EDITORIAL REVIEW

Immune restoration disease

Martyn French and Robert Colebunders

HIV/STD Unit, Department of Clinical Sciences, Institute of Tropical Medicine and Faculty of Medicine, University of Antwerp, Antwerp, Belgium

Correspondence to Martyn French, Department of Clinical Immunology and Immunogenetics, Royal Perth Hospital, GPO Box X2213, Perth, WA 6847, Australia
Tel: +61 8 9224 2899; fax: +61 8 9224 2920;
e-mail: Martyn.French@health.wa.gov.au

Current Opinion in HIV and AIDS 2008, 3:417–418

The efficacy and tolerability of combination antiretroviral therapy (ART) have improved substantially since this therapy was first introduced in the mid-1990s. It is, therefore, realistic to expect that most HIV patients who now commence ART will achieve at least partial reconstitution of the immune system, which should result in the restoration of pathogen-specific immune responses and the regression or prevention of immunodeficiency disease. It has, therefore, been puzzling to observe that a significant proportion of patients who were very immunodeficient when they commenced ART develops disease during the process of immune reconstitution. These disorders of immune reconstitution include immune-mediated inflammatory disease, such as sarcoidosis, autoimmune disease (mainly Graves' disease) and immunodeficiency disease resulting from residual T and B cell depletion or dysfunction [1]. By far the most common disorders, however, are inflammatory disease or cellular proliferative disease (such as Kaposi's sarcoma) associated with an active or resolved infection by an opportunistic pathogen.

Observations on inflammatory disease associated with mycobacterial infections after commencing zidovudine monotherapy or ART, from the perspective of clinical immunologists, lead to the suggestion that it resulted from the restoration of a cellular immune response against mycobacterial antigens [2–4]. Consequently, the term immune restoration disease (IRD) was introduced to indicate that this type of disease was different from immunodeficiency disease in that it resulted from the restoration rather than failure of a pathogen-specific immune response [3]. Observations by others from different perspectives have resulted in different nomenclatures being used. Some have highlighted the prominence of inflammation or the association with reconstitution of the immune system, as manifested by an increased circulating $CD4^+$ T cell count. Thus, the terms immune reconstitution syndrome [5,6], immune reconstitution inflammatory syndrome [7] or immune reconstitution disease [8] have also been used. Other observers have referred to these conditions from the perspective of their organ-based specialty; for example immune recovery uveitis affecting the eye [9] and hepatitis C virus or hepatitis B virus (HBV)-associated hepatotoxicity affecting the liver [10,11]. Finally, nomenclature has sometimes been taken from that used to describe well established complications of infectious diseases, such as ART-associated paradoxical reactions associated with *Mycobacterium tuberculosis* infection [12] and reversal reactions associated with *M. leprae* infection [13].

Authors in this section of the journal have used various terms to describe inflammatory and cellular proliferative disease associated with opportunistic infections in patients responding to ART. Until the pathogenesis of these conditions is understood better, this situation is likely to continue. Whatever nomenclature is used, it is generally accepted that these disorders are a consequence of heightened immune and/or inflammatory responses against opportunistic pathogens associated with ART-induced suppression of HIV replication. Pathogens may be viable, or nonviable as a result of the infection being treated. Essentially any pathogen that can cause an opportunistic infection can provoke IRD during the process of immune reconstitution. Sometimes, the infection is subclinical and unmasked by the immune/inflammatory response, giving rise to 'unmasking IRD'. In other patients, there appears to be a relapse or exacerbation of disease that had been treated before starting ART. This disease is generally referred to as 'paradoxical IRD'.

The clinical presentations of IRD are, therefore, protean and it is not possible to define a single syndrome. Disease characteristics are determined by both the type of provoking pathogen and its anatomical location. For example, there is often evidence of a $CD8^+$ T cell response in IRD associated with virus infections and this disease usually affects sites of persistent virus infection or viral antigen retention such as the nervous system, eye or skin (see Torok *et al.* pp. 438–445, Otiti-Sengeri *et al.* pp. 432–437 and Maurer *et al.* pp. 453–460). On the other hand, IRD associated with infections by 'intracellular pathogens' such as mycobacteria, many fungi and protozoans is often characterized by inflammation at sites of macrophage 'residence' such as lymph nodes, liver, spleen, gut, serosal surfaces and the meninges. The inflammatory response is often granulomatous, but in *M. tuberculosis* IRD it may result in suppuration and inflammation of the pleura or peritoneum may result in the formation of large effusions (see Lawn *et al.* pp. 425–431).

