THE CHRONIC INFLAMMATORY STATUS IN PATIENTS WITH HIV INFECTION

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Human immunodeficiency virus (HIV) has become one of the most extensively studied and notorious pathogen in history, becoming one of the major public health challenges of modern times. Nevertheless, since the introduction of combined antiretroviral therapy (cART) the life expectancy of HIV-positive patients has increased to such magnitude that nowadays HIV infection is thought-out as a chronic controllable disease leading to an unforeseen growth in chronic non-acquired immune deficiency syndrome (AIDS) comorbidities, similar to those experienced in the elderly, and to a decrease in immunodeficiency-associated episodes. The resemblance between ageing and the course of HIV infection, imply that HIV infection may compress the ageing process, accelerating some comorbidities [1–4]. The majority of these age-associated diseases are the result of the persistent inflammation and activation of the immune system [5], which is described as "inflammageing" [6, 7], or in the event of AIDS, "inflammaids", considering the alterations that appear during HIV infection (which are similar to those which occur during immunosenescence) [8].

The pathogenesis of chronic inflammatory status in the HIV infection can be simplified in three main features: the substantial depletion of CD4+ T-cells, the paradoxical immune activation and the exhaustion of the immune system.

One of the main causes of this persistent dysregulated systemic immune activation and inflammation is that during the initial stages there is a massive reduction of CD4+ (especially of Th17) of the intestinal mucosa leading to a chronic microbial translocation. Moreover, there is an incomplete recovery of these CD4+ (despite the effective treatment – cART), facilitating infections, such as cytomegalovirus, thus, both mechanisms contribute to the persisting activation of the immune system leading to its exhaustion. Moreover, the HIV is characterised by a constant low replication despite the ART (which is not fully effective) leading to a sustained antigenic cascade keeping the immune system activated, consuming itself and causing its exhaustion resulting in a premature immunosenescence [1–8].

The persistent immune activity and inflammation result in a series of comorbidities at metabolic, cardiovascular, neurological, renal, hepatic and osseous levels.

As for the metabolic level, the treated patient exhibits disturbances in the carbohydrate metabolism, particularly an increased incidence in insulin resistance, largely due to by the microbial translocation and ART effects [9]; alterations of body fat distribution, leading to the appearance of lipodystrophy [10, 11], and lipid metabolism disorders, presenting typically an atherogenic dyslipidaemic pattern [12]. The main mechanisms involved are the microbial translocation and the cART, highlighting first generation protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NRTIs).

Concerning the cardiovascular level, one the one hand the cardiovascular risk is augmented by metabolic alterations, but also there is a direct inflammatory damage caused by the virus itself on the vessels, along with other traditional risk factors that occur more frequently in HIV-positive patients that in the general population [13, 14]. Moreover, cART has also been implicated in several studies (mainly PIs) [15, 16].

The central nervous system (CNS) is one of the target organs where the HIV can be detected within a few weeks of the infection. There is a progressive neurological damage that is known as HIV-associated neurocognitive disorders (HAND). Aside from the fact that the HIV virus enters the CNS damaging it, the inflammatory mechanisms (such as the microbial translocation)

allow the entry of inflammatory cells into the CNS cells which continue harming the brain. This process is seen in the cerebrospinal fluid (CSF) viral escape syndrome, in which the virus is resistant to the treatment leading to HAND [17, 18].

Prior to the arrival of an effective treatment the main reasons for kidney damage among HIV infected population was due to HIV-associated nephropathy and HIV immune complex disease of the kidney. At present, renal injury in HIV infection is related to metabolic or cardiovascular disorders, infections and associated with cART nephrotoxicity, mainly caused by Tenofovir disoproxil fumarate (TDF) [19–24].

Liver disease has arisen as the most common related cause of death among HIV-positive individuals [25]. Liver dysfunction is due to especially co-infections, hepatitis virus C and B, and alcohol and non-alcoholic fatty liver diseases (NAFLD)/ non-alcoholic steatohepatitis (NASH), related to microbial translocation and the persistent immune activation and inflammation. To a lesser extent because of the cART hepatotoxicity [26-28].

The bone diseases found in the HIV infected patient are osteopenia, osteoporosis, osteomalacia, and osteonecrosis. These disorders appear more commonly among the HIV infected population than in the general population, besides arising in fairly younger individuals. The pathogenesis of these comorbidities is not clear yet, although it has been suggested that are derived from the persistent dysregulated systemic immune activation and inflammation and by the cART effects (especially TDF). Moreover, the start of cART causes a loss of bone mass stabilizing later [29-31].

Therefore, the notion of HIV infection as an infectious disease is changing to that of inflammatory disease among treated HIV-infected individuals. As HIV infected patients' age, the consequences of the HIV infection become apparent with the development of the persistent inflammatory and immune activation syndrome. Although the early initiation of cART has shown a decrease in the immune activation and inflammation, it needs to be kept in mind that the cART: does not eradicate the virus, does not prevent a continuous low level of replication, does not impede the persistence of the immune activation, and does not restore the gut-associated lymphoid tissue (GALT), therefore, the microbial translocation persists. However, the cART has achieved great goals in improving the health and quality of life of HIV infected patients, for that reason we continue using cART as the main treatment. Thus, the new research should be directed to establish the immunopathology of this chronicity, as HIV infection is not a fully controllable chronic disease.

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