Lamivudine-induced red cell aplasia

Melanie-Anne A. John,1† Yasin A. Rhemtula,2† Colin N. Menezes1,2 and Martin P. Grobusch1,2

1Infectious Diseases Unit, Division of Clinical Microbiology and Infectious Diseases, National Health Laboratory Service and School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
2Department of Internal Medicine, Helen Joseph Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Anaemia is frequent in patients with human immunodeficiency virus infection, and antiretroviral drugs have been implicated. Whilst therapy-induced anaemia is more readily attributed to zidovudine, lamivudine-associated, potentially life-threatening, pure red cell aplasia (PRCA) has been less recognized in the past and is only infrequently documented in the literature. We report on a patient suffering from what turned out to be lamivudine-induced PRCA who required 15 units of blood within 3 weeks before recovering swiftly following lamivudine (3TC) treatment withdrawal. As reviewed here, the nature of this condition is not well described in general, the onset appears to be variable and occurs at any CD4+ count, but rapid improvement after cessation of drug administration appears to be a consistent feature.

Introduction

Anaemia in general is a very common finding in human immunodeficiency virus (HIV) and AIDS sufferers, occurring in 70–80 % of patients (Zon et al., 1988). The commonest causes are the direct cytopathic effect of HIV on red cell precursors, autoimmune processes and drug therapy. Co-infection with common viral agents, e.g. hepatitis B or Epstein–Barr virus, or infiltration of the bone marrow by, for example, Mycobacterium spp. or lymphoma, may exacerbate anaemia. Several drugs that are used in opportunistic disease management, e.g. cotrimoxazole and gancyclovir, as well as the nucleoside reverse transcriptase inhibitors (NRTIs), are well described as causes of anaemia in this population (Costello, 1989; Claster, 2002; Sloand, 2005; Fangman & Scanden, 2005). The mechanism of NRTI anaemia, particularly with zidovudine (ZDV), appears to be attributed to myelosuppression (Morris, 1994). Macrocytosis has also been described with the entire class of NRTIs and is a reflection of bone marrow toxicity (Walker et al., 1988; Khawcharoenporn et al., 2007).

Lamivudine (3TC) is an affordable and well tolerated NRTI that forms part of many HAART (highly active antiretroviral treatment) regimens worldwide. It is the cornerstone of the first line regimen in the South African antiretroviral (ARV) roll-out programme. 3TC is usually combined with another NRTI, stavudine (d4T), and a non-nucleoside reverse transcriptase inhibitor, efavirenz (EFV).

In 1998, authors reported two patients with severe anaemia related to 3TC and ZDV combination therapy (Hester & Peacock, 1998). They postulated an activation of the haematotoxicity of ZDV by 3TC. However, in 1999, Weitzel and colleagues reported a patient who experienced severe anaemia associated with 3TC in the absence of ZDV (Weitzel et al., 1999).

Case report

We report the case of a 29-year-old HIV-infected female receiving 3TC, d4T and EFV treatment with a severe, non-responsive anaemia secondary to pure red cell aplasia (PRCA). We believe it is the first reported case from South Africa’s public sector ARV programme.

The patient, a part time data capturer with no travel history, was diagnosed with HIV infection in February 2006 at a primary health clinic. She presented to our HIV clinic in October 2006 for adherence counselling and HAART initiation. Her baseline CD4+ cell count was 21 cells µl−1, and she had no past hospital admissions or opportunistic infections.

In November 2006 HAART was initiated with 30 mg d4T twice daily, 150 mg 3TC twice daily and 600 mg EFV at night. The patient had been on cotrimoxazole primary prophylaxis for Pneumocystis jirovecii pneumonia since HIV diagnosis and was taking no other prescription.
traditional or herbal medication. Whilst her haemoglobin (Hb) was not assessed prior to cotrimoxazole commencement, her pre-HAART initiation full blood count revealed a Hb level of 11 g dl$^{-1}$, mean corpuscular volume (MCV) of 83 fl$^{-1}$, a white cell count of $5.9 \times 10^9$ l$^{-1}$ and a platelet count of $3.43 \times 10^{11}$ l$^{-1}$.

