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MAJOR ARTICLE

Intravenous Cyclophosphamide Therapy for Anti-IFN-γ Autoantibody-Associated *Talaromyces marneffei* Infection

Wen Zeng,[1,2,a] Mengxin Tang,[2,a] Meiling Yang,[2,a] Gaoneng Fang,[2] Shudan Tang,[2] and Jianquan Zhang[1]

[1]Department of Respiratory and Critical Medicine, The Eighth Affiliated Hospital, Sun Yat-Sen University, Shenzhen, Guangdong, China, and [2]Department of Respiratory and Critical Medicine, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China

High titers of anti-interferon-γ autoantibodies (AIGAs) are an important factor leading to persistent, relapsed, and refractory infections in HIV-negative hosts infected with *Talaromyces marneffei* (TM). We report 5 patients treated with pulses of high-dose intravenous cyclophosphamide (IVCY) who were followed for 2 years. Before IVCY therapy, all patients had multiple relapses, with a median (interquartile range [IQR]) of 2 (1–3) instances of relapse. The median serum AIGA titers (IQR) were 58 753 (41 203–89 605) ng/mL at diagnosis, 48 189.4 (15 537–83 375) ng/mL before IVCY therapy, and 10 721.2 (5637–13 245) ng/mL at the end of IVCY therapy ($P < .05$). After 3 months of follow-up, the median AIGA titers (IQR) rose gradually to 21 232.6 (9896–45 626) ng/mL, and to 37 464.2 (19 872–58 321) ng/mL at 24 months ($P < .05$). Five patients discontinued antimicrobial therapy within 3–12 months after completion of IVCY therapy, but only 1 patient had a relapse. In conclusion, pulses of short-term and high-dose IVCY can effectively reduce AIGA titers.

Keywords. anti-IFN-γ autoantibodies; intravenous cyclophosphamide therapy; *Talaromyces marneffei*.

Anti-interferon (IFN)-γ autoantibodies (AIGAs) are anticytokine autoantibodies that are closely related to a variety of severe disseminated intracellular pathogenic infections, such as *Talaromyces marneffei* (TM), nontuberculous mycobacteria (NTM), and *Salmonella* [1–3]. In a previous study, we found that AIGAs were independent risk factors for TM infection in HIV-negative hosts and one of the most important immunodeficiency mechanisms in HIV-negative *Talaromycosis marneffei* (TSM) patients. Despite intensive antifungal therapy, >50% of patients have persistent or recurrent infections and experience multiple adverse drug effects [3–5]. This is related to the abnormal production of AIGAs, which can effectively block the IFN-γ signaling pathway, leading to a state of immunodeficiency. It has been reported that the use of anti-CD20 monoclonal antibody and cyclophosphamide to reduce AIGA titers can achieve good clinical efficacy in AIGA-associated NTM patients [6, 7]. However, rituximab is a high-cost drug that can only be used by a certain group of patients. In contrast, cyclophosphamide, which is less costly, has comparable efficacy to rituximab and has broader application prospects [8, 9]. Currently, there is no therapy available for AIGA-associated TM infection. Therefore, we report the use of immunotherapy with pulsed intravenous cyclophosphamide (IVCY) in 5 patients with AIGA-associated TM infection who had an ongoing increase in AIGAs and multiple relapses of TM infection.

METHODS

Patients and Methods

A prospective study was conducted among 5 HIV-negative patients over 18 years old at the First Affiliated Hospital of Guangxi Medical University who had been diagnosed with disseminated TSM and/or coinfection with other pathogens between 2018 and 2019. After a clear diagnosis of TSM, serum samples were tested for AIGAs for the first time and were identified as AIGA-positive, and the titers of AIGAs rose continuously. Before enrollment, all patients were regularly treated with at least 1 antifungal agent for TSM or drugs for other coinfections and had at least 1 relapse after improvement, with >6 months of antifungal therapy. No patients had other contraindications for cyclophosphamide before IVCY therapy, such as liver and kidney dysfunction, leucopenia, and pregnancy. After completion of IVCY therapy, 5 patients continued treatment for the primary infection and were followed up for 2 years.

