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ORIGINAL RESEARCH

Outcome of Lenalidomide Treatment for Cognitive Impairment Caused by Immune Reconstitution Inflammatory Syndrome in Patients with HIV-Related Cryptococcal Meningitis

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Purpose: Cognitive impairment associated with human immunodeficiency virus (HIV)-related cryptococcal meningitis (HCM) in the context of immune reconstitution inflammatory syndrome is difficult to address. This study was a follow-up of lenalidomide treatment outcomes in patients with HCM and cognitive impairment after complete cryptococcal clearance.

Patients and Methods: Seven HCM patients with neuroinflammation and cognitive impairment after complete cryptococcal clearance were enrolled in this prospective study. Neurocognitive assessment, clinical examination and cerebrospinal fluid (CSF) assays were performed before and after lenalidomide treatment.

Results: After lenalidomide treatment, the Montreal Cognitive Assessment [week (W) 0 (median [interquartile range]: 23.0 (13.0–24.0) vs W24: 26.0 (24.0–28.00), P=0.018] and International HIV Dementia Scale scores [W0: 9.0 (2.5–10.5) vs W24: 11.0 (10.00–12.0), P=0.028] improved significantly, mainly in the domain of memory function. There was no significant difference in the Center for Epidemiological Research Depression scores for anxiety and depression before and after treatment. Further stratified analyses revealed that the patients with cognitive improvement group had higher levels of CSF white blood cells [94.0 (44.0–180.0) vs 0 (0–1.5), P=0.032], CSF protein [4.9 (3.0–6.6) vs 0.6 (0.5–0.7), P=0.034], CSF albumin [318.5 (190.9–346.5) vs 33.5 (30.4–46.2), P=0.034], and CSF IgG [160.5 (73.8–256. 0) vs 4.7 (4.3–7.4), P=0.034] but a lower CSF glucose level [2.4 (2.0–2.7) vs 2.8 (2.8–3.9), P=0.032] than the patients with cognitive non-improvement group before treatment. CSF inflammatory cytokines of the growth-related oncogene, interleukin [IL]-10, granulocyte-colony stimulating factor, IL-6, IL-8, complement factor H, tumor necrosis factor-α, and α-2 macroglobulin were obviously decreased in patients with cognitive improvement group after lenalidomide treatment.

Conclusion: Lenalidomide potentially reduces cognitive impairment caused by immune reconstitution inflammatory syndrome in patients with HCM after cryptococcal clearance by inhibiting intracranial inflammation.

Keywords: lenalidomide, HIV, meningitis, cognitive impairment, Cryptococcus

Introduction

Cryptococcal meningitis (CM) is a common opportunistic infection in patients with acquired immunodeficiency syndrome (AIDS) and is responsible for 15% of all human immunodeficiency virus (HIV)-related mortality.[1] Some patients might experience deterioration in neurological status with an increasing $CD4^+$ T-cell count and a decreasing HIV-RNA load in the peripheral blood after antiretroviral therapy (ART) and antifungal regimens. However, few studies on the cause and treatment of this cognitive impairment have been performed.[2]

Currently, it is postulated that cognitive impairment might be associated with paradoxical immune reconstitution inflammatory syndrome (IRIS).[3] IRIS is a common complication of cryptococcal infection, including unmasking CM-IRIS and paradoxical IRIS. Unmasking IRIS develops in previously undiagnosed CM in ART-naïve individuals, while

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paradoxical IRIS occurs in patients previously treated for CM with cryptococcal sterilization in cerebrospinal fluid (CSF) following the initiation of highly active ART (HAART). Worsening cognitive impairment and clinical manifestation frequently present in HCM patients with paradoxical IRIS.[3] It has been reported that approximately 25% of HCM patients develop CM-IRIS in the first 4 months of ART, with an average mortality of 20 ± 10%.[4] Thus, an effective treatment for IRIS would be helpful to decrease the likelihood of cognitive impairment.

