THE IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

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Abstract: *The Immune Reconstitution Inflammatory Syndrome (IRIS) occurs in HIV-infected patients initiating antiretroviral therapy (ART), where in spite of the immunological improvement, it brings about the clinical worsening. Global incidence according to retrospective studies varies between 17-32%. The multiple diseases associated with IRIS in HIV-infected patients may consist of infectious (Mycobacterium, viruses, bacteria, protozoars) or non-infectious etiologies (rheumatologic / autoimmune diseases, lymphomas). Due to the fact that, there is no consensus so far concerning the exact treatment for IRIS prevention, it still remains a challenge.*

Cuvinte cheie: *IRIS-ART*

Rezumat: *Sindromul de reconstrucție inflamatorie imună (IRIS) este prezent la pacienții infectați HIV cărora li se inițiază terapie antiretrovirală (ART), constând în agravarea paradoxală a simptomatologiei clinice, în ciuda îmbunătățirii imunității. Incidența globală conform studiilor retrospective variază între 17-32%. Afecțiunile posibil asociate cu IRIS la pacienții infectați HIV sunt numeroase, de etiologie infecțioasă (micobacterii, virusuri, bacterii, protozoare) sau non-infecțioasă (afecțiuni rheumatologice / autoimune, limfoame).La ora actuală nu există un consens privind terapia sau prevenția IRIS la pacienții infectați HIV, tratamentul rămânând o provocare în condițiile varietății simptomatologiei şi a multitudinii patogenilor capabili să declanşeze acest sindrom.*

The Immune Reconstitution Inflammatory Syndrome (IRIS) is a paradoxical inflammatory response that may occur in HIV-infected patients initiating antiretroviral therapy (ART), within the first several weeks after they begin the anti-HIV therapy and show signs of immunological improvement, owing to re-establish immunity to specific antigens. This may occur probably due to partial recovery of the immune system or to the exaggerated immunological response of the host to the antigenic stimulation.(1)

Global incidence of IRIS remains unknown, being variable in relation with studied population and the incidence of opportunistic infections.(1)

The suppression of CD4 T cells count, caused by HIV or by immunosuppressive medication is associated to a decrease of immune system's response to certain infections. The benefits of effective antiretroviral (ARV) therapy are proved by monitoring immunological (by rapid increasing of CD4 count) and also virusological reactions (decreasing of plasmatic HIV-1 viral charge). Despite these benefits, the ARV therapy is followed by sudden increase in the inflammatory response, leading to clinical deterioration (with nonspecific symptoms such as fever), possible even worsened of certain organs function.(6)

IRIS is perhaps most typically associated with mycobacterial infections (tuberculosis and disseminated MAC disease) and other opportunistic infections including cytomegalovirus (CMV) infection, varicella-zoster virus (VZV) infection, Pneumocystis jirovecii pneumonia (PCP), toxoplasmosis, hepatitis B and hepatitis C viruses, but also cryptococcal infection and histoplasmosis.

SHORT HISTORY

IRIS was defined for the first time in 2000, by Joseph A. DeSimone and colleagues from Thomas Jefferson University in Philadelphia. They observed that in some cases of HIV-infected patients, people appeared to develop a spectrum of illnesses after they had started and responded to ART, with increases in CD4 cell counts and decreases in viral load. Paradoxically, during improvement of the immune function, patients developed conditions associated with poor immune system function, such as Mycobacterium avium complex (MAC) and cryptococcal meningitis.(9)

Other terminology was used in the past for IRIS definition such as: immune restoration disease (IRD), immune reconstitution syndrome (IRS) or paradoxical reaction.

EPIDEMIOLOGY

To date, most studies are retrospective and reported that 17-32% of patients initiating ART will develop IRIS (4) but the global incidence of the syndrome is unknown.