This study was approved by the Faculty of Medicine at the First Affiliated Hospital of Guangxi Medical University (2021 [KY-E-262]). All patients provided written informed consent.

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[a]Equal contribution, co-first authors

Correspondence: Jianquan Zhang, PhD, Department of Respiratory and Critical Medicine, The Eighth Affiliated Hospital, Sun Yat-Sen University, No.3025 Shennan Road, Futian District, Shenzhen, Guangdong 518000, China (jqzhang2002@126.com).

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Treatment Regimens

Five enrolled patients were given pulsed IVCY at a dose of 0.8–1.0 mg/m^2 every 3–4 weeks for 6 cycles until 6 months of therapy were completed. All patients received continuous antifungal or antimicrobial therapy for other pathogens.

Clinical Monitoring

Five patients received routine safety monitoring during IVCY therapy, including complete routine blood tests, routine urine tests, liver and kidney function chemistries, T-lymphocyte cell counts, quantitative immunoglobulin levels, and other biochemical indexes. AIGA titers were also monitored in all patients. Disease activity was evaluated by observing clinical signs and evidence of active infection on imaging examinations or pathogen pathology, culture, or smear. Treatment and clinical data were prospectively collected and documented.

Diagnostic Criteria for TM, NTM and Other Pathogens

Each patient fulfilled the diagnostic criteria for each disease. TM infection was diagnosed as follows: (1) Positive cultures for TM were characterized by dimorphic fungi that grew either as a mold at 25°C or as yeast at 37°C. (2) The yeast form of TM was confirmed by cytology and histopathology of tissues and secretions using Periodic Acid-Schiff (PAS) staining or Wright's stain, which revealed a characteristic morphology including a transverse septum [10]. NTM infection was diagnosed according to the guidelines of the 2007 American Thoracic Society (ATS)/Infectious Disease Society of America [10, 11]. Other pathogens were identified based on the positive culture of this pathogen from clinical specimens. TM and/or other pathogens were also identified in clinical specimens using metagenomics next-generation sequencing (mNGS) but still needed to meet the above criteria. Disseminated disease was defined as infection of at least 2 noncontiguous and sterile sites.

Definitions of Clinical Outcomes

(1) Cured (no recurrence of TM and/or NTM infection for at least 6 months after discontinuation of antifungal/anti-NTM therapy); (2) Improved (improvement in clinical symptoms, radiologic manifestations, laboratory tests after antifungal/anti-NTM treatment, but not cured). (3) persistent or relapsed infection (persistent infection: no improvement in clinical symptoms, radiologic manifestations, laboratory tests after 2 weeks of antifungal treatment/4 weeks of anti-NTM treatment; relapsed infection: improvement of clinical symptoms, radiologic manifestations, laboratory tests, negative pathogen detection after antifungal/anti-NTM effective treatment, followed by the reappearance of pathogen-associated infectious signs and/or positive pathogen testing).

Anti-IFN-γ Autoantibody Assay

AIGAs in the plasma were determined by enzyme-linked immunosorbent assay kits (USCN Life Science, Inc., Wuhan, China). To make this determination, first we added 100 μL each of standard, blank, and sample dilutions into appropriate wells and incubated them for 1 hour at 37°C. Then, we removed the liquid from each well and added 100 μL of detection reagent A. We incubated the wells for 1 hour at 37°C. Next, we used 1× wash solution, completely washed the wells 5 times, and removed any remaining wash buffer. Then, we added 90 μL of substrate solution to each well. These were incubated in the dark for 10–20 minutes at 37°C. Once the first 3 of the standard wells turned blue, we gently added 50 μL of stop solution to each well. After the liquid turned yellow, the color change was finally measured spectrophotometrically at a wavelength of 450 nm. The concentration of AIGAs in the sample was then determined by comparing the optical density of the sample to the standard curve. The positive titer value was determined to be 9583.21 ng/mL according to the methods used in our previous study [1].

