10th International Congress on Drug Therapy in HIV Infection, P144

Haemoglobin and anaemia in the SMART study

A Mocroft[1], AR Lifson[2], G Touloumi[3], J Neuhaus[2], Z Fox[1], A Palfreeman[4], M Vjecha[5], S Hodder[6], S De Wit[7], JD Lundgren[8,9], AN Phillips[1] for the INSIGHT SMART study group

[1]University College Medical School, London, UK; [2]University of Minnesota, Minnesota, USA; [3]Athens University Medical School, Athens, Greece; [4]Medical Research Council Clinical Trials Unit, London, UK; [5]Veterans Affair Medical Centre, Washington, USA; [6]New Jersey Medical School, New Jersey, USA; [7]St Pierre Hospital, Brussels, Belgium; [8]Copenhagen HIV Programme, Copenhagen, Denmark; [9]Centre for Viral Disease KMA, Rigshospitalet, Copenhagen, Denmark

Professor Amanda Mocroft
HIV Epidemiology & Biostatistics Group, Research Department of Infection & Population Health
Royal Free Campus, UCL Medical School, University College London (UCL)
Rowland Hill Street, London, NW3 2PF, UK
Tel: +44 20 7794 0500
Fax: +44 20 7794 1224
Email : a.mocroft@ucl.ac.uk

INTRODUCTION

- In HIV-infected individuals, anaemia may lead to:
  - increases in morbidity and mortality
  - increases in fatal and non-fatal non-AIDS events
- Combination antiretroviral therapy (cART) leads to increases in haemoglobin (hb) levels → lower levels of anaemia are seen among patients on therapy
- The SMART trial (Strategies for Management of Antiretroviral Therapy) examined the effects of intermittent therapy in HIV-positive patients compared to continuous antiretroviral therapy (ARV) and found that those on intermittent therapy had a 2.6-fold (95% CI: 1.9 to 3.7) increased hazard of opportunistic disease (OD) or death compared to those on continuous therapy
- It is currently unknown whether interrupting therapy results in decreases in hb levels and/or increases in the number of patients with anaemia. If so, it is of interest to see whether increasing levels of anaemia could partly explain the association between interrupting therapy and the increased risk of AIDS, non-AIDS events and death in the SMART study

The aims of this study were to use data from the SMART study to investigate :

- Changes in hb levels and development of new or worsening anaemia
- The relationship between anaemia and AIDS, non-AIDS events and death

METHODS

- In SMART, individuals with a CD4+ count >350 cells/mm^3 were randomised to 1) the viral suppression (VS) arm involving continuous use of ARVs or 2) the drug conservation arm (DC) involving CD4+ guided treatment interruptions
- 5,472 HIV-infected individuals were enrolled by 318 sites in 33 countries. Enrolment was discontinued in January 2006 because of the observed increased risk of OD and death in the DC arm compared to the VS arm
- Hb levels were retrospectively collected at randomisation, month 1, 2, 4, 6 8, 10, 12 and every 4 months thereafter
- As decided *a priori,* sites with <20% data on participants who died or were lost to follow-up OR sites with <80% completeness of the measurements of interest at randomisation were excluded from these analyses
- Anaemia was defined as hb <12 mg/dl for females, <14 mg/dl for males; severe anaemia was defined as hb <8 mg/dl for either males or females
- New or worsening anaemia was defined as the development of anaemia in patients without anaemia at randomisation or the development of severe anaemia in patients with anaemia at randomisation
- Kaplan-Meier and Cox proportional hazards models were used to investigate factors associated with the first occurrence of new or worsening anaemia. Follow-up was stratified into: 1) the first 4 months following randomisation and 2) after this time, in order to satisfy the proportional hazards assumptions
- Poisson regression was used to investigate the relationship between the development of new or worsening anaemia and clinical events; using both fixed (i.e. anaemia at randomisation) and time-updated (i.e. currently anaemic) values