Recent studies have found an imbalance between the proinflammatory Th1/Th17 and anti-inflammatory Th2/Treg axes in paradoxical IRIS, followed by a hyperactive compensatory Th1 response, which leads to an inflammatory burst and aggravation of inflammation in the CSF compartment, manifesting as a deterioration in neurological status, such as cognitive impairment.[5,6]

Short courses of corticosteroids are the mainstay of treatment of IRIS; however, the limitations of corticosteroid treatment should not be ignored. The long-term use of corticosteroid will lead to osteoporosis, neuropsychiatric manifestations, aseptic joint necrosis, adrenal insufficiency, gastrointestinal and increased risk of other infections.[7] In the previous study, although corticosteroid therapy was used to treat IRIS, it was not successful, indicating that corticosteroid therapy has the risk of injuring patients.[8,9] Consequently, optimal therapeutics for cognitive impairment are urgently needed in clinical practice.

In recent years, thalidomide and its derivatives (lenalidomide and pomalidomide), termed immunomodulatory imide drugs (IMiDs), have been used in neurodegenerative disease due to their high blood–brain barrier permeability and bioavailability.[10] The use of thalidomide in the treatment of HIV-IRIS has also been reported.[9,11–13] Its side effects, such as bone marrow suppression, cardiotoxicity, vascular thrombosis, and neurotoxicity, limit its usage in clinical application. Lenalidomide, as a new generation IMiD drug, has an inhibitory effect on TNF-α that is 2000 times that of thalidomide.[14] Moreover, the side effects of thalidomide, such as constipation, peripheral neuropathy, sleepiness and neurotoxicity, were milder than those of thalidomide.[15] Lenalidomide has been studied in the treatment of central system diseases and HIV-related diseases, such as central nervous system tumors,[16,17] POEMS syndrome,[18] neuropathy,[10] relapsed AL amyloidosis,[19] Kaposi's sarcoma,[20] and pseudotumoral herpes simplex virus type 2 infection in HIV infection.[21] However, its application in cognitive impairment has never been reported in HCM patients with IRIS. In the present study, we observed the therapeutic effect of lenalidomide for the treatment of cognitive impairment caused by IRIS in HCM patients, aiming to explore an optimal therapy for psycho cognitive disorder in HCM patients.

Materials and Methods

Study Design and Patient Inclusion Criteria

This was an open-label, single-center, prospective observational study conducted in the First Affiliated Hospital of Zhejiang University. The primary inclusion criteria for this study were HIV-1-infected individuals who had a positive diagnosis of inflammation in the central nervous system and cognitive impairment during ART after successful induction therapy for CM. Patients who had been treated with immunosuppressants or other immunomodulators or cytotoxic drugs within 6 months before screening, those with severe underlying diseases of the heart, brain, liver, and kidney, those with an absolute neutrophil count of 1000 cells per μL or less and a platelet count less than 75,000/μL, those with known hypersensitivity or contraindication to lenalidomide, and those who were pregnant or breastfeeding were excluded from the study (see Supplementary Material for full criteria).

Definition of Cognitive Impairment

The Chinese version of the Montreal Cognitive Assessment (MoCA), International HIV Dementia Scale (IHDS), and Center for Epidemiological Research Depression Scale (CES-D) were used to assess patients' cognitive status. They all use Chinese questionnaires that have been validated for the evaluation of Chinese patients.[22–24] The MoCA tests eight major neurocognitive domains, including short-term memory recall (no score), visuospatial ability, naming, attention, language, conceptual thinking, working memory, and orientation of time and place. The MoCA, with a sensitivity of 90% and a specificity of 87%,[25] is used to identify patients with mild cognitive impairment. The IHDS measures timed finger tapping, timed alternating hand sequence, and recall of four items. It has a sensitivity of 80% and a specificity of 55%.[26]

The CES-D is a 20-item questionnaire that was used to assess the frequency of depression symptoms within the first 2 weeks of the study. A MoCA score <26 and/or an IHDS score <10 indicated cognitive impairment. A total CES-D score ≥16 indicated a clinically significant depressive state.

IRIS Definition Criteria

The IRIS definition criteria were as follows: an increase in CD4 count after ART (≥50 cells/μL or a ≥2-fold increase) and/or virologic suppression (>0.5 $\log_{10}$ decrease in plasma HIV viremia) is observed, but clinical symptoms consistent with an infectious or inflammatory condition, which cannot be explained by a newly acquired infection, an expected course of a previously recognized infection, or side effects of medications, are observed[27] (Table S1).

Screening Process

Fourteen patients were included in the lenalidomide treatment cohort based on the inclusion and exclusion criteria: eight patients had cognitive impairment at the time of enrollment; among them, one patient withdrew from the study due to skin allergy, so only seven patients were followed up for 24 weeks.

