Review Article

HIV & immune reconstitution inflammatory syndrome (IRIS)

Surendra K. Sharma & Manish Soneja

Department of Internal Medicine, All India Institute of Medical Sciences, New Delhi, India

Antiretroviral therapy (ART) initiation in HIV-infected patients leads to recovery of CD4+T cell numbers and restoration of protective immune responses against a wide variety of pathogens, resulting in reduction in the frequency of opportunistic infections and prolonged survival. However, in a subset of patients, dysregulated immune response after initiation of ART leads to the phenomenon of immune reconstitution inflammatory syndrome (IRIS). The hallmark of the syndrome is paradoxical worsening of an existing infection or disease process or appearance of a new infection/disease process soon after initiation of therapy. The overall incidence of IRIS is unknown, but is dependent on the population studied and the burden of underlying opportunistic infections. The immunopathogenesis of the syndrome is unclear and appears to be result of unbalanced reconstitution of effector and regulatory T-cells, leading to exuberant inflammatory response in patients receiving ART. Biomarkers, including interferon-γ (INF-γ), tumour necrosis factor-α (TNF-α), C-reactive protein (CRP) and inter leukin (IL)-2, 6 and 7, are subject of intense investigation at present. The commonest forms of IRIS are associated with mycobacterial infections, fungi and herpes viruses. Majority of patients with IRIS have a self-limiting disease course. ART is usually continued and treatment for the associated condition optimized. The overall mortality associated with IRIS is low; however, patients with central nervous system involvement with raised intracranial pressures in cryptococcal and tubercular meningitis, and respiratory failure due to acute respiratory distress syndrome (ARDS) have poor prognosis and require aggressive management including corticosteroids. Paradigm shifts in management of HIV with earlier initiation of ART is expected to decrease the burden of IRIS in developed countries; however, with enhanced rollout of ART in recent years and the enormous burden of opportunistic infections in developing countries like India, IRIS is likely to remain an area of major concern.

Key words Acquired immunodeficiency syndrome - cryptococcosis - human immunodeficiency virus - immune reconstitution inflammatory syndrome - tuberculosis

Introduction

Antiretroviral therapy (ART) in HIV/AIDS patients leads to dramatic reductions in plasma viral load, improvement in CD4+ T cell counts and partial restoration of overall immune function. These immunological changes correlate with reduction in the frequency of opportunistic infections (OI) and prolonged survival[1]. However, a subgroup of patients experience a clinical deterioration as a consequence of rapid and dysregulated restoration of antigen specific immune responses during the treatment[2]. This was first noted following the introduction of zidovudine monotherapy in the early 1990s, when localized forms of *Mycobacterium avium-intracellulare* (MAI) infection

were observed in association with the recovery rather than failure of cellular immune responses[3]. Over the past two decades, symptomatic deterioration in patients on ART has been described in relation to a number of pre-existing subclinical infections, inflammatory disorders and autoimmune diseases. This phenomenon is known by multitude of names including, "immune reconstitution inflammatory syndrome (IRIS)", "immune reconstitution" or "restoration disease (IRD)", and "immune reconstitution syndrome (IRS)". Although IRIS is now a well established entity, uncertainty exists with regards to its pathogenesis and management, and research in the field is hampered by lack of a consistent definition of the syndrome.

Definition

There is no gold standard definition of IRIS. Attempts to develop an all inclusive definition are hindered by the need to be broad enough to include IRIS caused by wide variety of pathogens and varied disease processes, which would be applicable in all clinical settings. It would also need to include both unmasking of clinically silent infections and worsening of previously diagnosed opportunistic infections, and address the issues of difficulty in excluding a new microbial process or drug resistance as the cause of deterioration.