RESULTS

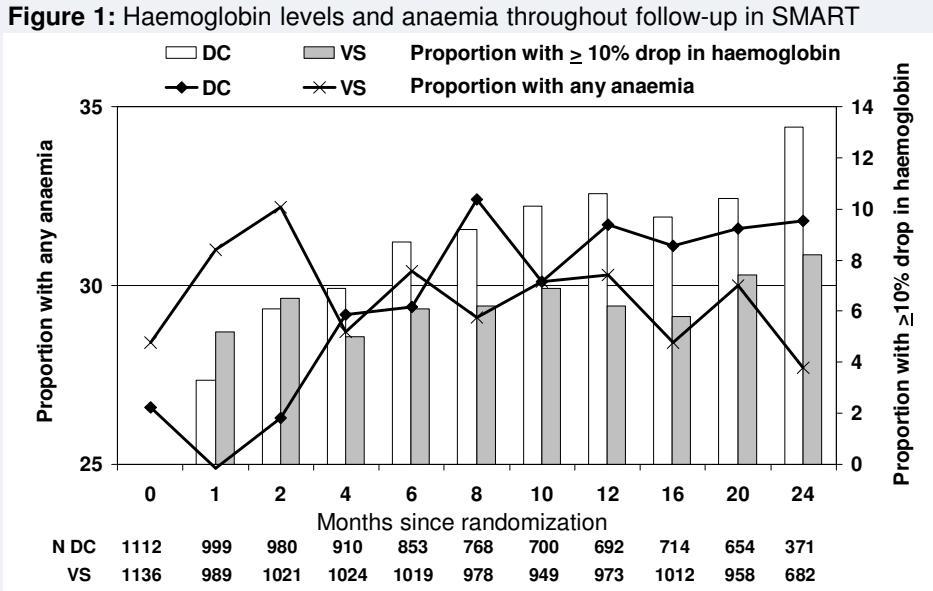
- There were 2248/5472 (41.1%) patients included in these analyses
- At randomisation, differences were observed between patients with anaemia and those without anaemia in race, HIV exposure group and CD4+ count (Table 1)
- The median (range) haemoglobin at randomisation for those without anaemia was 14.8 (12.1–24.2) mg/dl and in those with anaemia was 12.9 (5.1–14.0) mg/dl

Table 1: Characteristics of patients according to the presence/absence of anaemia

		All patients		No anaemia at randomisation		Anaemic at randomisation		P-value
		N	%	N	%	N	%	
All patients		2248	100	1630	72.5	618	27.5	
Gender	Male	1619	72.0	1168	71.7	451	73.0	0.53
Race	Black	594	26.4	389	23.9	205	33.2	<0.0001
	Other	1654	73.6	1241	76.1	413	66.8	
HIV exposure group	MSM	1069	47.6	804	49.3	265	43.0	0.0063
	Heterosexual	1060	47.2	730	44.8	330	53.4	0.0003
	Other	366	16.3	264	16.2	102	16.5	0.86
HBV coinfected	Yes	49	2.2	40	2.5	9	1.5	0.15
HCV coinfected	Yes	314	14.0	217	13.3	97	15.7	0.14
Prior AIDS	Yes	496	22.1	355	21.8	141	22.8	0.60
ARV naive	Yes	116	5.2	78	4.8	38	6.2	0.19
Treatment arm	DC	1112	49.5	816	50.1	296	47.9	0.36
		Median	IQR	Median	IQR	Median	IQR	
Age	years	43	38–50	43	38–50	44	38–52	0.11
Nadir CD4	/mm^3	250	161–349	248	153–350	250	174–338	0.60
CD4	/mm^3	600	470–779	617	482–806	567	444–714	<0.0001
Viral load	$\log_{10}$ copies/ml	1.9	1.7–2.7	1.9	1.7–2.6	1.9	1.7–2.8	0.71

- The median number of hb measurements during follow-up was 11 ([IQR] 9–13) per patient
- In the VS arm levels of anaemia increased over the first two months and then decreased to below initial values. Conversely, in the DC arm, there were temporary decreases in levels of anaemia followed by large increases (Figure 1)