Therapeutic Approaches

Antifungal Treatment

All patients had already completed initial therapy of CM with amphotericin B (AmB) and 5-flucytosine (5-FC) and had negative CSF fungal cultures; they continued treatment with fluconazole (FLU). The induction treatment comprised AmB (0.7–1.0 mg/kg) + 5-FC (100 mg/kg bid) for 2 weeks. The consolidation treatment comprised 800 mg FLU for 8 weeks, while the maintenance treatment comprised 200 mg FLU daily.[28]

Lenalidomide Treatment

Patients were treated with six cycles of lenalidomide (one cycle: 25 mg/day for 3 weeks followed by 1 week ceased lenalidomide) when they were enrolled. The drug was stopped at the end of 6 cycles.

Follow-Up Time

The subjects were followed up at 0, 1, 2, 3, and 6 cycles of lenalidomide treatment. During each follow-up session, blood and CSF examinations were performed. Blood examination included a full blood count, liver and kidney function tests, assessment of coagulation function, C-reactive protein, $CD4^+$ T lymphocyte cell count, and HIV viral load, as well as other pathogenic tests, such as polymerase chain reaction testing for Epstein–Barr virus DNA, cytomegalovirus DNA, and T-SPOT test for *Mycobacterium tuberculosis*. CSF was sent for routine analysis, including biochemistry, bacterial and fungal culture, Epstein–Barr virus DNA, cytomegalovirus DNA, India ink staining, cryptococcus antigen detection, and cytokine analysis. Cognitive evaluations were performed at baseline and after 2 and 6 cycles of lenalidomide.

Detection of Inflammatory Cytokines in CSF

CSF samples were collected from the participants and centrifuged immediately; the supernatant was stored at −80 °C until testing. Thirty-two CSF cytokines were analyzed using the Human Cytokine/Chemokine/Growth Factor Panel A (Merck Millipore, St. Louis, USA): α-2-macroglobulin (α-2-M), apolipoprotein A-I (apoA-I), Apo-E, complement C3, complement factor H (CFH), fibroblast growth factor 2 (FGF-2), granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-γ (IFN-γ), growth-regulated oncogene (GRO), soluble CD40 ligand (sCD40L), platelet-derived growth factor-AA (PDGF-AA), interleukin (IL)-12p40, IL-12p70, IL-13, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-6, IL-8, IL-10, IL-17α, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), MIP-1β, tumor necrosis factor-α (TNF-α), IL-17α, amyloid-β (1–42) (αβ42), total Tau (tTau), and phosphorylated tau 181 (pTau181). The cytokine concentrations are expressed in pg/mL pre- and post-lenalidomide therapy. The abbreviations of CSF cytokines are provided in (Table S2).

Ethics Approval and Informed Consent

This study was conducted in compliance with the Declaration of Helsinki and approved by the ethics committee of the First Affiliated Hospital of Zhejiang University (Reference Number: 2020–265). All patients provided written informed consent for the use of their clinical information and publishing of any accompanying images. This study was registered in the Chinese Clinical Trial Registry (Registration Number: ChiCTR1900023184).

Statistical Analyses

Continuous variables were compared using the Mann–Whitney *U*-test, whereas categorical variables were compared using Fisher's exact test. CSF profile data at week [W] 24 and W0 were compared using the Wilcoxon matched-pairs signed-rank test. The correlation between CSF profile and cognitive function data was analyzed using Spearman's rank test. Statistical analyses were performed using IBM SPSS 23.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism (version 8.0; GraphPad Software, La Jolla, CA, USA). A two-tailed P value <0.05 was considered statistically significant.

Results

Baseline Data

The patients' demographic data are shown in (Table 1). All seven patients were Chinese men, with an average age of 37.0 (interquartile range [IQR] 33.0–39.0) years. Of the seven patients, 85.7% had at least a junior high school education.

