IRIS in HIV ---A Review

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Introduction

Immune reconstitution inflammatory syndrome (IRIS) is an inflammatory reaction in HIV infected patients after initiation of anti retroviral therapy (ART) resulting from restored immunity to specific infectious or non-infectious antigens.(1)

Most frequently reported infections are-Mycobacterium tuberculosis(TB),cryotococcal meningitis, varicella zoster, herpes viruses, CMV, Pnumocytis(carinii)pneumonia(PCP),Hepatitis B and C(2).Mycobacterium avium complex(MAC)and latent cryptococcal infections are noticed.

Non infectious diseases include Rheumatiod arthritis and other autoimmune diseases. Some patients reacts due to genetic susceptibility PATHOGENESIS OF IRIS.

TABLE 1

Common Pathologic IRIS Scenarios(2)

"Unmasking" IRIS

Occult, subclinical opportunistic infection

Unmasked by ART

Infectious pathogens present

"Paradoxical" IRIS

Clinical recrudescence of a successfully treated infection

Symptomatic relapse despite microbiologic treatment success.

Antigen driven immune activation

Sterile cultures, typically

Current theories concerning the pathogenesis of the syndrome involve a combination of underlying antigenic burden, the degree of immune restoration following HAART, and host genetic susceptibility. The presence of an antigenic stimulus for development of the syndrome appears necessary. This antigenic stimulus can be intact, "clinically silent" organisms or dead or dying organisms and their residual antigens. IRIS that occurs as a result of "unmasking" of clinically silent infection is characterized by atypical exuberant inflammation and/or an accelerated clinical presentation suggesting a restoration of antigen-specific immunity. These characteristics differentiate IRIS from incident opportunistic infections that occur on ART as a result of delayed adequate immunity. The mechanism receiving the most attention involves the theory that the syndrome is precipitated by the degree of immune restoration following ART. An alternative immunological mechanism may involve qualitative changes in lymphocyte function or lymphocyte phenotypic expression. For instance, following ART an increase in memory CD4 cell types is observed [4] possibly as a result of redistribution from peripheral lymphoid tissue [5] . This CD4 phenotype is primed to recognize previous antigenic stimuli, and thus may be responsible for manifestations of IRIS seen soon after ART initiation. After this redistribution, naïve T cells increase and are thought to be responsible for the later quantitative increase in CD4 cell counts [6] . These data suggest IRIS may be due to a combination of both quantitative restoration of immunity as well as qualitative function and phenotypic expression observed soon after the initiation of ART. The third purported pathogenic mechanism for IRIS involves host genetic susceptibility to an exuberant immune response to the infectious or noninfectious antigenic stimulus upon immune restoration. Although evidence is limited, carriage of specific HLA alleles suggest associations with the development of IRIS and specific pathogens [7] . Increased levels of interleukin-6 (IL-6) in IRIS patients may explain the exuberant Th1 response to mycobacterial antigens in subjects with clinical IRIS [**9**,8] . Such genetic predispositions may partially explain why manifestations of IRIS differ in patients with similar antigenic burden and immunological responses to ART. Some patients reacts

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due to genetic susceptibility

CLINICAL FEATURES-

The onset of IRIS symptoms can occur as early as 1 week after the initiation of antiretroviral treatment. Yet, symptoms may also manifest as late as 1 year or more after initiation of treatment. More than 75% of patients symptomatic for IRIS, however, will have manifestations within 90 days of starting antiretroviral therapy.[10,11,12]

Table 2: Major and Minor Presentation of Immune Reconstitution Inflammatory Syndrome (IRIS)

Major Presentations

Tuberculosis

- Patients responding to TB treatment may have worsening of pulmonary symptoms or X-ray findings that indicate worsening of TB disease, enlarging lymph nodes, or meningeal symptom
- TB-IRIS can also result in hepatotoxicity, which may be difficult to distinguish from medication-induced toxicity
- Multidrug-resistant TB may increase the risk for IRIS

***Mycobacterium avium* complex**

- May present as localized lymphadenitis, pulmonary disease, or systemic inflammation that are indistinguishable from active MAC
- Patients with MAC-IRIS are not bacteremic

Cryptococcus

- Usually presents as worsening of meningitis symptoms

Cytomegalovirus

- Presents as retinitis, vitritis, or uveitis:
  - **Retinitis** is inflammation that is usually at the site of previous CMV retinitis lesions
  - **Uveitis** and **vitritis** are the presence of inflammatory cells in the eye as a result of IRIS and may help to distinguish IRIS from active CMV retinitis
- IRIS due to CMV in the eye can cause rapid and permanent vision loss
- The time to IRIS is variable; in one study, the median time to immune reconstitution vitritis was 20 weeks after initiation of ARV therapy

Hepatitis B or C

- Transient elevations in transaminases may occur after initiation of ARV therapy with immune reconstitution and can be difficult to distinguish from drug-induced hepatitis
- Hepatic flares are usually mild and self-limited but can result in decompensation in someone with preexisting cirrhosis

Progressive multifocal leukoencephalopathy

- PML lesions may be unmasked or worsen and could appear as new or worsening focal neurologic deficits or lesions on MRI scans

Kaposi's sarcoma

- Presents as worsening of Kaposi's sarcoma
- Fatal IRIS has occurred in patients with preexisting Kaposi's sarcoma and multicentric Castleman disease after initiating ARV therapy
- The frequency of human herpesvirus-8-associated IRIS is not known

Autoimmune diseases

- Preexisting autoimmune disorders such as sarcoidosis or Grave's disease may be exacerbated

