cells/mm^3.

During follow-up, three patients developed non-AIDS-related malignancies whose relationship with the antiretroviral regimen is difficult to establish, considering that HIV infection is a risk factor of AIDS and non-AIDS defining malignancies (Galli 2012).

The results we observed in relation to the safety parameters confirm the tolerability of maraviroc, raltegravir and etravirine (Wasmuth 2012, Lennox 2009, Girard 2012). The increase in body mass index and waist circumference could be related to an improvement in cachexia particularly evident in severely immunocompromised individuals who may be resistant to, or without access to effective antiretroviral therapy (ART) (Wren 2013). The amelioration of bone marrow and renal function could be explained by the removal of NRTIs (Imaz 2011).

Despite the removal of PIs, a modest improvement in metabolic parameters was found; lipid-related laboratory abnormalities and changes over time in lipid levels of etravirine were evaluated in the DUET-1 and DUET-2 trials, that considered the association with darunavir/ritonavir (Girard 2012); the lipid change in the etravirine-containing regimen without PI/r is not clear.

Diabetes mellitus occurred in four patients with and increase in fasting glucose levels and a decrease in insulin secretory capacity (Bigoloni 2012) even if the drugs included in these regimens have not been specifically associated with worsening glucose metabolism (particularly maraviroc, which has even been postulated to have a protective effect at least on type-1 DM).

No changes in hepatic function were observed. Etravirine showed a similar rate of liver toxicity to placebo in regulatory studies, but this seems to be lower in the clinical setting, as has been observed in the Expanded Access Program and in cohort studies including HCV/HIV-coinfected patients with different degrees of fibrosis (Bigoloni 2012, Schrijver 2013).

The analysis of the hepatic safety of maraviroc was performed in patients receiving maraviroc-based therapy in the Expanded Access Program (Lazzarin 2012). It was not associated with increased AST and ALT abnormalities, in particular in HBV and HCV-coinfected patients. There was no indication that the use of newer agents (raltegravir, etravirine, darunavir) altered the hepatic safety profile of the drug.

Some limitations of the study should be noted: the small number of the subjects included in this study and then a low power to evaluate significant differences for some parameters that seemed to change during follow-up. Other limitations are the absence of a control group for comparisons of our efficacy and safety results and a potential selection bias due to the fact that no random selection of patients was adopted. Despite the high pill burden, patients had a good adherence. A simplification of this salvage regimen in the setting of multiexperienced subjects is under study, and the preliminary results on the possible use of a dual therapy based on raltegravir and etravirine as a simplification strategy are encouraging (Calin 2012).

In the lights of the latest developments in antiretroviral therapy, the complexity of different combinations is almost endless (Lombardy region database of treated patients, 365 different regimens in failing patients - data not shown), all the information on the course of the infection/disease in patients treated with non-conventional combinations (Antinori *et al.*, 2012) and their long-term outcomes in multi-failing patients could be interesting for a better management of HIV patients in clinical practice .

In conclusion, despite the limited number of patients, out study suggests a salvage regimen including maraviroc, raltegravir, etravirine has a good long-term profile in terms of efficacy and safety and represents a potential option for a NRTI/PI-sparing strategy in failing patients with multidrug-resistant HIV-1 infection.

AUTHOR DISCLOSURE

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