Table 1 Clinical Features of the 7 Patients

Characteristics	Baseline Value*
Age (year)	37.0 (33.0-39.0)
Sex No (%)	
Male	7.0 (100)
Female	0 (0)
Education No (%)	
Primary	1.0 (14.3)
Middle school	5.0 (71.4)
High school	1.0 (14.3)
Graduate and above	0 (0)
BMI (kg/(m)^2)	20.8 (19.8-27.6)
Time from anti-CM to ART initiation, days	36.5 (25.0-40.0)
Time from anti-CM to LEN, days	477.0 (338.8-746.8)
Time from ART initiation to LEN, days	440.5 (310.0-710.5)
Time from ART initiation to cognitive decline, days	309.0 (265.0-694.0)
ART regimen No (%)	
2NRTI+1NNRTI	1 (14.3)
2NRTI+1PI	1 (14.3)
2NRTI+1 INSTI	5 (71.4)
CD4 cell count (Screen) No (%)	
<200 cells/ul	6 (85.7)
200-500 cells/ul	1 (14.3)
>500 cells/ul	0 (0)
CD4 cell count (Screen)	151.5 (119.3-239.0)
HIV RNA	0 (0-447.0)
Clinical presentation No (%)	
Fever	2 (28.6)
Headache	4 (57.1)
Alteration of consciousness	4 (57.1)
Seizures	1 (14.3)

Note: *The values are either medium (range) or # (%).

Abbreviations: ART: antiretroviral therapy; CM: cryptococcal meningitis; LEN: Lenalidomide; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; INSTI: Integrase strand transfer inhibitor; PI: protease inhibitor.

Most of the patients (71.4%) were treated with an antiviral regimen containing integrase inhibitors. The average CD4 count was 151.5 (119.3–239.0) cells/μL. The median HIV RNA copy number was 0 (0–447.0) copies/mL. The median time for cognitive impairment onset after ART initiation was 309.0 (265.0–694.0) days. The median time between ART initiation and lenalidomide initiation was 440.5 (310.0–710.5) days. Headache (four patients) and alteration of consciousness (four patients) were the most common clinical symptoms (Table 1). All patients received standard anti-cryptococcal treatment as mentioned in the Methods, and no pathogens were detected in the CSF. All patients had been treated with corticosteroids, but their cognitive function was not significantly improved. They had not been treated with corticosteroids in the last 6 months.

Cognitive Improvement Analysis

Six patients had MoCA scores <26 at baseline. The median MoCA score improved by three points after lenalidomide treatment [W0: 23.0 (13.0–24.0) vs W24: 26.0 (24.0–28.0), P = 0.018]. Five patients had IHDS scores <10 at baseline. There was a significant improvement in IHDS scores after lenalidomide treatment [W0: 9.0 (2.5–10.5) vs W24: 11.0 (10.0–12.0), P = 0.028] (Figure 1A). Improvements were mainly observed in recall of the four items in the IHDS [W0: 1.5 (1.0–3.5) vs W24: 4.0 (2.0–4.0), P = 0.042] (Figure 1B) and memory in the MoCA [W0: 1.0 (0–3.0) vs W24: 4.0 (3.0–5.0), P = 0.026] (Figure 1C). There was no significant difference in the CES-D score for anxiety or depression from before to after treatment. Spearman's correlation analysis showed a positive correlation between the MoCA score and IHDS score ($R^2 = 0.753$, P <0.001). Furthermore, there was a negative correlation trend of CES-D scores with MoCA ($R^2 = -0.349$, P = 0.029) and IHDS scores ($R^2 = -0.498$, P = 0.001).

Cognitive Grouping Analysis

Further analyses were performed for seven patients. Among them, the cognitive status of four patients returned to normal [the cognitive improvement group (CI group)], while that of three patients did not [the cognitive non-improvement group (CNI group)].