CD4+ Cell and Peripheral Blood Mononuclear Cell Assay

Whole-blood samples from *T. marneffei* infection patients and healthy control subjects were collected in ethylene diaminetetraacetic acid-treated tubes and inert separation gel vacuum procoagulant collective tubes. Peripheral blood mononuclear cells (PBMCs) were separated by Lymphoprep (Stemcell Technologies, Canada) centrifugation. Briefly, fresh blood samples were mixed with an identical volume of phosphate buffer saline and were carefully placed on the surface of Lymphoprep separation medium. After centrifugation at 500×*g* for 20 minutes at 28°C, PBMCs were collected at the interphase and washed with phosphate buffer saline by centrifugation for 10 minutes at 300×*g*. Cells were stimulated in the presence of GolgiStop at 37°C in 5% CO_2 for 5 hours. After stimulation, cells were surface-stained with an anti-CD4 monoclonal antibody (Percp-cy5.5; BD Pharmingen) for 30 minutes at 4°C. Intranuclear staining was performed with the use of anti-phosphor-signal transducer and activator of transcription 1 (STAT1; tyrosine 701) antibody (PE; BD Pharmingen). Data were collected with the use of FACS Can to flow cytometry (BD Biosciences) and analyzed with the use of FlowJo (Treestar).

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences for Windows (SPSS), version 24. P values <.05 were considered statistically significant. Descriptive analysis was applied to demographic data. The Student t test and Fisher exact test were used to compare parameters between the 2 independent, unrelated patient groups.

RESULTS

Five HIV-negative patients with AIGA-associated TM infection were enrolled. The median age (interquartile range [IQR]) of the 5 patients (3 males and 2 females) was 53 (33–63) years. The underlying diseases or comorbidities included paroxysmal atrial fibrillation (n = 1), bronchial asthma (n = 1), autoimmune antibody abnormalities (n = 3); patient 2: (antinuclear antibody) ANA 1:100; patient 3: ANA 1:100, anticardiolipin antibody (+), anti-Ro-52 antibody (±); patient 4: ANA 1:320, anti-SSA antibody (+), anti-SSB antibody (+). All patients were diagnosed with disseminated TSM, with lymph node, lung, and bone involvement in 5 (5/5, 100%), skin involvement in 4 (4/5, 80%), and blood, liver, and spleen involvement in 2 patients (2/5, 40%). Four patients had NTM infection of the lung and bone or *Salmonella* infection of the blood and digestive tract (Table 1). All patients received antimicrobial treatment for the primary infection before, during, and after IVCY therapy, with a median duration (IQR) of 13 (12–14) months. All patients had multiple relapses, with a median (IQR) of 2 (1–3) relapses (Table 2).

Before the initiation of IVCY therapy, complete blood count examinations revealed that the median white blood cell count, neutrophil count, and absolute lymphocyte count (IQR) were 9.66 (6.58–10.03) × 10^9/L, 4.7 (6.7–7.79) × 10^9/L, and 2.32 (1.62–2.53) × 10^9/L, respectively. The median hemoglobin concentration, platelet count, and total bilirubin level (IQR) were 231 (126–276) g/L, 187 (132–283) × 10^{12}/L, and 8.2 (7.6–10.1) μmol/L, respectively. Serum biochemical analysis showed a median serum albumin concentration and globulin concentration (IQR) of 36.3 (35.6–36.4) g/L and 37.4 (33.3–38.4) g/L, respectively. The median concentrations of aspartate aminotransferase, alanine aminotransferase, and creatinine (IQR) were 26 (20–31) U/L, 24 (23–36) U/L, and 68 (66–87) μmol/L, respectively. The median erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin (IQR) were 47 (37–49) mm/H, 32.5 (19.2–44.7), and 0.26 (0.19–0.55) ng/mL, respectively.