A number of case definitions for IRIS have been proposed[4-6]. The commonly used definitions are shown in Table I. It is generally accepted that certain minimum criteria should be fulfilled in order to diagnose IRIS. There must be temporal association between initiation of ART and subsequent development of symptoms (usually within 3 months), with evidence of immune restoration (virological and immunological response demonstrated by a decrease in plasma HIV RNA level by more than 1 $\log_{10}$ copies/ml and an increase in CD4+ T cell count from baseline) and must exhibit clinical symptoms and signs consistent with an inflammatory process. The clinical course should neither be consistent with the usual course of a previously diagnosed opportunistic infection or a new infectious process; nor should the symptoms and signs be explained by drug toxicity. Although, a rise in CD4+ T cells is commonly seen in IRIS, it is not an essential element for the diagnosis. A rise in blood CD4+ count is not a direct evidence of improved functional immune status; neither does the lack of rise indicate that there has been no restoration of functional T lymphocyte response[7]. A falling plasma viral load is a more important indicator.

Table I. General case definitions for IRIS

General IRIS case definition proposed by French *et al* (2004)[5]

Diagnosis requires two major criteria (A+B) or major criterion (A) plus two minor criteria to be fulfilled:

Major criteria

A. Atypical presentation of opportunistic infections or tumours in patients responding to ART, manifested by any of the following:

- Localized disease
- Exaggerated inflammatory reaction
- Atypical inflammatory response in affected tissues
- Progression of organ dysfunction or enlargement of pre-existing lesions after definite clinical improvement with pathogen-specific therapy prior to ART and exclusion of treatment toxicity and new diagnoses

B. Decrease in plasma HIV RNA level >1 $\log_{10}$ copies/ml

Minor criteria

- Increase in CD4 count after ART
- Increase in an immune response specific to the relevant pathogen
- Spontaneous resolution of disease with continuation of ART

General IRIS case definition proposed by Robertson *et al* (2006)[6]

Required criterion

- Worsening symptoms of inflammation/infection
- Temporal relationship with starting antiretroviral treatment
- Symptoms not explained by newly acquired infection or disease or the usual course of a previously acquired disease
- >1 $\log_{10}$ decrease in plasma HIV load

Supportive criterion

- Increase in CD4+ cell count of ≥25 cells/µl
- Biopsy demonstrating well-formed granulomatous inflammation or unusually exuberant inflammatory response

Superscript denotes the reference numbers; IRIS, immune reconstitution inflammatory syndrome; ART, antiretroviral therapy

The general definitions are intended to encourage clinicians to consider the diagnosis in their patients; however, these lack specificity and do not discriminate between different forms of IRIS. Disease specific IRIS case definitions have been proposed to address the issue[4,8,9]. Table II shows guidelines proposed for diagnosis of TB-IRIS in resource-constrained settings[4,8].

Epidemiology

IRIS has been reported in 10 to 32 per cent of patients starting ART[10-13]. The variation in reported

Table II. Case definitions for tuberculosis-IRIS

Case definition for tuberculosis-associated IRIS (Colebunders et al, 2006)[8]

Suspected case (must meet the following three criteria)

- An initial clinical response to tuberculosis treatment
- New persistent fevers without another identifiable cause and/or one or more of the following: worsening or emergence of dyspnoea, stridor, an increase in lymph node size, development of abscesses, development of abdominal pain with ultrasound evidence of abdominal adenopathies, unexplained CNS symptoms
- Adequate adherence to ART and tuberculosis treatment

Confirmed case (must meet the following three criteria)

- New/worsening radiological signs
- A good virological response and/or increase in CD4+ lymphocyte count, and/or conversion of tuberculin skin test from negative to positive, and/or adequate adherence to ART and tuberculosis treatment
- Exclusion of treatment failure or other concomitant infections, tumours, or allergic reactions.

INSHI case definition for paradoxical TB-IRIS[4]

(A) *Antecedent requirements* (both criteria must be met)

- Diagnosis of tuberculosis: the diagnosis of tuberculosis made before starting ART (WHO criteria).
- Initial response to tuberculosis treatment: initial improvement or stabilisation on appropriate anti-TB treatment before ART initiation (however, in patients starting ART within 2 wk of starting tuberculosis treatment, insufficient time may have elapsed for a clinical response to be reported).