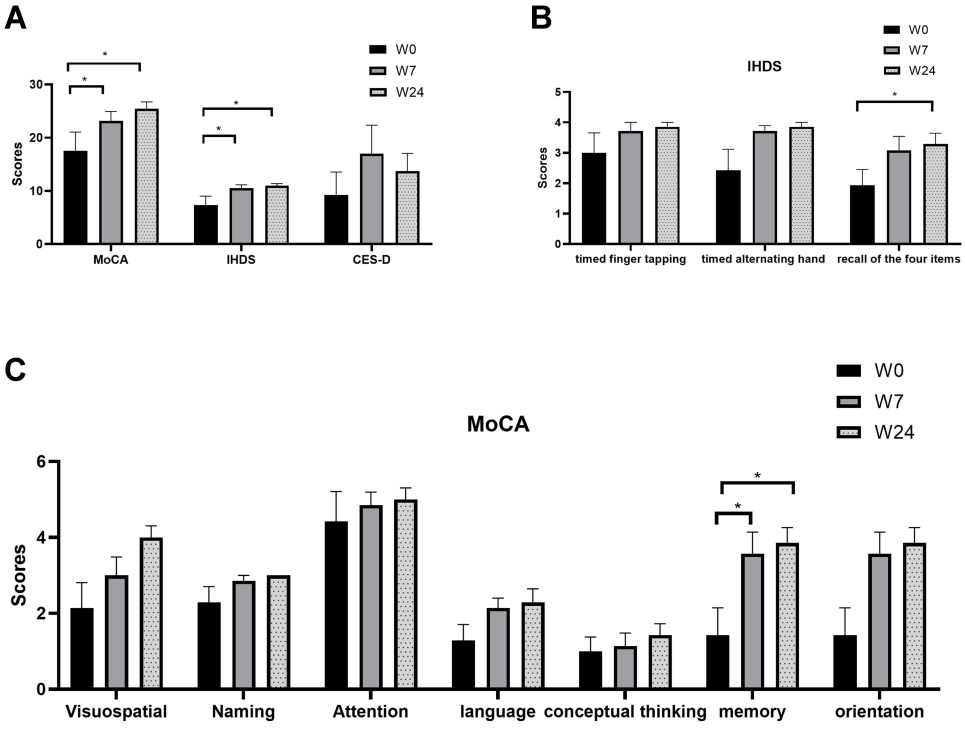

Figure 1 Cognitive improvement analysis. (**A**) The MoCA and IHDS scores had improved significantly after lenalidomide treatment (P = 0.018; P = 0.028)). (**B**) The recall of the four items in the IHDS was improved significantly (P = 0.042) among the components of IHDS. (**C**) Among the components of MoCA, the memory component was improved significantly (P = 0.026).

The pretreatment cognitive levels of the two groups were similar. The differences in the MoCA score abnormalities [CI group: 3/4 (75.0%) patients vs CNI group: 3/3 (100.0%) patients, P = 0.265] and IHDS score abnormalities [CI group: 3/4 (75.0%) patients vs CNI group: 2/3 (66.7%) patients, P = 0.462] between the two groups were not significant. However, after lenalidomide treatment, the MoCA scores of the patients in the CI group improved significantly, and the proportion of patients with abnormal MoCA scores was significantly lower [CI group: 0/4 (0%) vs CNI group: 3/3 (100%), P = 0.002]. Meanwhile, the difference in the IHDS score between the two groups was not significantly different.

CSF was further analyzed in both groups: the CI group had a more inflammatory milieu before lenalidomide treatment, with a higher level of CSF white blood cells (WBCs) [$\times 10^6$/L; CI group: 94.0 (44.0–180.0) vs CNI group: 0 (0–1.5), P = 0.032], CSF protein [g/L; CI group: 4.9 (3.0–6.6) vs CNI group: 0.6 (0.5–0.7), P = 0.034], CSF albumin [g/L; CI group: 318.5 (190.9–346.5) vs CNI group: 33.5 (30.4–46.2), P = 0.034], and CSF IgG [g/L; CI group: 160.5 (73.8–256. 0) vs CNI group: 4.7 (4.3–7.4), P = 0.034]. CSF glucose levels were much lower in the CI group than in the CNI group [mmol/L; CI group: 2.4 (2.0–2.7) vs CNI group: 2.8 (2.8–3.9), P = 0.032] (Figure 2A–E). Furthermore, there was no significant difference in CSF pressure or CSF chlorine levels between the two groups (Figure 2F–G). After lenalidomide treatment, there was a significant decline in the CSF WBC (P = 0.032), CSF protein (P = 0.034), CSF albumin (P = 0.034), and CSF IgG levels (P = 0.050) in the CI group (Table 2, actual values in Table S3). Spearman's correlation analysis revealed that the decrease in CSF albumin level (R^2:-0.757, P=0.049) and increase in CSF glucose level (R^2: 0.883, P=0.008) had a strong positive correlation with MoCA scores (Table 2).

