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Review

Immunopathogenesis, treatment and prevention of immune reconstitution inflammatory syndrome (IRIS)

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Immune reconstitution inflammatory syndrome (IRIS) is a clinical syndrome that has been described in human immunodeficiency virus (HIV) infected patients after initiation of highly active anti-retroviral therapy. The immunopathogenesis of IRIS is characterized by a dysbalanced restoration of the immune system or by paradoxical acute worsening of an underlying opportunistic infection (OI) or acquired immune deficiency syndrome (AIDS)-defining illness. The incidence of IRIS varies in different conditions and depends on the patient population, being higher in patients with greater burden of infection and advanced disease. The risk factors were found to be low baseline CD4-cell count, an excellent virological response, an increased antigenic burden of an opportunistic infection and early initiation of antiretroviral treatment after an OI. The clinical effect of IRIS ranges from mild, self-limiting illness to severe morbidity and mortality. Diagnosis is difficult because of a diverse range of clinical presentations. Treatment dilemma is also a big issue which includes discontinuation of antiretroviral treatment, corticosteroids or pathogen-specific therapy. Early screening of patients is needed to rule out any OIs before the start of highly active anti-retroviral therapy. The lack of appropriate treatment guidelines poses challenges in the management of these patients, hence provision of treatment guidelines and engaging in more research regarding immunopathogenesis, diagnosis and treatment of IRIS should be well thought-out.

Key words: Immune reconstitution inflammatory syndrome (IRIS), prevention, treatment, immuno-pathogenesis, human immunodeficiency virus (HIV) patients.

INTRODUCTION

Immune reconstitution inflammatory syndrome (IRIS) is a clinical syndrome that has been described in HIV infected patients after initiation of highly active anti-retroviral therapy (HAART) and measurable viral suppression, and is characterized by paradoxical or unmasked acute worsening of an underlying opportunistic infection (OI) or AIDS-defining illness (Shelburne et al., 2002; Manabe et al., 2007; Haddow et al., 2010). It is a serious condition that can occur shortly after a person starts HIV therapy for the first time. It happens when one's immune system recovers too quickly. Highly active antiretroviral therapy can start to restore immune cell function and respond to other infections that may or may not have been diagnosed before starting therapy, even the ones that may have already been under control. Because clinical deterioration occurs during immune recovery, this phenomenon has been described in different terms as immune restoration disease, immune reconstitution syndrome, Immune recovery disease, immune reconstitution disease, immune rebound illness, steroid-withdrawal disease, immune response reactions and paradoxical reactions (Cheng et al., 2000; Cooney, 2002;

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Abbreviations: AIDS, Acquired immune deficiency syndrome; **ART,** anti-retroviral therapy; **cART,** combined ART; **HAART,** highly active anti-retroviral therapy; **HIV,** human immunodeficiency virus; **IRIS,** immune reconstitution inflammatory syndrome; **KS IRIS**- Kaposi's sarcoma immune reconstitution inflammatory syndrome, **NSAIDs,** non-steroidal anti-inflammatory drugs; **OI,** opportunistic infection.

French et al., 2000; Shelburne et al., 2002).

There are two common clinical scenarios in IRIS: unmasking IRIS and paradoxical IRIS. In unmasking IRIS, the infection is newly identified after the initiation of antiretroviral treatment (ART), and usually the provoking pathogen is viable (French, 2009). In paradoxical IRIS, the infection was previously treated but worsened clinically after ART initiation and the causative pathogens can be either viable or non-viable (French, 2009).

It is a paradoxical deterioration in clinical status after ART initiation despite improved immune function due to inflammatory response against infectious antigen, which may or may not have been diagnosed at initiation of ART. Immune reconstitution inflammatory syndrome most often occurs in patients with low initial CD4 (usually <50/µl) and rapid decline in viral load; onset usually within 6 weeks of ART initiation, but sometimes several months later (Musey et al., 1999; Rosenberg et al., 2000). Although IRIS that is seen even in late-stage disease, is more prominent in patients who commence treatment during early HIV infection before substantial damage to the immune system, where robust responses are often seen after treatment (Oxenius et al., 2001).

It is speculated that IRIS results from the restoration of immunity to pathogen-specific antigens present at the time of ART initiation. Following ART, a quantitative increase in peripheral T cells occur which partially restores activity to recall antigens as a result of suppression of HIV viral replication in lymphoid tissue and reductions in immune activation (Bucy et al., 1999; Autran et al., 1997). Therefore, the aim of this review is to compile and provide the available information on the epidemiology, clinical presentation and pathogenesis and present treatment options of IRIS.