(B) Clinical criteria (one major criterion or two minor clinical criteria are required)

The onset of TB-IRIS manifestations within 3 months of ART initiation, reinitiation, or regimen change.

Major criteria

- New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement
- New or worsening serositis
- New or worsening CNS tuberculosis
- New or worsening radiological features of tuberculosis

Minor criteria

- New or worsening constitutional symptoms
- New or worsening respiratory symptoms
- New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy

(C) Alternative explanations must be excluded if possible

- Tuberculosis drug resistance, poor adherence to treatment, drug toxicity, and another opportunistic infection.

INSHI, International Network for the Study of HIV-associated IRIS; WHO, World Health Organization; ART, antiretroviral therapy

frequency reflect differences in case definitions, and more importantly, differences in study populations with differing risk profiles and underlying burden of opportunistic infections.

Most of the literature on epidemiology comes from the developed countries. In a series from southern India TB-IRIS was reported in 7.6 per cent of patients[14]. We have reported incidence rates of 7.5 per cent for paradoxical TB-IRIS and 3 per cent for ART-associated TB in a retrospective study using consensus case-definitions[15]. In a prospective study, using stringent case-definitions criteria[16], paradoxical TB-IRIS was seen in 4 per cent of patients and ART-associated TB in 7.5 per cent of patients. No cases of ART-associated TB fulfilling the criteria of unmasking TB-IRIS were identified in either of the studies. The higher incidence of TB-IRIS reported, particularly in the western literature, may be explained by leniency of clinical diagnostic criteria.

It is expected that IRIS will become more common in resource-constrained settings like India, where access to ART is increasing. The underlying prevalence of opportunistic infections like *M. tuberculosis* is high in this setting and the patients initiating ART are more likely to have advanced immunosuppression[12].

Risk factors

Several risk factors for the development of IRIS have been identified (Table III)[10-12,15-18]. Risk factors for IRIS have been investigated in many studies; however, the cohorts differ substantially with regards to the study populations and the type of IRIS examined, making conclusions regarding risk factors for IRIS difficult. Presence of opportunistic infection at the time of initiation of ART is a clear risk factor for the development of IRIS. Disseminated infection before initiation of ART has been shown to

Table III. Risk factors for developing IRIS

- Rapid decline in viral load (especially in first three months after ART)
- Low baseline CD4 count (especially <50 cells/µl or <10%) and rapid increase after initiation of ART
- Initiation of ART soon after initiation of treatment for opportunistic infection (OI)
- Disseminated versus localized OI
- ART-naïve patient

Source: Refs 10-12,15-18
IRIS, immune reconstitution inflammatory syndrome; ART, antiretroviral therapy; OI, opportunistic infection

be associated with increased risk of development of IRIS in patients with TB and cryptococcal disease[17,18]. A low baseline CD4+ T cell count, below 50 cells/µl, is a major risk factor for both the diseases[17,19]. However, IRIS is known to occur at higher CD4+ T-cell counts, suggesting that functional status of the cells also has a role in the pathogenesis of IRIS. The time interval between the treatment of opportunistic infection and the initiation of ART has been shown to be important for development of IRIS in a number of studies, particularly in context of TB-IRIS. A shorter interval is associated with a higher risk of IRIS in these patients[10,19].

There may also be a genetic predisposition and certain genes have been associated with an increased susceptibility to the development of IRIS in the presence of mycobacteria and herpes viruses[20]. Male gender and younger age have been inconsistently associated with IRIS[10,12]; whereas, ethnicity and type of ART regimen have not been shown to be risk factors for IRIS.

Pathogenesis

The immunopathogenesis of the syndrome is unclear and currently a subject of intense research. IRIS results from a dysregulated immune response to a variety of antigenic stimuli following initiation of ART. The antigenic stimulus in infectious conditions are either intact viable organisms or dead organisms and their residual antigens; whereas, autoimmunity to innate antigens are involved in the non-infectious causes of the syndrome. The pathophysiology of the syndrome is believed to involve a combination of factors, including the reconstitution of immune cell numbers and function, redistribution of lymphocytes, defects in regulatory function, changes in Th cell profile, the underlying antigenic burden, and host genetic susceptibility.