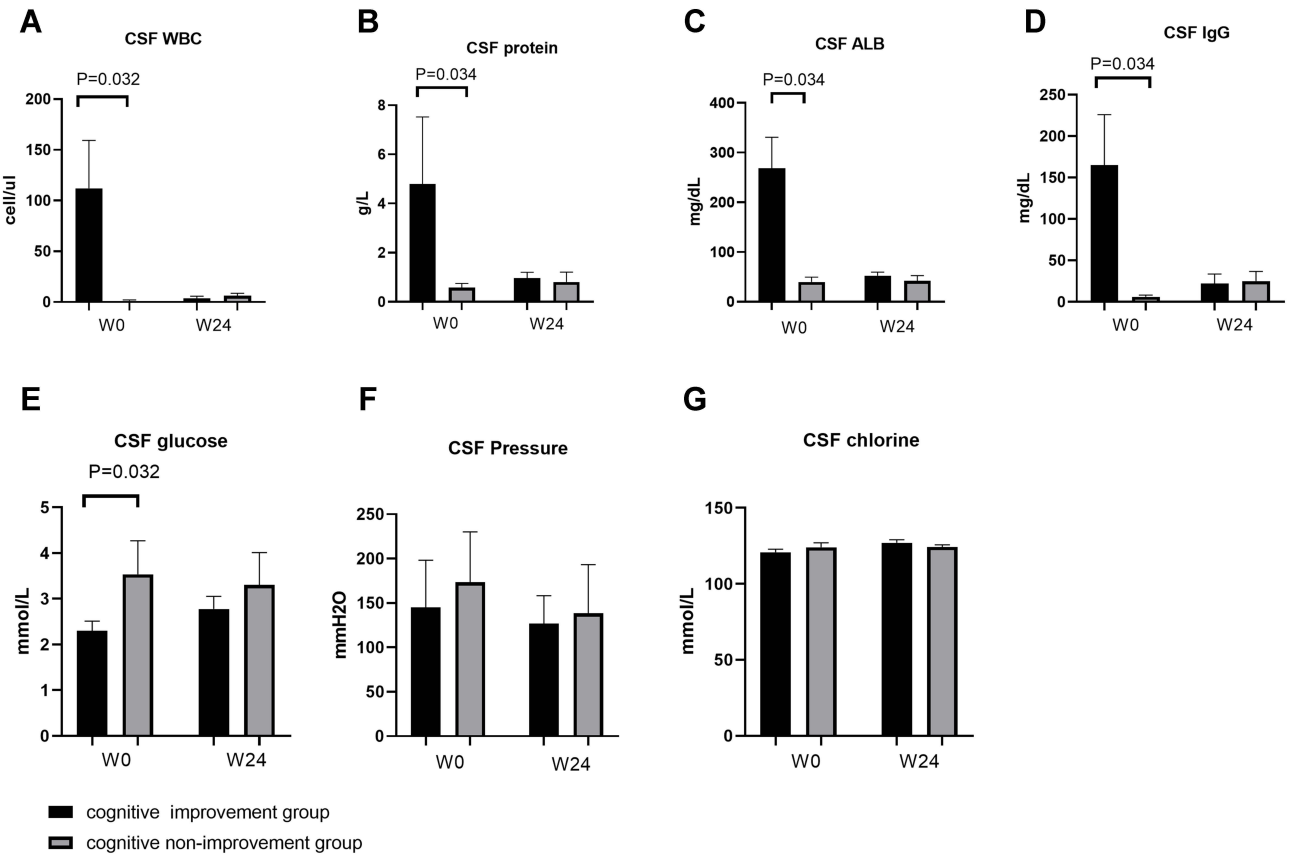

Figure 2 CSF analysis between CI group and CNIS group before LEN treatment. (**A-D**) CSF WBC, CSF protein, CSF albumin, CSF IgG in the CI group were much higher than those in the non-improve group (P = 0.032; P = 0.034; P = 0.034; 0.034). (**E**) CSF glucose was much lower in the CNIS group before LEN treatment (P = 0.032). (**F** and **G**) There was no significant difference in CSF pressure and CSF chlorine between the two groups.