EPIDEMIOLOGY AND RISK FACTORS OF IRIS

Despite numerous descriptions of the infectious and noninfectious causes of IRIS, the overall incidence of the syndrome itself remains largely unknown. The incidence of IRIS observed in HIV infected patients following initiation of HAART is variable (Li et al., 1998; Palella et al., 1998). The proportion of patients starting ART who develop IRIS is not well known, with estimates ranging from less than 10% to more than 50% in several studies (Kumarasamy et al., 2004; Narita et al., 1998; Lawn et al., 2005a; Ortega-Larrocea et al., 2005), but not all have reported an increased risk of the syndrome in patients starting ART who have advanced immunodeficiency (French et al., 2004; Colebunders et al., 2006; French et al., 2000; Jevtović et al., 2005; Bourgarit et al., 2006).

In a single study conducted in Ethiopia, the proportion of IRIS was 17.2% among 186 HIV/AIDS patients receiving HAART. According to the study, the mean number of days of IRIS occurrence for different diseases ranged from 26 to 122 days was 80 days.

Opportunistic diseases associated with IRIS were tuberculosis (68.8%), herpes zoster rash (12.5%), cryptococcosis (9.4%), toxoplasmosis (6.3%) and bacterial pneumonia (3.1%) (Huruy et al., 2008).

A retrospective study showed that among 47 patients on combined ART (cART) at a TB clinic, 11 (23%) experienced unmasking IRIS (Valin et al., 2010). The patients had lower CD4%, higher HIV-RNA load at baseline and a stronger CD4% increase with HIV-RNA decline after one month on cART than the 36 remaining patients without unmasking IRIS (Valin et al., 2010).

A study in sub-Saharan Africa and United Kingdom showed that 58 patients (13.9%) experienced Kaposi's sarcoma (KS-IRIS) among 436 patients during the first 3 months on cART. Independent predictors of KS-IRIS development were found to be having an advance KS-stage at KS diagnosis and having a pre-cART HIV viral load higher than 5 log10 copies/ml (Letang, 2011).

Essentially, any pathogen that can cause an opportunistic infection as a result of impaired cellular immune responses can provoke IRIS after pathogen-specific immune responses are restored by ART (French, 2009).

The risks of unmasking and paradoxical forms of IRIS in HIV infected patients starting ART are fuelled by a combination of the late presentation of patients with advanced immunodeficiency, the associated high rates of OIs and the need for rapid initiation of ART to minimize overall mortality risk. Risk factors identified for the development of IRIS in one cohort study included male sex, a shorter interval between initiating treatment for OI and starting ART, rapid fall in HIV-1 RNA after ART, and being ART-naïve at the time of OI diagnosis (Dhasmana et al., 2008; Manabe et al., 2007; Shelburne et al., 2005). Other significant predictors have also included younger age, a lower baseline CD4 cell percentage, a lower CD4 cell count at ART initiation, and a lower CD4 to CD8 cell ratio at baseline (Ratnam et al., 2006). The four principal factors associated with an increased risk of developing IRIS are: (1) Low baseline CD4+ T-cell count, (2) Excellent virologic response to ART, (3) Increased antigen burden of an OI and (4) Early initiation of ART in close proximity to starting therapy for an OI (Valin et al., 2010; French, 2009; Dhasmana et al., 2008; Manabe et al., 2007; Shelburne et al., 2005; Ratnam et al., 2006). These factors have been identified in different studies done; however, these risk factors are by any means universal. For example, extrapolating from a case series on TB-IRIS may not be informative for defining the risk of hepatitis B IRIS (Shuli et al., 2008).

CLINICAL PRESENTATION AND DIAGNOSIS OF IRIS

Almost any organ or system may be affected by IRIS, and the clinical spectrum of IRIS depends on the site affected, the pathogen involved, and the host-parasite interaction and manifestations are worsened than other

conditions. IRIS may be targeted at viable infective antigens, dead or dying infective antigens, host antigens, tumour antigens and other antigens, giving rise to a heterogeneous range of clinical manifestations. The commonest forms of IRIS are associated with mycobacterial infections, fungi and herpes viruses (Dhasmana et al., 2008). Tuberculosis, Mycobacterium avium complex, Cryptococcus, Cytomegalovirus, Hepatitis B or C, Progressive multifocal leukoencephalopathy, Kaposi's sarcoma, Autoimmune diseases, Herpes simplex virus, varicella zoster virus, a number of dermatologic manifestations, such as folliculitis and oral and genital warts, may appear or worsen during immune reconstitution (New York State Department of Health AIDS Institute, 2009).