IRD has been reported to occur in about 10–40% of patients starting ART but morbidity is usually manageable and mortality is uncommon. This association is best exemplified by disease that affects the skin (see Maurer *et al.*). IRD associated with hepatitis virus infections of the liver and active or resolved infections by *M. tuberculosis* and cryptococci often causes diagnostic uncertainty, however, and IRD of the central nervous system may cause substantial morbidity and mortality (see Crane *et al.* pp. 446–452, Lawn *et al.* and Torok *et al.*). This situation is just as much a problem for children as adults (see Boulware *et al.* pp. 461–467). It is, therefore, important to focus research efforts on these conditions so that the immunopathogenesis is understood and investigators are better informed when developing diagnostic methods and prevention and treatment strategies (see Meintjes *et al.* pp. 468–476). Studies on the immunopathogenesis of IRD are limited but available data suggest that there is an imbalance of effector and regulatory immune responses, particularly during the early phases of immune reconstitution (see Kestens *et al.* pp. 419–424).

IRD is particularly a problem in ART roll-out programs in countries with limited resources in which the underlying prevalence of infections with pathogens such as *M. tuberculosis*, *Cryptococcus neoformans* and HBV is high, and when patients initiating ART are more likely to have advanced immunodeficiency. In these countries there is, compared with the industrialized countries, a much higher incidence of opportunistic infections [14] and mortality [15] after the start of the ART, particularly in the first months after starting therapy. How much of this increased morbidity and mortality is caused by IRD is not known. Certainly we will need to further document the clinical spectrum of IRD. So far, only seven cases of IRD associated with helminth infections (schistosomiasis or strongyloidiasis) have been documented, all among immigrants living in high-income countries [16]. It is likely that in countries where these infections are endemic the burden of IRD caused by parasitic infections will be more important. Other important research questions for countries with limited resources include, 'what is the impact of IRD on the needs for hospitalization, transfer of patients and increased healthcare costs?' We also need to assess the effect of IRD on the patients' adherence with ART. Indeed, certainly in situations in which there is not enough awareness/knowledge about IRD, there is the risk that ART is stopped by either the patient or the healthcare worker when this therapy is not indicated. In order to scale up the roll out of ART in countries with limited resources, we need to decentralize HIV treatment to the level of the health centres. We need to know, therefore, how to diagnose IRD at the primary healthcare level and when healthcare workers should transfer patients to a referral centre. It was impossible to address all of these topics in this issue of *Current Opinion in HIV and AIDS*.

For the moment there is a lot of ongoing research concerning IRD, there is also an international network for the study of IRD (International Network for the Study of HIV-associated IRD; INSHI), which was established during a workshop in Kampala in 2006 (www.inshi.umn.edu). We are looking forward to seeing the results of these research efforts in the near future.

References

1 French MA. Disorders of immune reconstitution in patients with HIV infection responding to antiretroviral therapy. Curr HIV/AIDS Rep 2007; 4:16–21.

2 French MA, Mallal SA, Dawkins RL. Zidovudine-induced restoration of cell-mediated immunity to mycobacteria in immunodeficient HIV-infected patients. AIDS 1992; 6:1293–1297.

3 French MA, Lenzo N, John M, *et al.* Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. HIV Med 2000; 1:107–115.

4 French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. AIDS 2004; 18:1615–1627.

5 Behrens GM, Meyer D, Stoll M, Schmidt RE. Immune reconstitution syndromes in human immuno-deficiency virus infection following effective antiretroviral therapy. Immunobiology 2000; 202:186–193.

6 Phillips P, Bonner S, Gataric N, *et al.* Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. Clin Infect Dis 2005; 41:1483–1497.

7 Shelburne SA 3rd, Hamill RJ, Rodriguez-Barradas MC, *et al.* Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy. Medicine (Baltimore) 2002; 81: 213–227.

8 Lawn SD, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. Lancet Infect Dis 2005; 5:361–373.

9 Holland GN. Immune recovery uveitis. Ocul Immunol Inflamm 1999; 7:215–221.

10 Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. JAMA 2000; 283:74–80.

11 den Brinker M, Wit FW, Wertheim-van Dillen PM, *et al.* Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. AIDS 2000; 14:2895–2902.

12 Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. Am J Respir Crit Care Med 1998; 158:157–161.

13 Batista MD, Porro AM, Maeda SM, *et al.* Leprosy reversal reaction as immune reconstitution inflammatory syndrome in patients with AIDS. Clin Infect Dis 2008; 46:e56–e60.

14 Brinkhof MW, Egger M, Boulle A, *et al.* Tuberculosis after initiation of antiretroviral therapy in low-income and high-income countries. Clin Infect Dis 2007; 45:1518–1521.

15 Braitstein P, Brinkhof MW, Dabis F, *et al.* Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet 2006; 367:817–824.

16 Lawn SD, Wilkinson RJ. Immune reconstitution disease associated with parasitic infections following antiretroviral treatment. Parasite Immunol 2006; 28:625–633.