A recent prospective study, performed on 423 ART-naive HIV-infected South African patients by David M. Murdoch and col., showed that 44 patients (10.4%) experienced IRIS during the first 6 months. Most frequent diagnoses included tuberculosis (41%), followed by abscess formation and suppurative folliculitis (18.2%), varicella zoster (13.6%), herpes simplex (9.1%), cryptococcal meningitis (6.8%), molluscum contagiosum (6.8%), and Kaposi's sarcoma (4.5%).(4)

Commonly risk factors for developing IRIS are: male, young age, low CD4 cell count or percentage at ART initiation, low ratio CD4/CD8 at baseline, ARN-HIV high levels at ART initiation, rapid ARN HIV-1 decreasing after HAART, short period between initiating OI therapy and ART.(3)

ETHIOLOGY

AIDS patients have a higher risk for IRIS on ART initiation or if they were recently treated for opportunistic

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infections (OI).
Pathogens and diseases associated with IRIS in HIV-infected patients may be:(1)

1. Infectious etiologies:
   - **Mycobacteria** - Mycobacterium tuberculosis
     - Mycobacterium avium *complex*
   - **Cytomegalovirus (CMV)**
   - Herpes viruses - Herpes zoster virus
     - Herpes simplex virus (HSV)
     - Herpes virus-associated Kaposi's sarcoma **(KS)**
   - **Cryptococcus neoformans**
   - **Pneumocystiscarinii** (jirovecii) pneumonia (PCP)
   - **Histoplasma capsulatum**
   - Toxoplasmosis
   - Hepatitis B and C virus (HBV and HCV)
   - Progressive multifocal leukoencephalopathy
   - **Strongyloides stercoralis** infection and other parasitic infections
   - Molluscum contagiosum and genital warts (human papillomavirus - HPV)
   - Hansen's disease (leprosy)
   - Sinusitis
2. Non-infectious etiologies:
   - Rheumatologic/autoimmune (rheumatoid arthritis, systemic lupus erythematosus (SLE), Graves disease, autoimmune thyroid disease)
   - Sarcoidosis and granulomatous reactions
   - Tattoo ink
   - non-Hodgkin's lymphoma (NHL)
   - Guillain-Barre' syndrome (GBS)
   - Interstitial lymphoid pneumonitis

PATHOGENESIS

Despite of many clinical descriptions of the syndrome, IRIS remains poorly understood. There are two theories, concerning the mechanism of IRIS, such as: the "unmasking" of an occult opportunistic infection, but also the "paradoxical" symptomatic relapse of the same primary infection despite successfully microbiologic treatment, although in paradoxical IRIS, microbiologic examination are sterile. It also exists the hypothesis that following ART, may occur the reconstitution of antigen-specific T cell-mediated immunity, with activation of the immune system against persisting antigen.(3)

Current theories involve correlation among underlying antigenic load, the degree of immune recovery due to ART and genetic host susceptibility, depending on load of infectious or non-infectious agents.(1)

The first theory refers to unmasking of occult opportunistic infection, with an exuberant inflammatory response to previously latent pathogens (viruses, bacteria) and their antigens, due to immune antigen-specific restoration thanks to ART. These reactions suggest a protective process rather than worsening of the disease. They differentiate IRIS from opportunistic infections owing to delayed adequate immunity.

Mycobacterial and cryptococcal infections are most commonly mentioned.(10)

In these cases, IRIS is attributed to an abnormal overproduction of Th1 cytokines (chemical messengers that coordinate and regulate immune responses). In viral infections, clinicopathological characteristics suggest different pathogenic mechanisms, such as immune reconstitution associated with varicella-zoster virus correlate with a CD8 T-cell response in the central nervous system. Unmasking hepatitis C virus (HCV) infection following ART may also reflect pathogen-specific immune responses restoration, as titters of HCV-reactive antibodies rise in parallel with liver enzymes and plasma markers of T-cell activation. (11)

The most studied mechanism suggests that the degree of cellular (CD4 cell-guided) immunity restoration after HAART initiation, is the presumed reason for the apparent onset of illness.