Definition of IRIS is described as follows as stated by French et al. (2000) and must meet both major A and B criteria, or major A and any two minor criteria.

Major criteria A

a) Atypical presentation of OIs or tumors in patients responding to ART.
b) Localized disease (for example, lymph nodes, liver, spleen).
c) Exaggerated inflammatory reaction (for example, severe fever, painful lesions).
d) A typical inflammatory response in affected tissues (for example, granulomas, suppuration, necrosis, perivascular lymphocytic inflammatory cell infiltrate).
e) Progression of organ dysfunction or enlargement of preexisting lesions after definite clinical improvement with pathogen-specific therapy before ART and exclusion of treatment toxicity and new diagnoses.

Major criteria B

a) Decrease in viral load greater than one log.

Minor criteria

a) Increased CD4 T-cell count after ART.
b) Increase in an immune response specific to the relevant pathogen (for example, delayed-type hypersensitivity response to mycobacterial antigens).
c) Spontaneous resolution of disease without specific antimicrobial therapy or tumor chemotherapy with continuation of ART (French et al., 2004).

Possible differential diagnoses in patients experiencing clinical deterioration after initiating ART

a) IRIS—paradoxical reaction (deterioration of known condition that would otherwise be expected to improve).
b) IRIS—unmasking (new clinical presentation of undiagnosed but preexisting condition).
c) Failure of OI treatment because of drug-resistant organism.
d) Failure of OI treatment because of non adherence to OI treatment or prophylaxis.
e) Failure of ART because of drug resistance.
f) Failure of ART because of non adherence to ART.
g) Failure of OI treatment or ART for other reasons (for example, malabsorption).
h) Newly acquired OI or other condition.
i) Expected course of preexisting OI or other condition.
j) Adverse drug reaction.

There is no diagnostic test for IRIS and the differential diagnosis is complex as mentioned before. Therefore it is important to note that IRIS is a diagnosis per exclusion which means that first all other possible causes of clinical worsening should be ruled out before we can conclude that the patient has IRIS (Haddow et al., 2009).

IMMUNOPATHOGENESIS OF IRIS

The immunopathogenesis of IRIS remains incompletely defined or poorly understood but studies have shown associations with T-cell expansion, proinflammatory cytokine release and diminished regulatory T-cell activity (Dhasmana et al., 2008). The vast majority of cases of IRIS develop in the first 3 months of ART (Shelburne and Hamill, 2003; Lawn et al., 2005b) corresponding to the first phase of immune reconstitution in which there is a very rapid increase in both the number of circulating CD45RO+ memory cells as well as CD4 cell function (Autran et al., 1997). Delayed development of IRIS in minority of cases might be due to delayed immune recovery after ART is commenced.

Most cases of IRIS are associated with chronic bacterial infections, viral infections and deep fungal infections, which typically trigger immunopathology via cell-mediated T-helper type 1 (TH1) cytokine-secreting immune responses (Bourgarit et al., 2006; Shelburne and Hamill, 2003; Lawn et al., 2005b; Havlir and Barnes, 1999). Many different pathogens have been associated with the development of IRIS. The leading pathogens include: Mycobacterium tuberculosis, Mycobacterium avium complex, Cytomegalovirus, Cryptococcus, Pneumocystis, Herpes simplex virus, Hepatitis B virus and Human herpes virus 8 (associated with Kaposi's sarcoma). Some case reports have also documented IRIS associated with: hepatitis C virus, parvovirus B19 (Nolan et al., 2003), herpes simplex, *Bartonella henselae*, Histoplasma capsulatum (Breton et al., 2006), dermatophytosis (Van Hal et al., 2005), leprosy (Couppié et al., 2004; Lawn et al., 2003; Bower et al., 2005; Menezes et al., 2009), bacillus Calmette-Guérin (BCG) (Puthanakit et al., 2005), *Penicillium marneffei* (Gupta et al., 2007), *Schistosoma mansoni* (De Silva et al., 2006) and *Molluscum contagiosum* virus. In addition, some patients with Kaposi's sarcoma have developed an IRIS-like syndrome when HAART was initiated (Murdoch et al.,

2008; Shelburne et al., 2005; Connick et al., 2004) and other patients have developed grave's thyrotoxicosis or recurrence of sarcoidosis after starting HAART.