All patients received 6 pulses of IVCY and were treated with antimicrobial agents before and during IVCY therapy. AIGA titers were significantly elevated in 5 patients at diagnosis, with a median AIGA titer (IQR) of 48 450 (41 924–72 583) ng/mL. The median AIGA titer (IQR) of the 5 patients before the first pulse of IVCY was 46 124 (46 004–49 907) ng/mL. All patients' duration from diagnosis to IVCV treatment was 13 (12–14) months; we detected the AIGA titers 3, 6, 9, 12, and 15 months after diagnosis. The AIGA titers of all patients before IVCY therapy were higher than the positive titer value (Table 3, Figure 1). Serological testing in all patients showed a significant decrease in AIGA titers after receiving IVCY therapy. The median (IQR) number of AIGA titers in serum after 4 months was 14 234 (11 029–24 564), and it was significantly different from 46 124 (46 004–49 907) ng/mL before pulse IVCY ($P < .05$). The median AIGA titer (IQR) after completion of the sixth pulse of IVCY was 10 320 (6784–13 245) ng/mL, and it was also significantly different from the number before pulse IVCY ($P < .01$). After 3 months of follow-up, the median (IQR) AIGA titers of all patients began to rise gradually to 16 738 (14 954–18 948) ng/mL and then to 40 532 (21 234–47 362) ng/mL at the end of 24 months of follow-up. The AIGA titers monitored after 12 months of follow-up were 34 912 (18 721–35 462), and it was significantly different from those after completion of the sixth IVCY therapy session ($P < .05$) (Table 4, Figure 2).

The T lymphocyte count, B lymphocyte count, and related basic laboratory parameters of all patients were documented. A lymphocyte subpopulation analysis showed that the median $CD3^+$ T lymphocyte count (IQR) was 1522 (1432–1941) cells/μL before IVCY and decreased to 953 (932–982) cells/μL after

Table 1. Clinical Data Among Disseminated TM Patients Treated With IVCY

Patient No.	Age/ Sex	Organ Involvement	Underlying Diseases	Treatment Duration Before IVCY, mo	No. of Relapses Before IVCY Treatment	Other Opportunistic Infections/Organ
1	63/M	Blood, lymph nodes, lung, liver, spleen, skin, multiple bones	…	19	3	*M. chelonae*: lung
2	62/M	Lung, liver, multiple bones, lymph nodes	Atrial fibrillation ANA1:100	13	1	…
3	43/F	Lung, skin, blood, multiple bones, lymph nodes	Bronchial asthma Sweet's syndrome ANA1:100 anticardiolipin antibody (+), anti-Ro-52 antibody (±)	12	3	*M. abscessus*: lung, bones *Salmonella*: blood, alimentary canal
4	33/F	Lung, skin lymph nodes, multiple bones, liver, spleen	ANA 1:320, anti-SSA antibody (+), anti-SSB antibody (+)	6	1	*M. abscessus*: lung
5	64/M	Lung, skin, lymph nodes, multiple bones, blood	…	14	2	*Salmonella*: blood

Abbreviations: ANA, antinuclear antibody; IVCY, intravenous cyclophosphamide; NTM, nontuberculous mycobacteria; TM, *Talaromyces marneffei*.