Table 2 Cognitive Analysis and CSF Profile Analysis Between the Two Groups

	Cognitive CI Group	Cognitive CNI Group	P-value	$^{\Delta}$MoCA Spearman's Correlation[#a]	P-value	$^{\Delta}$IHDS Spearman's Correlation[#b]	P-value
$^{\Delta}$MoCA (scores)	8.5 (3.3-24.3)	1.0 (1.0-3.0)	0.154			0.505	0.248
$^{\Delta}$IHDS (scores)	5.25 (1.0-9.3)	1.5 (1.3-2.0)	0.480	0.505	0.248		
$^{\Delta}$ICP (mmH_2O)	10.0 (-57.5-41.0)	-20.0 (-57.5−5.0)	0.858	0.282	0.540	0.793	0.033
$^{\Delta}$WBC ($\times10^6$/L)	-118.0 (-179.0−64.0)	7.0 (4.0-7.0)	0.032	-0.264	0.568	-0.054	0.908
$^{\Delta}$ALB (g/L)	-299.2 (-302.5-166.1)	0.4 (-1.9-5.2)	0.034	-0.757	0.049	-0.679	0.094
$^{\Delta}$IgG (g/L)	-186.8 (-227.9−100.5)	24.3 (11.9-28.6)	0.050	-0.580	0.228	-0.600	0.208
$^{\Delta}$ Protein (g/L)	-4.4 (-5.6—2.5)	0.3 (0.1-0.4)	0.034	-0.595	0.159	-0.679	0.094
$^{\Delta}$Chlorine (mmol/L)	2.0 (1.5-7.5)	-4.0 (-4.0-2.5)	0.208	0.110	0.814	0.145	0.756
$^{\Delta}$Glucose (mmol/L)	0.4 (0.2-0.7)	-0.3 (-0.4−0.2)	0.077	0.883	0.008	0.536	0.215

Notes: [#a]This column showed Spearman's correlation between $^{\Delta}$MoCA and each of the other Δ value. [#b]This column showed Spearman's correlation between $^{\Delta}$IHDS and each of the other Δ value.

Abbreviations: Δ=week 24-week 0; CI group, the cognitive improvement group; CNI group, the cognitive non-improvement group; MoCA, Montreal Cognitive Assessment scores; IHDS, International HIV Dementia Scale scores; ICP, intracranial pressure; WBC, white blood cell; ALB, albumin.

CSF Cytokine Analysis

Thirty-two cytokines were analyzed before and after lenalidomide treatment in the CI group and CNI group. In the CI group, there was a significant decline in cytokine levels after treatment (GRO, IL-10, G-CSF, IL-6, IL-8, P all < 0.001; CFH, P = 0.002; TNF-α, P = 0.002; and α-2-M, P = 0.003) (actual values in Table S4). In the CNI group, only total taurine levels were increased significantly (tTau, P = 0.030). The cytokine signaling pathways that changed significantly after treatment in the CI group were mainly in the cellular response to lipopolysaccharide, regulation of acute inflammatory response, etc. (Figure S1).

Discussion

In this prospective study, we explored the effect of lenalidomide on cognitive function in patients with HCM after cryptococcal treatment. The overall cognitive function of some patients improved significantly after lenalidomide treatment, and the changes of CSF cytokines during this study suggested that the cognitive impairment in some patients may be related to IRIS.

Cognitive impairment is a common neurological disorder in patients with AIDS[29,30] and has several causes. Apart from opportunistic infections in the central nervous system and IRIS after ART initiation, the direct toxic effects of HIV and the adverse effects of ART may also cause further injuries.[31,32]

In this study, patients in the CI group were symptomatic, and CSF profiles supported the fact that IRIS may be the cause of their inflammatory CSF before lenalidomide treatment. IRIS occurs in patients previously treated for CM following initiation of HAART; it is a dysregulated Th1 immune response. In our study, the levels of inflammatory cytokines in the CI group (IL-8, GRO, IL-10, G-CSF, IL-6, CFH, TNF-α, and α-2-M) were significantly declined after lenalidomide treatment. IL-8 and GRO are associated with neutrophil-induced inflammation characterized by the sequential expression of neutrophil chemoattractants in CSF after subarachnoid hemorrhage. These cytokines and Th1 signals are related to neutrophil-induced inflammation, and the signaling pathway suggests that they are related to the downregulation of acute inflammatory factors. We speculate that lenalidomide, a TNF-α inhibitor that inhibits the Th1 response, can improve cognition mainly by downregulating inflammatory cytokines in the CI group. The CSF cytokine changes in the CI group were mainly related to the cell response to lipopolysaccharide and inflammatory regulation, reflecting the amelioration of intracranial inflammation after treatment.