The immunopathology of IRIS is determined by the inciting pathogen. IRIS is most often associated with CD4+ Th1-mediated immune response; however, both CD4+ and CD8+ effector T-cells are involved in the pathogenesis. The syndrome appears to result due to an unbalanced immune reconstitution of effector and regulatory T cells in patients receiving ART[21]. Two types of T cells are postulated to play an important role, the pro-inflammatory Th17 cell and the regulatory T cell (Treg). T regulatory Foxp3+CD25+CD4+ cells actively maintain physiological equilibrium of the immune system and T-cell homeostasis, and prevent collateral damage from exuberant inflammatory responses[22].

During immune reconstitution Tregs may be defective in either numbers or function and show blunted ability to suppress the release of pro-inflammatory cytokines[21]. Macrophages and natural killer cells are also suspected to play a role in IRIS[23,24]. The activity of natural killer cells is determined by the expression of cell-surface molecules (killer immunoglobulin-like receptors; KIRs), which activate or inhibit their function. Their role has been suggested in herpes IRIS[23]. Inappropriate activation of macrophages has been suggested in the immunopathogenesis of TB-IRIS.

Research is hampered by the lack of a diagnostic marker. Inflammatory markers, chemokines and cytokines that signify innate and adaptive immune activation may act as useful biomarkers. Several serological indicators of IRIS have been described in the recent years (Table IV)[21,25-27]. The role of these biomarkers has been assessed mainly in TB-IRIS and cryptococcal meningitis (CM)-IRIS[25,26].

Paradoxical TB-IRIS has been associated with elevations in interleukin (IL)-4, IL-6, IL-7, interferon gamma (IFN- γ) and tumour necrosis factor alpha (TNF-α) during clinical events[21,27]. In a case-control study, Haddow et al[26] reported higher pre-ART levels of plasma IFN- γ and C-reactive protein (CRP) in patients with unmasking TB-IRIS and lower levels of biomarkers of monocyte and regulatory T-cell activity, and higher CRP in patients developing paradoxical TB-IRIS. Similar to TB-IRIS, cryptococcal IRIS involves a proinflammatory cytokine response including Th1 cytokines[28]. In a prospective study Boulware et al[25] reported increased pre-ART levels of CRP, IL-4, and IL-17 and lower levels of vascular endothelial growth factor (VEGF), granulocyte colony-stimulating factor (G-CSF), and TNF-α among those who developed CM-IRIS. The profile of biomarkers suggests a paucity of cytokines involved in antigen processing and macrophage function (TNF-α), increased generalized inflammation (raised CRP, IL-17), lack of antigen recognition by CD4+ T cells (decreased VEGF), and inappropriate Th2 response (raised IL-4). The study

Table IV. Biomarkers of IRIS
C-reactive protein (CRP)
Interferon (INF)-γ
Inter leukin (IL)-2,6,7,12,13,17,18
Tumour necrosis factor (TNF)-α
INF- γ inducible protein-10 (IP-10)
D-dimer
Source: Refs-21,25-27

also reported increased levels of CRP, D-dimer, IL-1RA, IL-6, IL-7, and IL-13 following initiation of ART among those who developed IRIS.

IRIS has been associated with certain human leucocyte antigen (HLA) profiles and regulatory cytokine gene polymorphisms. Cytomegalovirus (CMV)-IRIS frequently carry HLA-B44 and an ancestral haplotype HLA-A2, B44, DR4[29]. Patients with mycobacterial IRIS rarely carry TNF-α-308*2 and IL-6–174*G[20]. These alleles are linked to low cytokine production. The observations suggest the role of IL-12 in CMV-IRIS and that of IL-6 and TNF-α in mycobacterial IRIS.