Table 2. Treatment and Outcome Among Disseminated TM Patients Treated With IVCY

Patient No.	Parenteral Antibiotic Before IVCY	No. of IVCY Cycles/ Total Dose/Duration	Parenteral Antibiotic During IVCY	Parenteral Antibiotic After IVCY	Follow-up After IVCY	Outcome
1	TM: AMB + voriconazole for 3 mo, changed to itraconazole for 3 mo, first relapse Then changed to voriconazole for 5 mo, second relapse Then AMB + voriconazole for 1 mo, changed to itraconazole for 4 mo, third relapse Then voriconazole for 3 mo, improved NTM: moxifloxacin + clarithromycin + ethambutol for 7 mo, improved	6/5.8 g/5 mo	Voriconazole for 5 mo	TM: itraconazole for 6 mo NTM: moxifloxacin + clarithromycin for 12 mo	2 y	Cured
2	TM: voriconazole for 8 mo, first relapse Then AMB for 1 mo, changed to voriconazole for 4 mo, improved	6/5.6 g/5.5 mo	Voriconazole for 5.5 mo	Voriconazole for 3 mo	2 y	Cured
3	TM: voriconazole for 2 mo, first relapse Then AMB for 1 mo, changed to itraconazole for 0.5 mo, second relapse Then AMB for 1 mo, changed to voriconazole for 4 mo, third relapse Then AMB for 0.5 mo, changed to voriconazole for 3 mo, improved NTM: moxifloxacin + clarithromycin + ethambutol for 4 mo, improved *Salmonella*: piperacillin/tazobactam + levofloxacin for 1 mo, cured	6/5.4 g/5.5 mo	Voriconazole for 5.5 mo	TM: itraconazole 3 mo NTM: moxifloxacin + clarithromycin for 6 mo	2 y	Relapsed with TM
4	TM: itraconazole for 2 mo, first relapse Then voriconazole for 2 mo, changed to itraconazole for 2 mo, improved NTM: moxifloxacin + clarithromycin + ethambutol for 4 mo, improved	6/4.8 g/4.5 mo	Itraconazole for 4.5 mo	TM: itraconazole for 8 mo NTM: moxifloxacin + clarithromycin for 8 mo	2 y	Cured
5	TM: voriconazole for 1 mo, changed to itraconazole for 1 mo, first relapse Then voriconazole for 3 mo, second relapse Then AMB for 1 mo, changed to voriconazole for 8 mo, improved *Salmonella*: imipenem for 0.5 mo, changed to piperacillin/tazobactam + levofloxacin for 0.5 mo, cured	6/5.6 g/5 mo	Voriconazole for 5 mo	Voriconazole for 3 mo	2 y	Cured

Abbreviations: AMB, amphotericin B; IVCY, intravenous cyclophosphamide; NTM, nontuberculous mycobacteria; TM, *Talaromyces marneffei*.

Table 3. Anti-IFN-γ Autoantibody Titer Changes in Plasma From 5 Patients Before Treatment With IVCY (ng/mL)

Patient No.	Treatment Duration Before IVCY, mo	AIGAs Titers at Diagnosis	After 3 mo	After 6 mo	After 9 mo	After 12 mo	After 15 mo	Pretreatment
1	19	89 605	90 875	76 581	91 234	65 981	94 321	49 907
2	13	48 450	56 443	23 451	45 674	…	…	15 537
3	12	41 203	38 764	40 321	42 251	…	…	46 004
4	6	72 583	78 943	…	…	…	…	83 375
5	14	41 924	42 312	45 321	40 321	…	…	46 124

Abbreviations: AIGA, anti-interferon-γ autoantibody; IFN, interferon; IVCY, intravenous cyclophosphamide.

completion of IVCY therapy. The median $CD4^+$ T lymphocyte count (IQR) was 873 (676–1127)/μL before IVCY therapy and decreased to 486 (453–491)/μL after completion of IVCY therapy ($P < .05$). The median $CD8^+$ T cell count (IQR) was 463 (744–824)/μL before IVCY therapy and then decreased to 443 (432–453)/μL after completion of IVCY therapy. The median proportion of the natural killer (NK) cell population (IQR) was 14.46% (13.44%–15.35%) before IVCY and then decreased to 12.9% (10.2%–13.3%) after completion of IVCY. All the relevant laboratory values of lymphocytes gradually increased after IVCY therapy (Table 5, Supplemental Table, Figure 3). The median proportion of $CD19^+$ B cells (IQR)

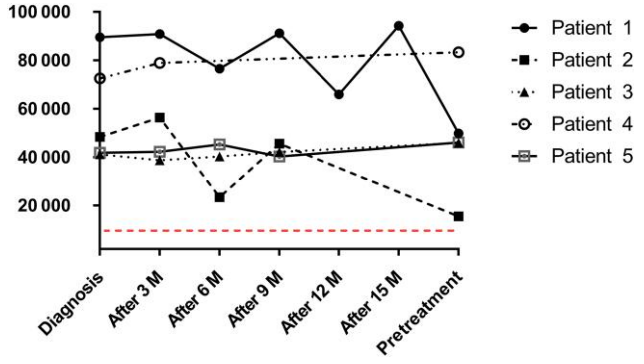

Figure 1. Anti-IFN-γ autoantibody titer changes in plasma from 5 patients before treatment with IVCY: The AIGA titers of all patients before IVCY therapy were higher than the positive titer values. Abbreviations: AIGAs, anti-IFN-γ autoantibodies; IFN, interferon; IVCY, intravenous cyclophosphamide.

