REVIEW ARTICLE

Therapeutics targeting inflammation in the immune reconstitution inflammatory syndrome

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Immune reconstitution inflammatory syndrome (IRIS) is characterized by improvement in a previously incompetent human immune system manifesting as worsening of clinical symptoms secondary to the ability of the immune system to now mount a vigorous inflammatory response. IRIS was first recognized in the setting of human immunodeficiency virus, and this clinical setting continues to be where it is most frequently encountered. Hallmarks of the pathogenesis of IRIS, independent of the clinical presentation and the underlying pathogen, include excessive activation of the immune system, with increased circulating effector memory T cells, and elevated levels of serum cytokines and inflammatory markers. Patients with undiagnosed opportunistic infections remain at risk for unmasking IRIS at the time of active antiretroviral therapy (ART) initiation. Systematic screening for opportunistic infections before starting ART is a key element to prevent this phenomenon. Appropriate management of IRIS requires prompt recognition of the syndrome and exclusion of alternative diagnoses, particularly underlying infections and drug resistance. Controlled studies supporting the use of pharmacologic interventions in IRIS are scare, and recommendations are based on case series and expert opinions. The only controlled trial published to date, showed reduction in morbidity in patients with paradoxical tuberculosis–related IRIS with the use of oral corticosteroids. There are currently limited data to recommend other anti-inflammatory or immunomodulatory therapies that are discussed in this review, and further research is needed. Ongoing research regarding the immune pathogenesis of IRIS will likely direct future rational therapeutic approaches and clinical trials. (Translational Research 2015; ■:1–16)

Abbreviations: ART = antiretroviral therapy; CCR = chemokine receptor; CI = confidence interval; CMV = *Cytomegalovirus*; CNS = central nervous system; CRP = C-reactive protein; CSF = cerebrospinal fluid; HIV = human immunodeficiency virus; HR = hazard ratio; IFN = interferon; IP = interferon-γ-inducible protein 10; IL = interleukin; IRIS = immune reconstitution inflammatory syndrome; KS = Kaposi sarcoma; MAC = *Mycobacterium avium* complex; MHC = major histocompatibility complex; OI = opportunistic infection; OR = odds ratio; PML = progressive multifocal leukoencephalopathy; TB = tuberculosis; Tregs = regulatory T cells; TNF = tumor necrosis factor

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INTRODUCTION

Immune reconstitution inflammatory syndrome (IRIS) is characterized by improvement in a previously incompetent human immune system manifesting as worsening of clinical symptoms secondary to the ability of the immune system to now mount a vigorous inflammatory response. The syndrome was first reported in the mid-1990s at the time when effective antiretroviral therapy (ART) became available for patients with human immunodeficiency virus (HIV) infection. The first reported series by French et al[1] presented cases of worsening *Mycobacterium avium intracellulare* infection occurring concurrently with the restoration of cutaneous delayed-type hypersensitivity responses to mycobacterial antigens after the initiation of zidovudine therapy in immunodeficient HIV-infected patients. The clinical syndrome of IRIS is well recognized at this time with increasing literature focusing on the immunopathogenesis and emerging therapies. The aim of our review was to present a concise evidence-based summary of the presentation, immunopathogenesis and potential treatments of IRIS.

COMMON SCENARIOS OF IRIS

Paradoxical vs unmasking form. IRIS most commonly occurs, although not exclusively, in individuals with previously diagnosed opportunistic infections (OIs) and results from the rapid restoration of pathogen-specific immune responses. IRIS may occur in 2 different scenarios. The "paradoxical" form of IRIS occurs when an OI diagnosed initially responds successfully to treatment, but then clinical deterioration occurs as a direct result of immune recovery, most commonly after ART initiation. By contrast, the "unmasking" form of IRIS occurs when an OI remains undiagnosed and subsequent immune recovery triggers the overt presentation of this OI with the development of unusual inflammatory features.

HIV infection. IRIS was first recognized in the setting of HIV,[1] and this clinical setting continues to be where it is most frequently encountered. The incidence of IRIS in patients initiating ART is not well defined, with published estimates ranging from $<10\%$ to $>50\%$. Several studies, but not all, found an increased risk of IRIS in patients starting ART with advanced immune deficiency. A meta-analysis that included 13,103 HIV-infected patients from 54 cohort studies which was done to better define the incidence and lethality of IRIS events in patients starting ART estimated that 16.1% of patients developed IRIS and 4.5% of these patients died.[2]

Several risk factors for developing IRIS have been identified (Table I). Presence of an undiagnosed OI before starting ART, degree of immunodeficiency (baseline CD4 count and HIV viral load), timing of ART during OI treatment, and response to ART in terms of improvement in the viral load and CD4 count have been recognized as important factors.[2,3] The diagnosis of IRIS can be challenging because of reliance on clinical criteria (Table II). In cases of unmasking IRIS, the diagnosis involves using conventional diagnostic tests to identify the underlying OI. In paradoxical IRIS, patients have apparent clinical deterioration despite being on effective treatment for the OI. The diagnosis in such situations relies on the presence of improvement of symptoms while receiving treatment before the initiation of ART, deterioration with features of the OI soon after starting ART, and demonstration of a CD4 and/or HIV viral load response as a result of ART. Further factors, such as relapse or a new OI, drug toxicity, poor adherence, or resistance to OI treatment, need to be excluded.[4]

Table I. Risk factors for developing immune reconstitution inflammatory syndrome in HIV infection*

Rapid decline in HIV viral load
Lower CD4 cell counts before starting antiretroviral treatments
Rapid increase in the CD4 cell after starting antiretroviral treatment
Presence of opportunistic infection

*Adapted from Mori and Levin.[3]

Many experts now favor moving away from the term "unmasking" IRIS toward a broader term, "ART-associated OI," especially in HIV-infected patients. Because ART-related immune recovery is a time-dependent process with some patients initially failing to mount an adequate immune response, a proportion of OIs might present as a result of persisting immunodeficiency. Diagnosis of an OI before ART initiation might be missed because of poor diagnostics in patients with advance immunodeficiency and only confirmed later when the patient is started on ART. Other patients might have active subclinical disease at the time of ART initiation and presentation of symptomatic disease results from ART-induced restoration of an immune response against the pathogen causing inflammation. Owing to a variety of the above reasons, there have been suggestions in the literature to change case definitions from "unmasking IRIS" toward "ART-associated OI," especially in tuberculosis (TB)- and cryptococcal disease–related IRIS.[5,6]

IRIS in immunocompromised, non-HIV–infected patients. The IRIS has been described in various immunocompromised patient populations in the absence of HIV infection.[7] The proposed pathogenesis in these situations involves a shift from the normal T-helper responses that restrain inflammation (Treg and Th2) toward generation