Further research is needed to elucidate the immunopathogenesis of IRIS, to identify markers (HLA types or cytokine levels) which may be useful screening diagnostic tests to identify patients at risk, develop better therapeutics, and monitor response to therapy.

Infection and IRIS

A variety of mycobacterial, viral, fungal and parasitic opportunistic infections are associated with IRIS (Table V)[2,11,12,15-17,30-47]. The inflammatory response may be to viable pathogens or to the non-viable pathogens or its residual antigen. The syndrome manifests as either of two patterns, 'unmasking IRIS' or 'paradoxical IRIS'. 'Unmasking IRIS' is an immune response against a pathogen that was not causing overt clinical disease before initiation of ART. This type of presentation is usually caused by viable organisms. In 'paradoxical IRIS', opportunistic infections is present at initiation of ART which worsens on therapy. This may be a response to living pathogens or a response to the antigens of non-viable pathogens. Alternative explanations for deterioration, such as the failure to treat opportunistic infection or the failure of ART because of poor adherence or drug resistance must be excluded.

Specific IRIS manifestations

Tuberculosis

Mycobacterium tuberculosis (TB) is one of the commonest pathogen known to cause IRIS with reported incidence varying from 8 to 43 per cent[10,15,16,19,48]. Earlier studies from developed nations had reported a high incidence of TB- IRIS (17-43%) as compared to studies from developing nations (8-13%)[10,14-16,19,48]. However, the lack of uniform case-definitions for TB-IRIS makes direct comparison of these results difficult.

Several risk factors for the development of paradoxical TB-IRIS have been identified including shorter delay between commencing tuberculosis treatment and ART, low baseline CD4+ cell count, higher baseline viral load, rapid reduction in viral load on ART, and disseminated tuberculosis[7]. The majority of the cases develop IRIS within the initial 2 months of ART when the antigen burden is high and recirculation of previously sequestered CD45RO memory lymphocyte allows the pathogen-specific cells to gain access to the sites of infection and mount an inflammatory response.

TB-IRIS generally presents as paradoxical disease within the first two months and commonly in the first two to three weeks of ART initiation[15,48]. The patient usually presents with worsening or appearance of new clinical or radiological features. Common manifestations include return of symptoms like fever, lymph node enlargement or suppuration, and appearance of fresh infiltrates, mediastinal lymphadenopathy or enlarging effusion on chest radiograph. TB-IRIS may also manifest as visceral or cutaneous abscesses, CNS disease, pericardial effusion, acute respiratory distress syndrome (ARDS), airway obstruction and acute renal failure[49-52].

The association with a shorter delay between initiation of anti-TB treatment and ART is an area of debate. Whereas, some studies have failed to show any difference between timing of TB therapy to initiation of

Table V. Infections associated with IRIS

Mycobacteria:	Protozoa:
Mycobacterium tuberculosis	Toxoplasma
Mycobacterium avium complex	Microsporidia
Mycobacterium leprae	Leishmania
Bacille-Calmette-Guerin	Cryptosporidia
Fungal infections:	*Bacteria*:
Cryptococcus species	Bartonella
Pneumocystis jiroveci	
Histoplasma species	
Candida	
Viruses:	*Helminth*:
Herpes simplex virus	Schistosoma
Herpes zoster virus	Strongyloides
Cytomegalovirus	
JC virus	
HIV encephalitis	
Hepatitis B and C virus	
Parvovirus B19	
Molluscum contagiosum	

Source: Refs- 2,11,12,15-17,30-47

ART[18], other studies have shown significant differences in incidence of IRIS[10,15,49]. Multiple retrospective studies and prospective randomized SAPIT trial provide evidence that initiation of ART should not be delayed pending completion of TB treatment for HIV/TB-co-infected patients[53-56]. CAMELIA trial reported improved survival of these patients with early initiation (2 wk) compared to late initiation (8 wk) of ART[57]. The most recent WHO guidelines recommend the initiation of ART between 2 and 8 wk subsequent to the initiation of TB therapy for patients with a CD4 count <200/µl[58].

