TITLE PAGE

Week 96 results of the randomised, multicentre Maraviroc Switch study (MARCH).

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Running title: MARaviroc switCH study 96-week results

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ABSTRACT (248 words)

Objectives: The MARCH study week 48 data demonstrated that maraviroc, a CCR5-inhibitor, was a safe and effective switch for the ritonavir-boosted protease inhibitor (PI/r) component of an 2N(t)RTI+PI/r based antiretroviral regimen in patients with R5-tropic virus. Here we report the durability of this finding.

Design: MARCH, an international, multicentre, randomised, 96-week open-label switch study enrolled HIV-1-infected adults with R5-tropic virus, stable (>24weeks) and virologically suppressed (pVL<50cp/mL) to continue their current regimen PI/r-based regimen (PI/r) or switch to MVC+2N(t)RTI (MVC) (1:2 randomisation).

Methods: The primary endpoint was the difference in proportion with pVL<200cp/mL at 96-weeks. The switch arm was defined as non-inferior if the lower limit of the 95% confidence interval (CI) for the difference was <-12% in the intention to treat (ITT) population. Safety endpoints, difference in mean change from baseline or comparison of proportions, were analysed as key secondary endpoints.

Results: Eighty-two (PI/r) and 156 (MVC) were randomised and analysed in ITT; 71 (87%) and 130 (83%) were in follow-up and on therapy at week 96. At week 96, 89.0% and 90.4% in the PI/r and MVC arms respectively had pVL <50cp/mL (95% CI -6.6,10.2). Moreover, in those switching away from the PI/r, there were significant reductions in mean total cholesterol (diff=0.31 mmol/L, p=0.02) and triglycerides (diff=0.44mmol/L, p=<0.001). Changes in CD4+ T-cell count, renal function, serious and non-serious adverse events were similar between arms.

Conclusions: MVC as a switch for a PI/r is safe and effective at maintaining virologic suppression while having significant lipid benefits over 96-weeks.

MAIN TEXT (WORD COUNT 1721)

BACKGROUND

The main aims of recently completed and/or ongoing treatment switch studies in HIV-infection, have been to explore the safety and efficacy of new treatment paradigms either using new formulations of existing drugs or novel partnering of licensed antiretroviral/antiviral agents. The rationale for this approach is as follows. First, to reduce longer-term side-effects and co-morbidities e.g. cardiovascular disease and bone disease, to which some current antiretroviral regimens may contribute. Second, to reduce the lower grade but persistent side-effects, such as diarrhoea, that may negatively impact quality-of-life, and subsequently affect treatment adherence (1-3).

We have previously reported the week 48 findings from the MARCH study (4). In summary, these data demonstrated that maraviroc (MVC) as a switch for a ritonavir-boosted protease Inhibitor (PI/r) with retention of the dual nucleoside/nucleotide (2N(t)RTI) reverse transcriptase inhibitor backbone, was safe and effective. In contrast, the N(t)RTI-sparing switch arm, consisting of PI/r with MVC was significantly inferior in regards to virological control compared to the control, PI/r+2N(t)RTI arm, which we will refer to henceforth as the PI/r arm, over 48 weeks of follow-up. As a consequence, at the completion of week 48, the MVC+PI/r arm was discontinued, participants were informed of the results and site clinicians advised to switch these participants away from this N(t)RTI-sparing combination. The other two arms of the study continued as planned. Here we report the 96-week data for the control (PI/r), and MVC+2N(t)RTI (MVC) arms.

METHODS

Study design, study population and assessments as described in the published 48-week data (4). The protocol and patient information statement and consent form were approved by the Ethics committee/Institutional Review Board at all participating sites. Written informed consent was obtained from all participants (ClinicalTrials.gov number: NCT01384682). Assessments in year 2 of the study consisted of face-to-face visits at weeks 60, 72, 84 and 96 at which vital signs, a targeted physical examination, review of antiretroviral therapy and concomitant medications, adverse event assessment and routine pathologies including plasma HIV-1 RNA pVL), T-cell subsets and safety labs were collected. Additional annual assessments (week 48 and 96) included, fasted (≥8 hours) lipid and glycaemic parameters , anthropometric measurements, bone mineral density (BMD) and Dual-energy X-ray absorptiometry (DXA), Quality of life (QoL) using the SF-12 patient-completed questionnaire. The 7-day recall adherence tool was repeated at week 96. Stored samples were

collected at all visits, with additional samples at the time of confirmed virological failure using the algorithm previously described (4). MVC was dosed BID, at a standard dose of 300mg BID (5).

Endpoints

The MARCH study had a number of other pre-defined secondary endpoints included virologic, immunological, metabolic/body composition, safety, adherence, QoL.

Statistical analysis

The first participant was randomised on 19th January 2012 and last participant was randomised on the 12th of February 2014. The last randomised participant completed 96 weeks of follow-up or had permanently withdrawn from follow-up by the end of January 2016. As previously described, the switch arm was defined as non-inferior if the lower limit of the 95% confidence interval for the difference was <-12% in the intention to treat (ITT) population. Safety endpoints, difference in mean change from baseline or comparison of proportions, were analysed according to randomised arm. All statistical tests were two-sided and considered significant at α<0.05. Statistical analyses were performed on SAS 9.4 and Stata 13.

