Association between Resistance and CD4 Count Changes in Patients on ART with Ongoing Viraemia

For the UK Collaborative Group on HIV Drug Resistance, EuroSIDA and UK CHIC Studies

BACKGROUND

Among patients with ongoing viremia (i.e. two consecutive viral loads > 500 copies/mL) CD4 count changes are more favourable in patients receiving antiretroviral therapy (ART) compared to patients with comparable viral loads who are not on ART. This could be because the presence of resistance mutations may cause a virus to have a reduced capacity for inducing CD4 count declines. We hypothesized that in patients on ART with a given viral load or a given amount of suppression from their pre-ART viral load levels, differences in the rates of CD4 count decline may relate to differences between the resistance mutations that are present. If such an effect does exist we wanted to ascertain whether it is specific to the class of ARTs affected by the mutations or whether it can be attributed to individual mutations specifically.

A reduction in viral fitness associated with viruses containing resistance mutations has been shown previously, but this reduced fitness may act entirely through a reduction in the viral load. In this comparison we aimed to address whether resistance mutations are associated with CD4 count declines for a given viral load or extent of viral suppression from the pre-ART level.

OBJECTIVES

We studied viremic patients on ART to assess whether resistance mutations were associated with CD4 count changes, independent of viral load levels.

METHODS

Combined data from the following sources were analysed:

- UK Collaborative Group on HIV Drug Resistance
- UK CHIC
- EuroSIDA
- Austria:
  - (L Machala) H Rozsypal, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen.
- Belgium:
  - (N Amacker) J D'Hoore, J Faucon, J Vanhalst, J Martin, J M Massiot, Catholic University Hospital, Brussels; A Goujon, University Hospital, Liege; M Van Grieken, University Hospital, Ghent; L Flieger, Chaine Hospital, Gent; H Vandenbussche, University Hospital, Antwerp.
- Czech Republic:
  - (J Nosek) A Liška, J Sedlacek, Crenova General Hospital, Prague; I Borec, P Pavlik, University Hospital, Olomouc.
- Denmark:
  - (M Gommes) J Jepsen, University Hospital, Copenhagen; C Pedersen, Odense University Hospital, Odense.
- Germany:
  - (J Kohler) D Schmitt, O. Radke, J. Birk, J. Eickhoff, German Red Cross, Berlin; J. Gullikson, University Hospital, Hamburg; W. Siemers, University Hospital, Marburg.
- Greece:
  - (J Kosmidis) P Gargalianos, G Xylomenos, J Perdios, Athens General Hospital, Athens; G Panos, A Filandras, E Karabatsaki, 1st IKA Hospital, Athens.
- Italy:
  - (A Chiesi) Istituto Superiore di Sanità, Rome; R Esposito, I Mazeu, Università Modena, Modena; C Arici, Ospedale Riuniti, Reggio Emilia; P Turrini, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, R Finazzi, Ospedale San Raffaele, Milan; A Colombo, A Montanari, University Hospital, Padua; A Monini, Bocconi University, Milan; E Della Giustina, University Hospital, Florence.
- Luxembourg:
  - (K Fauvert) C. Rousset, Centre Hospitalier Universitaire Sainte Elisabeth, Luxembourg; M. Matschiner, Centre Hospitalier Universitaire, Luxembourg.
- The Netherlands:
  - (A van der Groen) J. van Hal, J. van der Peet, J. van der Steege, Amsterdam; J. van den Hoogen, Medical Center Alkmaar, Alkmaar; J. van der Pal, Dom Care Zevenbergen, Beuningen; B. van der Steege, Medisch Centrum Alkmaar, Alkmaar; A. van der Vellen, Medisch Centrum Alkmaar, Helmond.
- Norway:
  - (C Mæland) T. Gislason, R. M. Gislasson, R. Johansen, H. A. H. Hoff, University Hospital, Oslo; D. Gudjonsson, University Hospital, Reykjavik; A. G. Grimsby, University Hospital, Tromso.
- Poland:
  - (T. Bajgar) J. Biernat, R. Podkowa, D. Wachowicz, Medical University, Poznan; J. W. Wierzbicki, Medical University, Lodz.
- Portugal:
  - (J. S. Magalhães) L. Craveiro, J. M. N. Pedrosa, Porto; V. Vaz, J. Bike, F. Horta, Lisbon.
- Romania:
  - (M. Cretu) M. C. Gruia, A. Dumitru, C. Draghicescu, University Hospital, Bucharest; M. Blaga, University Hospital, Cluj.
- Spain:
- Sweden:
  - (A Thorstensson) S. J. Olsson, J. Sundström, K. Svensson, Karolinska Institute, Stockholm; R. H. Ohlson, Central Hospital, Gothenburg; C. J. Sundström, Central Hospital, Malmö; A. Thorstensson, Central Hospital, Uppsala.
- Switzerland:
  - (K. Balague) J. H. Van Houdt, University Hospital, Basel; J. B. F. Aeschlimann, University Hospital, Geneva; B. Platt, University Hospital, Zürich; B. Hirschel, Centre Hospitale Universitaire de Genève, Geneva; G. Furrer, Inselspital Bern, Bern.
- United Kingdom:
  - (S. G. Wainberg) J. E. Haynes, A. R. McCombs, L. J. Pletcher, University College Hospital, London; E. A. Perkins, St George’s Hospital, London; J. M. Podzamczer, National Institute for Health Research, Southampton; D. K. Wood, Hospital of the University of Pennsylvania, Philadelphia.
- France:
  - (S. G. Wainberg) J. E. Haynes, A. R. McCombs, L. J. Pletcher, University College Hospital, London; E. A. Perkins, St George’s Hospital, London; J. M. Podzamczer, National Institute for Health Research, Southampton; D. K. Wood, Hospital of the University of Pennsylvania, Philadelphia.