An increased risk of IRIS was observed in the integrated arm of the SAPIT trial as well as in the early arm of the CAMELIA trial, consistent with the findings of previous studies. However, lack of mortality attributable to IRIS in the SAPIT trial and a decision analysis study showing benefit of early initiation in the setting of low mortality rates from TB-IRIS, favour early initiation of ART[59].

Non-tuberculous mycobacteria

The reported incidence of non-tuberculous mycobacterial IRIS is 3.5 per cent among patients with a baseline CD4+ count of <100 cells/µl[30]. MAC-associated IRIS typically develops in severely immunosuppressed individuals, who have an excellent response to ART. The syndrome manifests usually after 2-8 wk of ART in patients with low CD4 counts[7]. Most common manifestation of MAC-IRIS is fever with suppurative painful lymphadenitis (69%), followed by pulmonary disease (19%)[7]. It may also involve the joints, spine, skin and soft tissue[30]. In contrast to disseminated MAC disease of advanced AIDS, MAC-IRIS usually presents as localized disease[7,30].

TB diagnosis in patients with HIV is challenging, particularly in resource-limited settings. These patients frequently have atypical clinical presentations, extrapulmonary disease, and normal chest radiographs, particularly in presence of advanced immunosuppression[60]. The current guidelines suggest that the use of mycobacterial blood culture in suspected disseminated TB may be beneficial[61]. The yield of blood cultures have been reported between 4-56 per cent in various studies[62-65]. Mycobacterial blood cultures have been shown to have additive yield for diagnosis of drug resistant TB in these patients[66]. The adjunctive use of mycobacterial blood cultures may be considered in patients with advanced immunosuppression suspected of disseminated TB and in cases of suspected drug-resistant TB[61,66].

Cryptococcosis

Manifestations of cryptococcal IRIS include meningitis, lymphadenitis, pneumonitis, and localized abscess. Overall incidence of neurological IRIS is 1.5 per cent in individuals with CD4+ count of <200 cells/µl[67]. Paradoxical CM-IRIS incidence has been reported as 10-42 per cent, in ART naïve patients with CM[9,17,68,69]. Approximately 60 per cent of cases occur within the first month, although the symptoms may present as late as 10 to 12 months after treatment[17,68]. Specific risk factors for the development of cryptococcal IRIS include shorter duration between cryptococcal diagnosis and ART initiation, low CD4 counts (<100 cells/µl), higher baseline plasma HIV RNA levels; and higher CSF cryptococcal antigen titres, opening pressures, WBC counts, and glucose levels[9]. Unlike many other forms of IRIS, which produce less dramatic consequences, CM-IRIS is exceptional for its substantial morbidity and mortality[69]. A randomized controlled trial evaluated antifungal combination therapies in the treatment of *Cryptococcus neoformans* meningitis in HIV patients[70]. Although significant reductions in colony forming units were observed with all combinations, substantial numbers of patients remained culture positive two weeks after therapy. It has been suggested to delay ART until CSF sterility is achieved with antifungal combinations such as amphotericin B and flucytosine. However, the exact timing of ART initiation and whether attaining CSF culture sterility is important in avoiding IRIS is unknown. Although the role of steroids remains unclear, it is reasonable to administer corticosteroids in cases with unresponsive inflammatory effects. Serial lumbar punctures have also been advocated for the management of raised intracranial pressures[71].

Pneumocystis jiroveci pneumonia

Pneumonia caused by *Pneumocystis jiroveci* is one of the common opportunistic infections in patients with advanced HIV disease. Worsening of treated infection may occur within the first 2 to 3 wk after initiation of ART[31]. Patients with *P. carinii* pneumonia (PCP)-IRIS present with recurrence of fever, worsening hypoxia, and fresh pulmonary infiltrates on chest radiograph. Risk factors for developing PCP-IRIS include severe disease (PaO$_2$ <70 mmHg), early initiation of ART, and recent completion of steroid therapy for PCP[32].