RESULTS

The last randomised participant completed 96 weeks of follow-up (or had permanently withdrawn) by the end of January 2016. Data for this analysis were extracted on 27-February-2016.

Participant disposition: The ITT population for this 96-week analysis comprised 238 participants (82 PI/r and 156 MVC participants), who commenced randomised therapy, attended baseline and had ≥1 study visit. Seventy-one (87%) PI/r and 130 (83%) MVC participants were in follow-up and on therapy at week 96.

Baseline Characteristics

These have been previously described in the week 48 published data (4) and were well-balanced across both arms. As noted before, abacavir/lamivudine was used in 22% of the PI/r arm vs. 12% in the MVC arm; the most common PI/r was ritonavir-boosted atazanavir followed by lopinavir/r, the latter was used in 35% and 21% of the PI/r and MVC arms respectively.

Outcomes at week 96

Virological: As shown in Table 1, in the ITT analysis, 89.0% and 92.7% of the PI/r arm and 90.4% and 91.7% of the MVC arm had virologic suppression to thresholds of <50 copies/mL and <200 copies/mL respectively at week 96. Both results were within the 95% CI bounds defined in the protocol, demonstrating that the MVC switch arm was virologically non-inferior to the PI/r arm. In the 'Per protocol' analysis (Table 1), the MVC arm was non-inferior to the PI/r arm, with pVL <50 and <200 copies/mL of 96.9% and 98.5% vs. 94.4% and 98.6% (PI/r arm) at week 96 respectively.

Change to randomised therapy, Reasons for stopping randomised therapy and self-reported adherence: The hazard ratio for changes to randomised therapy over 96 weeks, was 1.31 (95% CI 0.67, 2.56) for the MVC arm vs. PI/r (Figure 1). Similar proportions i.e. 13% and 17% of participants in the PI/r and MVC arms respectively stopped randomised therapy, there were nine different reasons given for stopping randomised therapy; the commonest reasons given in the MVC vs. PI/r arms were participant decision (27% (n=7) vs. 9% (n=1)), adverse event (23% (n=6) vs. 9% (n=1)), 'high' HIV RNA (19% (n=5) vs. 9% (n=1)) and physician decision (15% (n=4) and 18% (n=2)).

Adherence: At week 4 all participants in whom the 7-day recall data had been captured as per protocol (96%) reported taking all or most of their pills in the 7 days prior to the week 4 visit; no participants reported taking none of their pills. At week 96, data was available for 95% (n=227), in whom 73(91%), six and one and 137(93%), nine and one of the PI/r and MVC arms respectively reported taking all, most or none of their pills in the 7 days prior to the week 96 visit.

Changes in Immunological, renal, metabolic parameters and quality of life over 96 weeks: There were similar small increases in CD4+ T-cells over the first 48 weeks of the study i.e. +40 and +39 cells/μL in the PI/r and MVC+2N(t)RTI arms respectively. Little further change was seen over 96 weeks, with an overall mean change from baseline of 45 (95% CI, 7-84) and 42 (95% CI, 14-70) cells/uL in the PI/r and MVC arms respectively. Renal function (GFR in mL/min), declined by 4.31 (95% CI -0.67,-7.96) and 6.53 (95% CI, -3.68, -9.38) mil/min (p=0.3525) in the PI/r and MVC arms respectively. In year 2, lipid parameters were measured once at 96 weeks. Over 96 weeks, the MVC arm had a mean decrease in total cholesterol (-0.46mmol/L), triglyerides (-0.41mmol/L) and LDL cholesterol (-0.22mmol/L); these declines were significant for both total cholesterol (p=0.0229) and triglycerides (p=<0.001) with a trend toward significance for the changes in LDL cholesterol, p=0.0916, compared to the PI/r arm. Over 96 weeks, there were no significant percentage changes in physical or mental QoL domains on the SF-12 for the PI/r vs. MVC switch arm.

Safety findings over 96 weeks: Seventy-nine percent of the PI/r and 87% of the MVC arm (p=0.146) reported ≥1 adverse events during the study; of these, none were grade 4. Of the 863 events reported, the majority were either grade 1 (total 542 AE, 204 in the PI/r and 338 in the MVC arm) or grade 2 (total 304, 85 in the PI/r and 219 in the MVC arm). Very few events were considered definitely or probably related to study drugs with only 3 events investigator-determined as definitely related (all in the PI/r arm); 16 AEs in the MVC arm and 13 in the PI/r arm were considered probably related. Ninety-two percent and 89% of AE were considered not related or probably not related to

study drug in the MVC and PI/r arms respectively. AE leading to a change in study medication occurred in none of the PI/r participants and 3 of the MVC group (p=0.553). Overall, there were 28 (12%) SAE reported, 10 (12%) in the PI/r and 18 (11.5%) in the MVC arms respectively, none were considered related to study drug.