RESULTS

We included 1912 patients with 5520 paired measurements (Figure 1). The median (IQR) length of the interval was 13 (10 to 17) weeks.

The median (IQR) CD4 count at the start of the episode was 274 (168 to 410) cells/μL and there was a median change of -7 (-10 to -5) cells/μL during the interval.

The median (IQR) viral load at the start of the episode was 3.95 (3.39 to 4.54) log_10 cps/µL with a median increase of 0.68 (-0.19 to 0.41) log_10 cps/µL during the interval.

Overall, 52% of patients had primary PI mutations, 64% had NNRTI mutations and 84% had NRTI mutations (IAS-USA 2004).

Mean monthly CD4 count changes according to resistance mutations and drugs used are shown in Table 1.

Patients on NNRTIs had more favourable CD4 count changes if they did not have NNRTI-specific mutations present. Conversely patients receiving PIs or PI/rt's have more favourable CD4 count slopes if they had PI-specific mutations present.

After adjustments for confounders there was little evidence for a difference in the CD4 count change according to which IAS-USA mutations were present (Table 1). Adjusted mean (95% CI) CD4 count changes were: -1.53 (-2.17 to -0.89), -2.56 (-4.18 to -0.73), and -3.79 (-5.10 to -2.44), and -1.27 (-2.10 to -0.56) cells/μL/month for patients on PI/rt's with PI mutations, on PI/rt's without PI mutations, on NNRTIs with NNRTI mutations, and on NNRTIs without NNRTI mutations, respectively.

All NNRTI-specific mutations were associated with greater CD4 count declines, but only two reached borderline significance. In separate models the presence of K103N and Y181C was associated with a mean (95% CI) -1.86 (-3.76, 0.10) and -2.78 (-5.30, 0.76) cells/μL/month respectively for the association between the pre-ART level and the CD4 count changes.

We restricted the analysis to patients whose resistance test was taken within the viral load required.

Sensitivity analysis

Viral load changes within the interval are likely to influence CD4 count slopes so we repeated the analysis on patients with minimal viral load changes (i.e. <0.25 log_10 cps/µL). We also adjusted the main analysis for viral load changes in the interval to quantify the effect of these changes on our estimates.

We restricted the analysis to patients with a viral load non-zero cps/µL during the interval because the effect of specific mutations may be stronger in this virologically failing population.

We restricted the analysis to patients whose genotypic sensitivity score (GSS) was >2, but with at least one IAS-USA mutation present, to investigate the effect of mutations in adherent patients who had limited benefit from the ARTs they were receiving.

We restricted the analysis to patients with a GSS to see whether clearer differences can be seen in patients with limited treatment options available.

We restricted the analysis to patients whose resistance test was taken within the viral load interval to eliminate the possibility of reverse causality between mutation development and CD4 count slopes.

All of the above methods provided results consistent with what we have shown in the main analysis.

DISCUSSION POINTS/CONCLUSIONS

We did not identify any clear differences in CD4 count slopes for a given viral load (or for a given viral load change from the pre-ART value) according to the presence of resistance.

Although there is an indication that patients on NNRTIs have greater CD4 count declines if NNRTI mutations are present and patients on PIs have smaller CD4 count declines if PI mutations are present these differences are not as clear after adjustments. This is consistent with the high fitness of K103N mutants that has been reported by others.

The presence of mutations may have affected the CD4 count prior to the interval covered by the pair. This makes it hard to quantify the relationship between CD4 counts, viral load levels and mutations.

This analysis has limited power so further analyses using a larger number of patients is still required.