The development of IRIS requires advanced HIV infection with severe immune damage, improving immunity in response to ART, the presence of inciting antigens that trigger an immune response and the apparent loss of normal homeostatic control of immune responses, resulting in an over exuberant inflammatory response. The strongest predictor for the development of IRIS, however, is a low CD4+ T-cell count prior to starting ART (French et al., 2000; Ratnam et al., 2006).

In AIDS patients, damage to homeostatic control mechanisms followed by rapid ART-restoration of pathogen-specific immune responses, could promote exaggerated inflammatory responses, especially if viable pathogens or pathogen debris are present at high concentrations. Nevertheless, it is intriguing that restoration of pathogen specific immunity is uneventful in some patients but leads to severe immunopathology in others (Munier and Kelleher, 2007). Highly active anti-retroviral therapy induced metabolic derangements are being described for IRIS related to autoimmune disease (Calabrese et al., 2005).

Conditions for IRIS require: antigen, restoration of antigen-specific immunity, dysregulated immune response which is hypothesized to be functional imbalance in pro-inflammatory (Th1, Th17) versus anti-inflammatory (Treg) T-cell populations. Cytokine profiles of IRIS events are heterogeneous based on the inciting pathogen (for example, viral, fungal, mycobacterial, etc) with marked individual variation. Pro-inflammatory cytokines are generated at time of mycobacterial and fungal IRIS events, such as IL-6, IL-17, IFN-γ, and TNF-α (Shuli et al., 2008).

When comparing cytokine levels between IRIS cases and non-IRIS controls by the type of IRIS presentation, different cytokine expression patterns were observed and most IRIS cases showed an increase in IL-6 and IFN-g in comparison to non-IRIS controls (Catherine et al., 2010).

During HAART and immune reconstitution, pathogen derived antigens are processed and presented to CD4+ T-cells leading to T-cell activation and secretion of macrophage-activating interferon-γ. Vitamin D inhibits this IFN-γ production. In case of low vitamin D levels prior to HAART, a defective clearing of pathogens and a delayed negative feedback on macrophage activation due to low vitamin D production, can lead to excessive granuloma formation and an exacerbated inflammatory response described as IRIS (Baeke et al., 2007).

One possible mechanism that illustrates the immunology of IRIS in a subject with HIV/TB co-infection shows that compromised gut immunity leads to increased translocation of luminal gram negative bacterial lipopolysaccharides into the systemic circulation. Initiation of HAART in the subject leads to abrupt restoration of CD4+ T-cells and almost any pathogen-specific immune response. IRIS developers have a high burden of lipopolysaccharids and pro-inflammatory cytokines produced against lipopolysaccharids could result in an exaggerated, nonspecific attack on latent mycobacterial antigens that are presented in the local lymph nodes leading to localized inflammation (Esaki et al., 2007).

Higher pre-ART levels of interleukin (IL)-4 and IL-17 as well as lower tumor necrosis factor (TNF)-a, granulocyte colony-stimulating factor (GCSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and vascular endothelial growth factor (VEGF) predicted future IRIS. After ART was initiated, increasing levels of C-reactive protein (CRP), D-dimer, IL-6, IL-7, IL-13, G-CSF, or IL-1RA were associated with increasing hazard of IRIS (David et al., 2010).

Patients who had experienced an IRIS demonstrated increased levels of bioavailable IL-6 and increased expression of CCR5 and CCR3 on monocytes and granulocytes, but numbers of γδT-cells were similar to patients with similar CD4 T cell counts without an IRIS. Carriage of HLA-A2, HLA-B44 was associated with a history of Cytomegalovirus (CMV) retinitis and/or encephalomyelitis as an IRIS, but not with IRIS initiated by *Mycobacterium* spp., cutaneous varicella zoster or herpes simplex infections or hepatitis c virus (HCV). It also identified that a patient with graves' thyrotoxicosis and pronounced lymphadenopathy after HAART, demonstrated that thyroid stimulating hormone receptor antibody production was associated with an increase in serum soluble CD30, suggesting acquired immune dysregulation (Priceab et al., 2001).

Genetic polymorphisms of IL-6, IL-12, and TNF-α have been also implicated as possible factors in risk and protection from IRIS. Differences in gene expression exist prior to beginning HIV therapy which may predict the risk of subsequent IRIS. The genes differentially expressed involve immune activation and anti-viral responses (Shuli et al., 2008).