One month later she was admitted to hospital, being febrile (38.5 °C taken orally), hypotensive (blood pressure 90/60 mmHg) and in sinus tachycardia (117 beats per min), with a respiratory rate of 18 breaths min$^{-1}$.

There was marked conjunctival and oral mucosal pallor without evidence of active bleeding from the gastrointestinal, respiratory or genitourinary tract; she was not jaundiced and had no palpable lymphadenopathy or skin rash. Cardiovascular examination revealed a 3/6 pansystolic murmur without congestive cardiac failure. There was a 3 cm non-tender hepatomegaly but no splenomegaly. Respiratory and gynaecological examinations were normal.

Haematological investigations on admission revealed a pancytopenia with severe microcytic anaemia and a RPI (red cell production index) of 0, neutropenia and lymphopenia, with occasional fragments on a smear (Table 1). Inflammatory markers were elevated, with a C reactive protein = 55 mg l$^{-1}$ and an erythrocyte sedimentation rate = 96 mm/first hour. Liver function tests demonstrated a mild elevation of gamma glutamyl transferase (38.5 U l$^{-1}$). Iron studies revealed an increase in serum iron (33.6 μmol l$^{-1}$) and ferritin (2000 μg l$^{-1}$) with a decrease in serum transferrin (1.5 g l$^{-1}$). This was in keeping with previous oral iron supplementation received from the primary health clinic. Vitamin B12 and folate levels were normal, and a direct Coomb’s test (polyspecific) was negative. Urine microscopy yielded 40 000 leukocytes ml$^{-1}$ and urine cultures were negative. Parvovirus B19 and cytomegalovirus serology suggested previous exposure as – a pathognomonic sign of parvovirus B19-associated red cell aplasia (Young & Brown, 2004). In January 2007 (3 weeks post admission), when 3TC was withdrawn and replaced by tenofovir, an NRTI, the patient had received 15 units of packed red blood cells with only transient recovery of Hb. Shortly after discontinuing 3TC, Hb levels improved markedly, reaching 6.3 g dl$^{-1}$ and 12.1 g dl$^{-1}$ at 1 and 3 weeks, respectively. RPI also recovered to 1.1 % within 8 days of the transfusions and stopping 3TC. A CD4$^+$ count at the end of January 2007 showed an increase to 226 cell mm$^{-3}$. Monthly follow-up showed a normalization of the Hb level.

### Discussion

Anaemia on HAART is reported to occur in 3.8 % of Thai and 23 % of Indian patients, usually within the first 2 years of the initial regimes (Nuesch et al., 2006; Kumarasamy et al., 2007). In 1998 Hester and Peacock reported two patients with severe anaemia related to 3TC and AZT combination therapy, and postulated an activation of the haematoxicity of ZDV by 3TC (Hester & Peacock, 1998).

<table>
<thead>
<tr>
<th>Date</th>
<th>White cell count ($\times 10^9$ cells l$^{-1}$)</th>
<th>Hb (g dl$^{-1}$)</th>
<th>Haematocrit (l l$^{-1}$)</th>
<th>MCV (fl)</th>
<th>Platelets ($\times 10^9$)</th>
<th>RPI (%)</th>
<th>Packed red cell transfusion (units)</th>
<th>ARV treatment stopped &amp; EFV initiated</th>
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<tr>
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<td>140</td>
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TDF, Tenofovir.

*Values in parentheses are the normal values.
Anaemia is experienced in 9.6/100 person years with the commonly prescribed combination of 3TC and AZT (Moh et al., 2005). While AZT is well known to cause anaemia, the role of 3TC in this combination is difficult to evaluate. However, one study of 1029 adults on 3TC, stavudine and nevirapine or efavirenz, suggests that anaemia on 3TC regimes that exclude AZT is rare as it was reported in ≤0.5% of individuals (Forna et al., 2007). We have presented here an uncommon case of red cell aplasia secondary to 3TC. This finding has been previously documented in only a few cases in the literature written in English.

Majluf–Cruz et al. (2000) described 5 male AIDS patients (median age of 32 years) with 3TC-induced red cell aplasia out of 269 patients that received 3TC at their clinic (1.9%). Before starting 3TC, all five patients had Hb levels greater than 11.8 g dl⁻¹. After receiving 3TC for a median time of 12 weeks, Hb levels dropped within 3 weeks to 5.2 g dl⁻¹ (4.3–6.1 g dl⁻¹) with high transfusion requirements. After stopping 3TC, Hb levels rose to 12.8 g dl⁻¹ (11.3–13.8 g dl⁻¹) by the end of the seventh week.