We also found no significant change in CSF profiles or cytokines in the CNI group after lenalidomide treatment. However, the level of tTau increased, suggesting that cognitive impairment in the CNI group may not be caused by inflammation. There is a strong relationship between tTau levels in CSF and dementia in patients with Alzheimer's

disease. Therefore, we speculated that their cognitive impairment could have been caused partially by HIV-associated neurocognitive disorders (HAND). HAND is the most common neurocognitive disorder in HIV-infected people, affecting 50% of patients, and low CD4 levels are a risk factor for HAND.[32] According to Frascati criteria, acquired abnormality in at least two cognitive areas leading to impairment in work or daily living activities and could not have other etiologies that might explain the disorder was the basis for diagnosing HAND.[33] In our study, for all patients who had cognitive decline, other opportunistic infections were excluded as the cause, and patients with CM are in the advanced stages of AIDS and may have an increased risk of HAND.[34] We speculate that HAND may be behind the observation of no cognitive improvement after lenalidomide treatment in CNI group.

Sequelae of CM may also cause neurocognitive impairment. A study found that the global neurocognitive impairment of cryptococcal infection survivors was significantly worse than that of HIV-positive patients at each evaluation; by 12 months after CM diagnosis and treatment, 41% of the participants had persistent global neurocognitive impairment.[35] A similar finding was observed in HIV-negative patients with cryptococcal infection in a previous study: patients who were admitted initially with cognitive deficits improved very slowly, this was seen in the variation of their MoCA scores and the inability of some to return to baseline despite a year of therapy.[36]

Similarly, the side effects of ART cannot be disregarded. One of the three patients in the CNI group was treated with efavirenz, which causes nightmares, headache, depression, anxiety, and other central nervous system side effects. Moreover, these symptoms usually start during the early stages of treatment and thus prolong the cognitive impairment duration. Therefore, ART neurotoxicity may also be one of the causes of neurocognitive impairment in these patients.

We used the classical MoCA and IHDS for cognitive assessment. The MoCA and IHDS are well-recognized instruments for the detection of cognitive impairment associated with neurocognitive diseases. The use of the MoCA in central nervous system diseases may help further identify therapeutic strategies to minimize long-term cognitive impairment morbidity.[36] From our limited dataset, both MoCA and IHDS were able to diagnose cognitive deficits in these patients. After lenalidomide treatment, however, there was little difference between the CI group and CNI group based on IHDS scores. MoCA, on the other hand, did still detect a difference. The MoCA is also simple to use and feasible and might be a good screening tool for nonpsychiatrists.

This study has some limitations. First, the sample size was small, and a study based on a large population is needed for further validation of the results. As a pilot study, this study provides new information that may be helpful for future research with the potential for future scaled up studies to develop new treatments to help combat the cognitive impairment morbidity from CM. Second, there was a lack of randomization; as previous reported that corticosteroid treatment has side effect[7] and has the risk of injuring patients,[8,9] we found it difficult to ethically randomize. There was also prior study involving postinfectious inflammatory responses in which treatment was administered without randomization.[37] Third, repeated cognitive function assessment at 2 and 6 months may lead to an increase in cognitive assessment scores due to patients' increased familiarity with cognitive assessment exercises. However, the two groups of patients underwent these assessments simultaneously, which reduced the test error.

Conclusion

There are various reasons for cognitive impairment after Cryptococcus clearance, with IRIS being one of them. Lenalidomide potentially reduces cognitive impairment caused by IRIS in patients with HCM after cryptococcal clearance by inhibiting intracranial inflammation.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from corresponding author on reasonable request.

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Author Contributions

Ran Tao: Investigation (Lead), Data curation (Lead), Formal analysis (Lead), Writing-original draft (Lead), Writing-review& editing (Lead), Conceptualization (equal); Xiaorong Peng: Investigation (equal), Data curation (equal); Xiang Liu: Investigation (equal); Lijun Xu: Writing-original draft (equal), Writing-review & editing (equal), Junwei Su: Data curation (equal); Guanjing Lang: Data curation (equal); Ying Huang: Data curation (equal); Biao Zhu: Conceptualization (Lead), Investigation (Lead), Funding acquisition (Lead), Project administration (Lead). All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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