Viral infections

Genital ulceration related to herpes simplex virus and genital warts related to human papillomavirus are among the most common presentations of IRIS[12].

Herpes zoster IRIS usually manifests as uncomplicated disease limited to a single dermatome[33]. Eye disease is the most common presentation of cytomegalovirus (CMV) IRIS. Three distinct ocular lesions associated with CMV-IRIS have been described: retinitis, vitreitis, and uveitis. IRIS provoked by hepatitis B and C viruses is characterized by hepatitis flare[34]; or rarely, life-threatening progression of cirrhosis[72]. Progressive multifocal leukoencephalopathy (PML)-IRIS due to John Cunningham (JC) virus presents either as paradoxical or unmasking disease associated with marked inflammatory changes on histology and neuroimaging[35,36].

IRIS and malignancy

Given the known associations of Kaposi sarcoma and non Hodgkin lymphoma (NHL) with underlying viral infections (human herpesvirus-8 for Kaposi sarcoma and Epstein-Barr virus for NHL), it is not surprising to observe these cancers occurring or worsening in the context of IRIS. Kaposi sarcoma in patients with HIV/AIDS is very rare in India (unpublished observation). ART has reduced the incidence of Kaposi's sarcoma[73]; however, both clinical 'flares' (sudden progression) and new Kaposi sarcoma have been reported after ART initiation[74,75]. In a cohort of 150 patients, 10 (6.6%) starting ART with Kaposi sarcoma developed new Kaposi sarcoma lesions and/or progression of established lesions[76]. In another cohort of 138 patients initiating ART, four patients developed new onset Kaposi sarcoma and four had Kaposi sarcoma flares[77]. This manifests with inflammation or enlargement of existing lesions, appearance of new lesions or the development of lymphoedema. The NHL has also been reported as a rare manifestation of immune reconstitution. In a recent study, it was shown that IRIS may transiently increase the risk of Kaposi sarcoma or NHL in HIV-infected patients and the timely initiation of ART remains the best strategy to avoid the development of these malignancies[78]. The various non-infectious conditions associated with IRIS are shown in Table VI[74,79-91].

Immune-mediated inflammatory disease and IRIS

Patients may present with manifestations of autoimmune disease following initiation of ART. The reported associations (Table VI) are limited to case reports. Graves disease and sarcoidosis are recognized as potential complications of immune reconstitution[86-88,92].

Table VI. Non-infectious conditions associated with IRIS

Autoimmune:
Systemic lupus erythematosus (SLE), lupus-like disease
Thyroid disease
Rheumatoid arthritis
Guillain-Barre syndrome
Reiter's syndrome
Polymyositis

Inflammatory:
Sarcoidosis
Lymphoid interstitial pneumonitis
Folliculitis

Malignancy:
Kaposi's sarcoma
Lymphoma

Source: Refs-74,79-91

Immune reconstitution sarcoidosis has been reported in several patients on ART, and needs to be distinguished from IRIS associated with mycobacterial pathogens. The clinical manifestations and histological features are similar to patients without HIV[93].

Prognosis

Majority of patients with IRIS have a self-limiting disease course. Mortality associated with IRIS is relatively uncommon; however, associated high morbidity places considerable burden on the health-care system[10,94]. Morbidity and mortality rates vary according to the pathogen and organs involved. IRIS in the setting of opportunistic infections involving the CNS has high mortality rates. The heightened immune response in a relatively closed space leads to raised intracranial pressures, with potentially irreversible damage leading to increased morbidity and mortality. High mortality rates are reported for cryptococcal meningitis[69]. Overall mortality rate of TB-IRIS is low; however, significant morbidity and mortality may be seen with ARDS and CNS involvement in TB-IRIS[95,96].