Minor Presentations

Herpes simplex virus and varicella zoster virus

- HSV and VZV can reactivate after initiation of ARV therapy
- Presentations are usually similar to non-IRIS disease; however, IRIS may worsen a patient's symptoms
- Some patients become aware of their HSV infection only after the presentation of IRIS

Nonspecific dermatologic complications

- A number of dermatologic manifestations, such as folliculitis and oral and genital warts, may appear or worsen during immune reconstitution

Epidemiology

Studies to date are often retrospective and focus on specific manifestations of IRIS, such as tuberculosis-associated IRIS (TB-IRIS). In a large retrospective analysis examining all forms of IRIS, 33/132 (25%) of patients exhibited one or more disease episodes after initiation of ART [13] . Other cohort analyses examining all manifestations of IRIS estimate that 17–23% of patients initiating ART will develop the syndrome [14-15] . Another large retrospective study reported 32% of patients with *M. tuberculosis, M. avium* complex, or *Cryptococcus neoformans* coinfection developed IRIS after initiating ART. *Mycobacterium tuberculosis* (TB) is among the most frequently reported pathogen associated with IRIS. TB-IRIS is reported to be around 36% in the developed countries where patients were on dual therapy (antiretroviral therapy or ART) in 1990s when HAART was not available. [2] The symptoms in the groups which received ART and TB therapy were severe than in the control group which received only TB therapy. [3] IRIS-TB is also prevalent in the developing countries. It is reported to be between 11 to 43%. [16] In resource limited developing countries like India it was reported to be 8% in 2007. [17] The low prevalence was probably due to non-availability of HAART to HIV patients with TB. The incidence of IRIS is expected to rise in this patient group because of the wide availability of HAART in India now.

Table 2Clinical factors associated with the development of IRI

†Risk factor
Male sex
Younger age
Lower CD4 cell count at ART initiation
Higher HIV RNA at ART initiation
Lower CD4 cell percentage at ART initiation
Lower CD4:CD8 ratio at ART initiation
More rapid initial fall in HIV RNA on ART
Antiretroviral naïve at time of OI diagnosis
Shorter interval between OI therapy initiation and ART initiation

Derived from cohorts where IRIS due to multiple pathogens were reported (i.e. cohorts which examined only TB-IRIS were excluded) (3)

Management options for patients with IRIS are not well established. Even though IRIS is self-limiting, treatment is utilized in the hope of assuaging the morbidity. Treatment strategies include corticosteroids, discontinuation of antiretrovirals, and other modalities. The approach should be tailored to the patient and the opportunistic infection or situation encountered.

In life threatening presentations like acute renal failure or acute respiratory distress syndrome (ARDS), systemic corticosteroid in the doses of 1-1.5mg/kg/day along with non-steroidal anti-inflammatory drugs (NSAIDs) should be started without delay. The duration of IRIS treatment is usually for four weeks. The dose of the steroid should be reduced after two weeks. The guidelines to start the treatment with HAART depend on the absolute CD4 counts. If CD4 count is less than 100 cells/µl, both anti tuberculosis drugs and HAART can be started together, If CD4 cells are in the range of 100-200, HAART is started two months after starting TB treatment. If the CD4 cells are above 200, HAART is started six months after completing TB treatment. These guidelines are issued by BHIVA. [16]

Rifampicin in the treatment of TB-IRIS induces the metabolism of steroids and effectively reduces the efficacy steroids by 33-50% only after one to two weeks Multi-drug resistant TB (MDR-TB) and Extensive drug resistant TB (XDR-TB) are to be treated by specialist docters .

In case of cryptococcal meningitis induced-IRIS, antifungal treatment is given in three phases; the induction phase for 14 days with amphotericin B, the consolidation phase with fluconazole for eight weeks and finally suppressive phase with maintenance dose of fluconazole. [17] During induction phase, amphotericin B is given IV in the doses of 0.7mg/kg/day

and 5 fluorouracil given orally 100mg/kg/day. After 14 days in the consolidation phase, fluconazole is given orally 400 mg /day for eight weeks. It is expected that in eight weeks of fluconazole therapy, the CSF would be sterile, if not the treatment is continued until the CSF is sterile after which maintenance therapy starts with 200mg of fluconazole/day for life. It is possible that during lumbar puncture (LP) the intracranial pressure may be elevated. If the opening pressure is less than 250 mm H_2O, there is no need to take any action to reduce the pressure further. If it is more than 250 mm it should be reduced to 200mm or if it is too high it should be reduced to half of the opening pressure, by CSF drainage. This low pressure should be maintained even with daily LP.

Treatment of IRIS associated CMV retinitis and Immune recovery vitritis (IRV) or immune recovery uveitis (IRU) may involve anti-CMV therapy with gancyclovir or valgancyclovir . The use of systemic corticosteroids has been successful, and IRV may require periocular corticosteroid injections

Oral acyclovir is effective for dermatomal zoster in HIV-infected patients, facilitating healing and shortening the time of zoster-associated pain (3). The combination of corticosteroids and acyclovir decreased healing times, improved acute pain, and quality of life, but did not affect the incidence or duration of postherpetic neuralgia (3)

CONCLUSION

- Improving immune function can be associated with an inflammatory process that poses a significant threat to patients even though their immune status is improving.
- The onset of immune reconstitution inflammatory syndrome (IRIS) symptoms can occur as early as 1 week after the initiation of antiretroviral treatment. Yet, symptoms may also manifest as late as 1 year or more after treatment initiation.
- IRIS is estimated to affect approximately one-quarter of patients who start antiretroviral therapy.
- A paradoxical worsening of symptoms has been noted with other disease processes that are similar to HIV infection. Thus, although most of the information we have focuses on HIV, the implications for IRIS may be broader.

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