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Research Article

CLINICAL OUTCOMES OF USE OF HYDROXYCHLOROQUINE IN PARADOXICAL TUBERCULOSIS-IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME IN HIV-INFECTED PATIENTS

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ABSTRACT

Objective: Immune reconstitution inflammatory syndrome (IRIS) is an inflammatory reaction in HIV-infected patients after initiation of antiretroviral therapy (ART) resulting from restored immunity to specific infectious or non-infectious antigens. The most common condition where IRIS has been reported is tuberculosis (TB). Various mechanisms have been proposed and studied to account for the immune regulatory role of hydroxychloroquine (HCQ). This study is done to identify clinical outcome in HIV-TB patients with IRIS after given with HCQ.

Methods: An uncontrolled longitudinal study was conducted among HIV-infected patients with TB initiated on ART and developed IRIS between July 2013 and June 2015 in a South Indian HIV care hospital.

Results: A total of 40 patients have developed IRIS with mean age of 35.87 years and 77.5 % of them were males. At the time of IRIS occurrence, the mean body mass index was found to be 19.17 kg/m^2 and CD4 count was 200 cells/mm^3. The time duration took to get improvement in majority of the patients was 4–12 weeks.

Conclusion: There was definite improvement seen in patients who received HCQ in TB-IRIS condition.

Keywords: Hydroxychloroquine, Immune reconstitution inflammatory syndrome, HIV, Tuberculosis.

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INTRODUCTION

The benefits of antiretroviral therapy (ART) in improving survival, reducing morbidity, and enhancing the quality of life in HIV-infected patients have been widely demonstrated. However, during the early period of immune restoration with ART, immune reconstitution inflammatory syndrome (IRIS) develops in a subset of patients (15–25%). IRIS manifests as clinical deterioration resulting from ART augmented immune responses that cause inflammation in tissues directed at infective, or less frequently, non-infective antigens. The clinical presentation of IRIS varies, with comorbidities associated with it. The etiology of IRIS is unknown but thought to be a reactivation of suppressed immune system after profound suppression by the HIV [1].

IRIS, a life-threatening condition, presents challenges to the clinicians in terms of diagnosis and management as there is lack of proper diagnostic tests and evidence-based guidelines for the management [2,3]. Infective IRIS results from an inappropriate or dysregulated immune response directed to pathogen-specific antigens. 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. Most cases occur within the first 3 months of starting ART, coinciding with a rapid rise in peripheral blood CD4+ cells. Mycobacterial and fungal forms of IRIS usually present with features of T-helper 1 immune response, manifesting with granulomatous inflammation, or suppuration. In contrast, CD8+ T-cells are the dominant inflammatory cells found in IRIS related to viruses [4,5].

To date, no prospective therapeutic trials concerning the management of IRIS have been conducted. All evidence regarding the management of IRIS in the literature relates to case reports and small case series reporting on management practice. Majority of patients with IRIS have a self-limiting disease course. Mortality associated with IRIS is relatively uncommon; however, associated with high morbidity places considerable burden on the health-care system. Morbidity and mortality rates vary according to the pathogen and organs involved [6,7].

The antimalarial drug hydroxychloroquine (HCQ) is endowed with immune modulatory effects including the reduction of inflammatory cytokine production and of immunoglobulin (IgG) levels, and a down-modulation of natural killer cell activity; these properties have warranted its use in some of the autoimmune conditions [8]. HCQ is used in the treatment of various inflammatory disease conditions, and short-term HCQ is generally well tolerated at a dosage of 400 mg/day. Based on these findings, data exploration was performed from PubMed and Scopus databases using the search terms HCQ, HIV management, and paradoxical tuberculosis (TB)-IRIS. The search conducted did not cite any relevant published literature, where HCQ is tried to treat the HIV patients with TB-IRIS. Hence, this study was conducted to understand the efficacy of short-term HCQ use in the treatment of paradoxical TB-IRIS condition.

METHODS

A prospective uncontrolled longitudinal study was conducted at an HIV care hospital, Mysore, India, between July 2013 and June 2015. The study was approved by the Institutional Ethical Committee of study site hospital. HIV-infected patients who developed paradoxical TB-IRIS during the study were included in the study. The TB-IRIS was defined as per the International Network for the Study of HIV-associated IRIS (INSHI) criteria - (INSHI; World Health Organization; ART) (Table 1). The data regarding the concurrent use of other drugs, laboratory values, opportunistic infections, and other prescribed drugs to any other disease condition were collected from the medical records and treating physician notes. Patients were given with HCQ

Table 1: INSHI criteria

A. Antecedent requirements (both criteria must be met)s	B. Clinical criteria (one major criterion or two minor clinical criteria are required)		C. Alternative explanations must be excluded if possible
	Major criteria	Minor criteria	
Diagnosis of tuberculosis: The diagnosis of tuberculosis made before starting ART (WHO criteria)	New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement	New or worsening constitutional symptoms	Tuberculosis drug resistance, poor adherence to treatment, drug toxicity, and another opportunistic infection
Initial response to tuberculosis treatment: Initial improvement or stabilization on appropriate anti-TB treatment before ART initiation (however, in patients starting ART within 2 weeks of starting tuberculosis treatment, insufficient time may have elapsed for a clinical response to be reported)	New or worsening central nervous system tuberculosis	New or worsening respiratory symptoms	
	New or worsening radiological features of tuberculosis	New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy	
	New or worsening serositis		