Prevention

In the light of the available data, it appears prudent that ART should be initiated before the onset of severe immunodeficiency and after the treatment of opportunistic infections. A detailed evaluation should be done for identification of opportunistic infections before ART initiation to prevent the unmasking form of IRIS. Patients with high risk features for the development of IRIS should be identified. In the presence of opportunistic infections, the benefit of reducing the likelihood of IRIS by deferring ART must

be balanced with the risk of delaying ART, particularly in patients with advanced disease. In the case of HIV-TB co-infection, WHO recommends that ART be initiated as soon as TB therapy is tolerated by the patient. Ideally, this may be as early as 2 wk and not later than 8 wk[58]. The optimal time for ART initiation following treatment of other opportunistic infections is unclear.

Management

Historically, the evidence base for the management of patient's with IRIS had relied on clinical observations and expert opinions only. In a randomized controlled trial, Meintjes et al[97] reported the utility of prednisolone in the treatment of paradoxical TB-IRIS.

Opportunistic infections should be optimally treated. In general, non-steroidal anti-inflammatory drugs (NSAIDS) should be reserved for milder manifestations of IRIS and steroids for cases with severe inflammation. Meintjes et al[97] demonstrated the reduced need for hospitalization and therapeutic procedures and hastened improvements in symptoms, performance, and quality of life in patients with TB-IRIS receiving prednisolone at a dose of 1.5 mg/kg per day for 2 wk followed by 0.75 mg/kg per day for 2 wk. The study included patients with worsening chest radiograph, enlarging lymph nodes, serous effusion, and cold abscess; thereby, corticosteroids are indicated in TB-IRIS for these indications. Patients with respiratory failure, altered level of consciousness, new focal neurological findings or compression of a vital structure were excluded from the study. However, it appears prudent to use corticosteroids in TB-IRIS with CNS manifestations, tracheal compression due to lymphadenopathy, and ARDS, though only anecdotal reports of benefit have been published[50,51,95].

Cryptococcal meningoencephalitis, the most severe form of cryptococcosis, is associated with high mortality rates. CM-IRIS requires prompt control of raised intracranial pressure or hydrocephalus. Corticosteroids are indicated for cerebral oedema and raised intracranial pressure[98]. Respiratory failure due to ARDS in pulmonary cryptococcosis should also be treated with corticosteroids[98].

The development of PCP-IRIS after discontinuation of steroid therapy suggests a role for the reintroduction of steroids in these patients[32]. Acyclovir is beneficial in IRIS-associated zoster. In cases of ocular CMV-IRIS, systemic or periocular steroid injections have been used, but a clear benefit

has not been demonstrated. The role of corticosteroids in PML-IRIS is not clear[99].

Adjunctive corticosteroid therapy is harmful for patients with suboptimally treated opportunistic infections and may lead to dissemination of the disease increasing the morbidity and mortality. Further, increased risk of progression of herpes zoster, Kaposi's sarcoma, and reactivation of latent infections are also reported with corticosteroids therapy in these patients[100,101].

IRIS is seldom, if ever, an indication for cessation of ART. It is generally accepted that ART should be continued, unless IRIS causes severe illness, pathogens involved are not controllable by specific antimicrobial treatments (JC virus), or if ART toxicity is the main differential. Interruption of ART may place a patient at risk for additional opportunistic infections, and the IRIS may recur when ART is reintroduced. Surgical drainage of necrotic mycobacterial lymphadenitis or abscesses has been reported to be beneficial.

Conclusion

Paradigms shifts in HIV management, with current guidelines recommending an earlier commencement of ART, it is expected that fewer cases of IRIS will be seen in developed countries. However, the same is not true in resource constrained settings, where the patients present with advanced immunosuppression. The problem is further compounded by rampant tuberculosis in India. Overall, IRIS related mortality is low; however, the associated morbidity will continue to pose a major challenge and strain on resource-poor health systems with poor diagnostic and therapeutic facilities.

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Reprint requests: Dr S.K. Sharma, Head, Department of Internal Medicine, All India Institute of Medical Sciences,
New Delhi 110 029, India
e-mail: sksharma.aiims@gmail.com; sksharma.aiims@yahoo.com