Resistance: In the week 96 analysis, 5 individuals (2 PI/r and 3 MVC participants) met the criteria for virological failure, viral load at confirmed failure was low level i.e. between 282 and 2006 copies/mL. The reasons for the virological failure in the MVC arm were likely related to non-adherence in 1 (no genotypic resistance detected and R5-tropic virus on repeat tropism testing); emergent X4 virus in 1 participant with a minor PI mutation (L33I); and the M184V mutation (tropism testing failed to amplify). In the two PI/r virologic failures, tropism testing failed to amplify in both; in one participant the genotype also failed to amplify, in the other the M184V and 2 minor PI mutations (L10V, A71T) emerged.

DISCUSSION

MARCH is the largest randomised study using genotypic assessment of virus tropism to determine the likelihood of maraviroc activity in a switch setting. Suppression of plasma viraemia to below the levels of quantification i.e. <50 copies/mL, the current threshold for most guidelines in high income settings (1), was similar between the arms, demonstrating the durability of the virological response to maraviroc over 96 weeks. Importantly, switching to maraviroc was associated with significant lipid benefits that might be important long-term in reducing cardiovascular risk. Both the PI/r and MVC arms were safe and well-tolerated. While there has been a drive to once-daily dosing for antiretroviral therapy (1,2), the twice-daily dosing of maraviroc did not appear to be associated with an adherence cost as captured in the 7-day recall. There was a slightly increased risk of switching away from randomised therapy in the maraviroc arm compared to the PI/r arm, but to what extent this might have been driven by twice-daily dosing is unclear. Last, in the very few patients with confirmed virological failure, the emergent resistance mutations, in those where a genotype and/or tropism assay was successfully amplified, was only associated with the loss of future use of maraviroc, not other classes of antiretrovirals.

In summary, this large international randomised study, demonstrates that MVC with a 2N(t)RTI - backbone, in those with R5-tropic virus measured using pro-viral DNA, is a switch/simplification option for a ritonavir-boosted protease inhibitor plus 2N(t)RTI regimen, showing durable virologic suppression, favourable metabolic changes and good tolerability over 96-weeks.

Statement re unlabelled use of a commercial product.

The manuscript does not include any unlabelled use of a commercial product, but does reference the week 48 data in which there was an experimental switch arm, which included maraviroc with a ritonavir-boosted protease inhibitor.

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Conflict of interest

Janaki Amin, David Silk, Elise Tu, Juan Arnaiz, Marcelo Wolff, Jaime Andrade-Villanueva, Andrejz Horban, Waldo Belloso, Norma Porteiro: no conflicts to declare;
Professor Sean Emery reports grants from ViiV Healthcare/Pfizer,during the conduct of the study;
Professor Jurgen Rockstroh reports grants from Gilead, personal fees from Abbott, Abbvie, Bionor, BMS, Cipla, Gilead, Jansen, Merck and ViiV, outside the submitted work;
Professor Wataru Sugiura became an employee of GlaxoSmithKline K.K. Tokyo, Japan on 01-April-2015, and at this point relinquished his role as PI of the Nagoya Medical Center and membership of the MARCH PSC;
Dr Andrew Clark is an employee of ViiV Healthcare;
Dr Rolf Kaiser reports grants from ViiV, during the conduct of the study; personal fees from ViiV, personal fees from MSD, personal fees from Janssen, personal fees from Gilead, personal fees from Siemens, personal fees from Roche, outside the submitted work;
Dr Amanda Clarke reports other from Gilead sciences, Janssen and BMS: travel bursaries, outside the submitted work;
Professor P. Richard Harrigan has received grants from, served as an ad hoc advisor to, or spoke at various events sponsored by: Pfizer, Glaxo-SmithKline, Abbott, Merck, Tobira Therapeutics, Virco and Quest Diagnostics and served as a consultant for ViiV Health Care, Tobira Therapeutics, Selah Genomics Inc, and Quest Diagnostics. He holds stock in Merck, Illumina and Gilead, Zizowist Diagnostics and, Northern Lipids. Funding: Dr. Harrigan is supported by CIHR/GSK Research Chair in Clinical Virology.
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Dr John Gill reports grants from University of New South Wales,during the conduct of the study; personal fees from Occasional Ad hoc member of National HIV advisory Boards to Janssen, Merck,Gilead and Viivhhealthcare, outside the submitted work;
Professor Anthony Kelleher reports 'other' from St Vincent's Hospital, outside the submitted work;
Dr. Thierry Prazuck reports personal fees and other from null, outside the submitted work;
Dr Sarah Pett received support to attend an international conference from Merck Sharp and Dohme and Gilead; outside the submitted work.

Dr Patrick Mallon has received support in the form of research grants awarded to the institution, attendance at advisory boards, honoraria, and/or travel to conferences from Janssen Cilag, Gilead Sciences, ViiV Healthcare, Bristol Myers Squibb and Merck Sharpe & Dohme, outside the submitted work.
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*Appendix

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