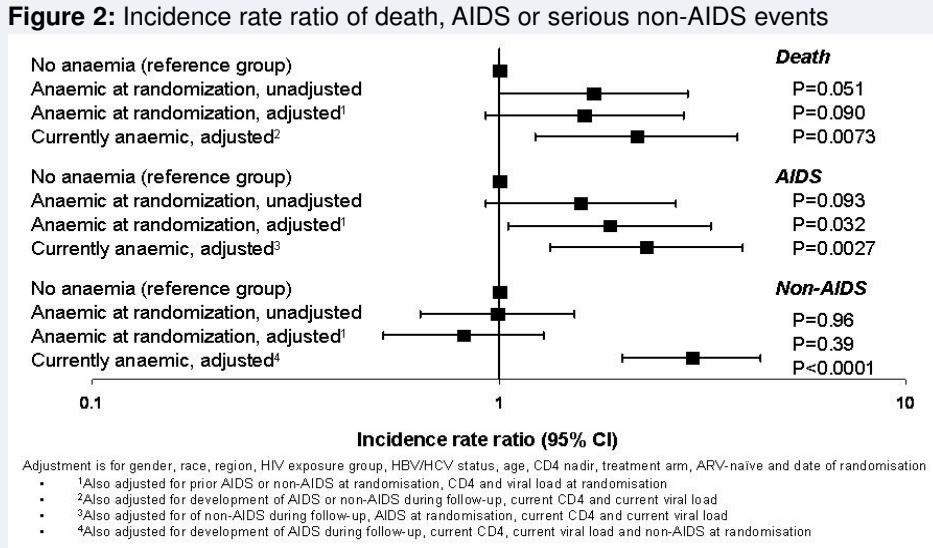
Figure 1: Haemoglobin levels and anaemia throughout follow-up in SMART



Patients in DC arm were censored at restarting treatment. Anaemia defined as haemoglobin ≤14 mg/dl (Male) / ≤12 mg/dl (Female)

- There were 759 patients who developed new or worsening anaemia; 420/1106 (38.0%) in the DC arm versus 339/1127 (30.1%) in the VS arm, p<0.0001
- In the first 4 months following randomisation, there was no difference in the risk of new or worsening anaemia when comparing the DC to the VS arm (adjusted relative hazard [RH] 1.02, 95% CI 0.82–1.25, p=0.88)
- After the initial 4 months, patients in the DC arm had a significantly increased risk of new or worsening anaemia (adjusted RH 1.56, 95% CI 1.28–1.89, p<0.0001)
- Among patients with a clinical event (combining AIDS, non-AIDS and deaths) and haemoglobin measured <28 days prior to the event, anaemia was seen in 25/55 (45.5%) patients in the DC arm and 24/47 (51.1%) patients in the VS arm, p=0.57
- Figure 2 shows that compared to non-anaemic patients, those who were currently anaemic had a significantly higher incidence of death (IRR 2.19; 95% CI 1.23–3.87, p=0.0073), AIDS (IRR 2.31; 95% CI 1.34–3.98, p=0.0027) and non-AIDS events (IRR 2.98; 95% CI 2.01–4.40, p<0.0001)

Figure 2: Incidence rate ratio of death, AIDS or serious non-AIDS events



Adjustment is for gender, race, region, HIV exposure group, HBV/HCV status, age, CD4 nadir, treatment arm, ARV-naïve and date of randomisation

- [1]Also adjusted for prior AIDS or non-AIDS at randomisation, CD4 and viral load at randomisation
- [2]Also adjusted for development of AIDS or non-AIDS during follow-up, current CD4 and current viral load
- [3]Also adjusted for of non-AIDS during follow-up, AIDS at randomisation, current CD4 and current viral load
- [4]Also adjusted for development of AIDS during follow-up, current CD4, current viral load and non-AIDS at randomisation

CONCLUSIONS

- Interruption of cART is associated with an increased risk of new or worsening anaemia
- Patients who developed anaemia during follow-up have an increased incidence of death, AIDS and non AIDS events.
- Whether this relationship is causal or a consequence of emerging sub-clinical disease is not clear but suggests that anaemia, or drop in haemoglobin, might be of use as a pre-clinical marker of disease
- These results provide further evidence of the detrimental effects of interruption of ARVs
- They also emphasize that close attention should be paid to haemoglobin and anaemia in both patients on and off ARVs as low and decreasing levels are associated with increased likelihood of a wide spectrum of clinical disease