Weitzel et al. (1999) reported the case of a 62 year old HIV-and hepatitis B-infected man with profound anaemia associated with 3TC treatment. HAART was initiated with 300 mg ZDV orally twice daily, 150 mg 3TC twice daily and 200 mg nevirapine twice daily. A marked anaemia was diagnosed 9 months later and his Hb reached a nadir of 4.6 g dl⁻¹ at month 10. NVP and ZDV were substituted with EFV and stavudine without an improvement in Hb levels. Six weeks after discontinuation of 3TC, the Hb increased markedly reaching 12.5 g dl⁻¹. This illustrated the potential of 3TC to maintain a severe anaemia in the absence of ZDV.

The onset of severe anaemia within 4 weeks, in our case, is earlier than reported by Majluf–Cruz et al. (2000) where the anaemia manifested within 12 weeks of commencing 3TC. Rapid Hb recovery was noted within 6 weeks in reported cases and within 3 weeks in our patient, emphasizing the short-lived suppressive effect. Due to the severity of the initial anaemia we did not rechallenge our patient even though Tseng et al. (1998) reported recurrence in only 1 of their 12 patients who developed anaemia on 3TC and ZDV.

The role of the CD4 count appears to be independent of the occurrence of PRCA. The report from Majluf–Cruz et al. (2000) does not document this parameter but mentions that all their patients had AIDS. Weitzel and colleagues’ patient’s CD4⁺ count was 500 cells mm⁻³ (Weitzel et al., 1999) while our case had a CD4⁺ count of 21 cells mm⁻³ at HAART initiation and 227 cells mm⁻³ 3 months later at resolution of the severe anaemia. Whether immune reconstitution inflammatory syndrome played a role in anaemia development is unknown.

The mechanism of PRCA under 3TC remains unclear but clinically resembles the one of ZDV. Possible mechanisms include synergistic haematosuppression with ZDV and myelodysplasia. *In vitro* studies have shown inhibition of colony formation of human haematopoietic progenitors (burst-forming unit-erythroids) in patients on HAART (Dornsife & Averett, 1996). Our patient did not receive ZDV, and there was no evidence of myelodysplasia on bone marrow histology (Morris, 1994; Hester & Peacock, 1998; Majluf-Cruz et al., 2000).

Immune dysregulation in AIDS resulting in an autoimmune haemolysis is unlikely as direct Coomb’s test was negative. However, the haptoglobulin level in our patient was 0.2 g l⁻¹ (0.03–2.00 g l⁻¹) and there were minimal red blood cell fragments seen on initial blood smear. Hence we cannot exclude haemolysis as contributing to the anaemia. A repeat blood smear showed occasional pencil and target cells with features of infection but no fragments. This was after stopping 3TC, suggesting a probable drug-induced immune-mediated haemolysis contributing to the anaemia. Cotrimoxazole may have contributed as the patients’ pre-HAART Hb was 11 g dl⁻¹ and we do not have a pre-cotrimoxazole Hb value. However, the anaemia responded only to 3TC cessation despite continuing cotrimoxazole.

The potential for 3TC to cause a PRCA is less known than the anaemia associated with AZT. Lamivudine is integral to the first line regimen in the South African ARV roll-out programme that officially had approximately 120 000 patients on therapy in January 2006 and a further 100 000 estimated cases funded by the private and not-for-profit sector (Hassan, 2006). Our current protocol requires that any patient on AZT receives Hb monitoring.

With the report from other authors that the incidence of PRCA with 3TC was 1.9%, and assuming normal distribution, approximately 4200 patients on our current ARV programme would be at risk of developing this condition (Majluf-Cruz et al., 2000). Early Hb monitoring is not routine in patients receiving our first line regimen (3TC, d4t, EFV) in many countries, including South Africa, and instituting this step further increases the cost and care of national ARV programmes in resource-poor countries. We recommend that clinicians have a high index of suspicion when patients on 3TC present with anaemia.

**References**