An increase in CD4 cells count is seen soon after initiation of ART, possible due to redistribution of CD4 lymphocytes from peripheral lymphoid tissues, suggesting that quantitative differences in baseline CD4 cell counts contribute to the pathogenesis of the disease rather than the rapidity of viral load suppression.(4)

The third plausible pathogenic mechanism of IRIS implies host genetic susceptibility, with exaggerated immune response to infectious or non-infectious antigenic stimulus, soon after immune recovery. Some studies suggest that equipment of HLA alleles may be associated with progressing of IRIS and specific pathogens.(12)

DeSimone's group pointed out that decreases in HIV viral load may alter levels of interleukin 12 (IL-12), a mediator of anticryptococcal activity (involved in meningitis symptoms). (9)

High levels of interleukin 6 may suggest an exuberant response of Lf Th1 to mycobacterial antigens in patients with clinical IRIS.(1)

CLINICAL MANIFESTATIONS

IRIS manifestations are diverse and have not been precisely defined, generally characterized by fever, loss of weight, elevated white blood cell count, depending on infectious or non-infectious agent involved. These manifestations may also include mycobacterial-induced lymphadenitis (2), paradoxical tuberculosis reactions (5), expansion of Kaposi's lesions, worsening of multifocal encephalopathy, recurrence of cryptococcosis and PCP, CMV retinitis and viral B or C hepatitis. Skin conditions such as folliculitis (inflammation of hair follicles) or genital warts (associated with human papillomavirus) may be manifestations of IRIS.

IRIS and mycobacterium tuberculosis

Mycobacterium Tuberculosis is the most frequent pathogen associated with IRIS. Retrospective studies focusing on disease-specific forms of IRIS, such as TB-IRIS patients initiating ART, varied with estimates ranging between 11-45%. (4)

The majority of cases occur within 2 or 3 months of ART initiating, with a maximum range within 12-15 days.(4) It is also hard to decide not to initiate ART, knowing that withholding or deferring ART until 2 or 6 months of TB therapy may direct to high risk of mortality.(1)

Most common manifestations of TB-IRIS are fever, lymphadenopathy and exacerbation of respiratory simptomps, (8) but also pulmonary infiltrates, mediastinal lymphadenopathy, pleural effusion and extrapulmonary affection.(1) Other simptoms are nonspecific and include prolongue fever, loss weight, abdominal pains and icter.

Paradoxical CNS reaction (meaning intracranial tuberculomas, tuberculous meningitis and spinal cord lesions) usually occurs 5-10 months after ART initiation.(1)

Though these symptoms can be dangerous, they also indicate that the body is now stronger in defeating the infection.

TREATMENT OF IRIS

The best treatment remains unknown as far no guidelines for managing IRIS being available. The treatment depends on underlying infectious agent, clinical presentation and illness severity. Most patients with paradoxical IRIS have no life-threatening symptoms, usually getting better spontaneously with no additional therapy. But also may occur

threatening live affections, such as acute renal failure (2) and acute respiratory distress syndrome (ARDS) (7) with high morbidity and mortality. In unmasking IRIS, the most common treatment for inflammatory reactions is to administrate antimicrobial agents (antibiotic or antiviral drugs) directed at the underlying infection, with possible intensification of medications already in use.(9)

Severe cases demand corticosteroids or nonsteroidal anti-inflammatory agents to suppress inflammation until the infection has been eliminated. Professional literature mentioned 40 mg Methylprednisolone in intravenous administration every 12 hours or Prednisone 20-70 mg/day for 5-12 weeks.(3)

Because so far, the exact incidence of IRIS remains unknown and ethiology and clinics are variable, but rising, the treatment of IRIS for HIV-infected patients initiating ART remains a challenge. The consensus is that ART should not be stopped in almost all IRIS cases, except for severe life-threating forms.

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