CD4 T-cells are involved in mycobacterial and other granulomatous IRIS whereas CD8+ T cells are more frequently associated with viral IRIS. Immune reconstitution disease could be the consequence of unbalanced reconstitution of over activated T cells and regulatory T cells (Tregs). Direct activation of monocytes and dendritic cells during immune reconstitution, in particular by living or dead mycobacteria or antigenic debris could be a possibility. Antigen load during immune restoration may be a determining factor as well. Finally, the cytokine environment during immune restoration, IL-7 and IL-10 in particular, both important in T-cell homeostasis, could have a pivotal role in the development of IRIS (Kestens et al., 2008).

PREVENTION OF IRIS

To prevent development of IRIS, initiation of ART before

advanced immunosuppression would be expected to reduce the risk of IRIS because advanced immunosuppression increases the risk for opportunistic infections, which is a risk factor for IRIS (Bonham et al., 2008). Recognize that the highest risk occurs in patients with CD4<50 and HIV viral load >100,000 who have a rapid response to ARV (Shuli et al., 2008; Beishuizen et al., 2009). To prevent unmasking IRIS, a thorough screening for active opportunistic infections before ART initiation is critical, because patients with advanced immunosuppression may have atypical or minimal symptoms owing to the absence of an inflammatory response (Dhasmana et al., 2008; Meintjes and Lynen, 2008). For paradoxical IRIS, a shorter delay between starting treatment for tuberculosis and cryptococcosis and ART has been identified as a risk factor (Navas et al., 2002; Breen et al., 2004). However, delaying ART to the end of tuberculosis treatment may reduce the risk of tuberculosis-IRIS occurrence, but is likely to come at the cost of advancing immunosup- pression, other opportunistic infections and increased AIDS-related mortality (Lawns and Woods, 2007).

TREATMENT OF IRIS

The evidence base for producing guidelines on the treatment of IRIS is very limited and relies heavily on clinical observations and expert opinion (Meintjes and Lynen, 2008). Basically, treatment of IRIS should be started after all other alternatives are ruled out which can be used as mono or combination therapy. The treatment approaches are: temporary ART discontinuation until the clinical condition has improved, use of non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids, pathogen-specific therapy or other therapy (Battegay and Drechsler, 2006). ART interruption should be recommended only for patients with severe, life-threatening symptoms until their condition is established. Immune reconstitution inflammatory syndrome can recur during re-initiation of ART, so this has to be monitored carefully. However, stopping ART in the setting of incompletely suppressed HIV replication may be associated with an increased risk of antiretroviral resistance (Meintjes et al., 2008).

Anti-inflammatory therapy may be effective but should be reserved for the most severe cases; this is especially true of corticosteroid therapy, which can increase the risk of reactivating other latent infections. Anti-retroviral therapy should only be ceased if disease is life threatening. In cases of paradoxical IRIS, treatment of the opportunistic infection should be continued to suppress replication of the provoking pathogen and to reduce antigen load (French, 2009).

Non-steroidal anti-inflammatory drugs are advised for the management of mild and moderate cases, and corticosteroids for the individuals with severe or life-threatening disorders. On the other hand, corticosteroids have been shown to be associated with an excess of Kaposi's sarcoma and herpes virus reactivation in HIV-infected patients with low CD4 counts but not in patients with increasing CD4 counts after initiation of ART. Pathogen-specific therapy should be started or continued in the case of unmasking or paradoxical IRIS (Meintjes and Lynen, 2008). Prednisone reduced the need for hospitalization and therapeutic procedures and hastened improvements in symptoms, performance, and quality of life (Meintjes et al., 2010).

CONCLUSION

Immune reconstitution inflammatory syndrome is the result of an exaggerated cellular immune response to living or dead pathogens or debris. It is associated with restoration of pathogen-specific effector T cells and regulatory T cells. T regulatory cells may be suppressed; however, by the disrupted cytokine environment because of impairment of the homeostatic control mechanisms. A part from this fact, it is not clear which factors or combination of factors trigger IRIS. These factors could be pathogen related (antigen load), genetic or immune related such as for instance the diversity of pathogen-specific T cells during immune restoration. Clinicians treating patients with AIDS need to be aware that HAART-engendered immune recovery may result in pathological inflammation in a subset of patients. Vigilance needs to be especially high during the first several months of therapy where the incidence of IRIS peaks, but cases continues to occur even after 1 or 2 years of therapy. Early monitoring of CD4 counts in HIV patients is needed so that cART should not be delayed in patients with AIDS defining diseases. The lack of appropriate treatment guidelines poses challenges in the management of these patients hence provision of treatment guidelines and performing more research regarding immunopathogenesis, diagnosis and treatment of IRIS.

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