ART: Antiretroviral therapy, WHO: World Health Organization

Table 2: Patient characteristics

S. No.	Category	Characteristic properties	Total (%)	Recovered
1	Age	<40 years	27 (67.5)	23
		41–60 years	11 (27.5)	9
		>61 years	2 (5)	1
2	Gender	Male	31 (77.5)	27
		Female	9 (22.5)	6
3	BMI (Kg/m^2)	<20	18 (45)	16
		21–25	20 (50)	16
		>25	2 (5)	1
4	CD4 CD4 count (cells/ml)	<200	4 (10)	2
		>200	36 (90)	31
5.	Type of TB	TB-lymphadenitis	30 (75)	25
		Pulmonary-TB	6 (15)	4
		Abdominal-TB	4 (10)	4

BMI: Body mass index, TB: Tuberculosis

200 mg/day for a maximum period of 6 months and were followed up at every 15 days for the measurement of treatment outcomes and IRIS progression condition. The data collected were entered into a specially designed excel sheet for easy retrieval of data and analysis. Categorical variables were described using relative frequencies; whereas the standard deviation and mean were used for continuous variables. All analyses were carried out using SPSS software version 21.0.

RESULTS

A total of 40 patients were included in the study. All patients were given with HCQ and followed for the clinical outcomes. The mean age of the patients was found to be 35.87 (±8.54), mean CD4 count was 200 (±263), and mean body mass index was 19.17. The patient's characteristic is further detailed in Table 2. The ART regimens involved in the study population and the duration of time for the occurrence of IRIS is detailed in Table 3. INSHI criteria of patients show that patients with one major criteria are 30 (75%), one major and one minor are 6 (15%), one major and two minor are 2 (5%), and two minor are 2 (5%). Of the 40 patients, IRIS symptoms improved in 33 patients, and mainly observed as decreased lymphadenopathy (enlarged lymph nodes) among the patients with major criteria and decreased worsening of constitutional symptoms (headache and fever) among the patients with minor criteria with an overall recovery rate of 82.5%.

DISCUSSION

Data from *in vitro* study, as well as results obtained in the murine model, have shown that HCQ also modulates the intracellular toll-like receptor (TLR) pathway as it also reduces the production of interferon gamma, tumor necrosis factor-α, and interleukin 6. Notably, HCQ decreases Tat-mediated transactivation of HIV-1 TLR *in vitro* as well-thereby decreasing HIV-1 production and alters the immunogenic properties of gp120 [9]. Based on these findings, the use of HCQ has been evaluated in HIV infection. Results showed that decreases in viral load, IL-6, and serum IgG titers, as well as a reduction of immune activation and a decrease of CD38+CD8+ T-cell and Ki-67 memory CD4+ T-cells can be observed in HIV-infected patients receiving HCQ.

The effect of this compound on these immune parameters is important given the fact that immune activation is believed to play a key role in HIV pathogenesis. This suggestion stems from a number of observations [10]. Thus, the massive destruction of CD4+ T-cells in the gastrointestinal mucosa observed in the initial phases of the infection would provoke severe mucosal alterations. These observations led to therapeutic approaches based either on therapy intensification or immunomodulation that, nevertheless, did not result in any significant effect. Based on these observations and on the ability of HCQ to downregulate TLR-mediated activation, this compound has an effect on immune modulation in HIV-infected IRIS individuals [11].

Systemic corticosteroids or non-steroidal anti-inflammatory agents are used to alleviate the symptoms of IRIS [12,13]. There are no standard guidelines recommending the defined dosage regimen of these agents in the treatment of IRIS. Often, the dosage regimen and choice of anti-inflammatory agents used depends entirely on personal experience of treating physicians. Hence, the therapeutic outcomes are variable. These practices reflect the lack of evidence from controlled trials for the use of anti-inflammatory agents in IRIS [11]. HCQ has established immunomodulatory effects, and due to its relatively low and well-established side effects, the drug may be potentially useful in IRIS patients. However, to rationalize the therapeutic usefulness,

Table 3: ART regimen responsible for IRIS

Category	Regimen	Number of patients (%)
ART regimen	Tenofovir+Lamivudine+Efavirenz	30 (75)
	Zidovudine+Lamivudine+Efavirenz	5 (12.5)
	Stavudine+Lamivudine+Efavirenz	2 (5)
	Zidovudine+Lamivudine+Nevirapine	2 (5)
	Stavudine+Lamivudine+Atazanavir/Ritonavir	1 (2.5)
Time duration for improvement (weeks)	1–4	17
	4–12	11
	12–24	5
Time duration between ART initiation and IRIS occurrence (weeks)	1–4	22 (55)
	4–12	13 (32.5)
	12–24	5 (12.5)

ART: Antiretroviral therapy, IRIS: Immune reconstitution inflammatory syndrome

further studies are necessary, as there are currently insufficient data to recommend HCQ in the management of IRIS.

CONCLUSION

Our observation suggests that prompt recognition of early symptoms of paradoxical TB-IRIS and short-term HCQ may be useful in the management of paradoxical TB-IRIS.

AUTHORS CONTRIBUTION

A. Pramod Kumar – Preparation of Manuscript
G. Parthasarathi - Editing of Manuscript
S. N. Mothi, A.P. Sudheer, V.H.T. Swamy, Sri Rama – Collection of Data

CONFLICTS OF INTEREST

None to declare

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