was 10.2% (8.22%–13.2%) before IVCY, which decreased to 6.5% (6.4%–8.3%) at completion of IVCY. Patients 1, 2, and 5 returned to normal levels 3 months after the end of IVCY, and patients 3 and 4 returned to normal levels 12 months after the end of IVCY. The median titers of serum immunoglobulin (Ig)G, IgA, and IgM were 12.61 (12.1–15.79) g/L, 1.62 (1.5–1.67) g/L, and 1.52 (1.21–1.77) g/L before treatment, respectively, and all decreased during pulsed IVCY therapy. All of these titers gradually increased after IVCY therapy (Table 6, Figure 4).

Patient 3 developed Sweet's syndrome 2 months after her diagnosis with TM infection and was ANA 1:100, anticardiolipin antibody (+), and anti-Ro-52 antibody (±). She was treated with prednisone at 30 mg/d, which was then reduced by 5 mg every 2–4 weeks to 5–10 mg for 9 months. The rash associated with Sweet's syndrome in this patient gradually subsided. Patient 4 was ANA 1:320, anti-SSA (+), and anti-SSB (+). She was treated with prednisone at 40 mg/d, which was reduced by 5 mg every 2 weeks to 5 mg for 14 months.

No significant adverse effects were observed among the 5 patients during the pulsed IVCY therapy. Patients 2 and 3 had anorexia the day after IVCY therapy and improved 2–3 days later. No one had nausea or vomiting. No patients had frequent urination, urgent urination, painful urination, hematuria, scanty urination, proteinuria, or liver function impairment during or after IVCY therapy. No patients had bone marrow suppression such as decreased white blood cells, decreased platelets, or anemia during or after IVCY therapy. All patients had no bladder cancer, skin cancer, myeloproliterative neoplasms, or myelodysplastic syndromes for 24 months after discontinuation of the 6 pulses of IVCY. After completion of 6 pulses of IVCY therapy, complete blood count examinations revealed that the median white blood cell count, neutrophil count, and absolute lymphocyte count (IQR) were 8.0 (7.66–8.84) $\times 10^9$/L, 5.64 (5.03–5.7) $\times 10^9$/L, and 1.12 (1.94–1.98) $\times 10^9$/L, respectively.

Table 4. Anti-IFN-γ Autoantibody Titer Changes in Plasma From 5 Patients Treated With IVCY (ng/mL)

Patient No.	AIGAs Titers at Pretreatment	Treatment Duration, mo						Post-treatment Duration, mo					
		1	2	3	4	5	6	3	6	9	12	18	24
1	49 907	56 085	39 636	31 554	24 564	23 101	13 245	45 626	93 520	54 211	35 462	43 412	47 362
2	15 537	7975	7551	6388.8	6873	5902	5637	16 738	28 342	14 321	18 721	16 251	19 872
3	46 004	18 056	20 387	27 295	28 299	21 234	17 620	18 949	23 303	57 510	43 767	56 973	58 321
4	83 375	20 461	13 615	17 986	11 029	9876	10 320	14 954	23 209	28 325	34 912	47 181	40 532
5	46 124	46 475	29 461	16 474	14 234	10 832	6784	9896	10 921	15 432	12 334	23 123	21 234
IQR	46 124 (46 004–49 907)	20 461 (18 056–46 475)	20 387 (13 615–29 461)	17 986 (16 474–27 295)	14 234 (11 029–24 564)*	10 832 (9876–21 234) *	10 320 (6784–13 245)**	16 738 (14 954–18 949)	23 303 (23 209–28 342)	28 325 (15 432–54 211)	34 912 (18 721–35 462) ***	43 412 (23 123–47 181) ***	40 532 (21 234–47 362) ***

Compare with AIGA titers at pretreatment (*$P < .05$; **$P < .01$). Compare with AIGA titers at 6-month treatment duration (***$P < .05$).

Abbreviations: AIGA, anti-interferon-γ autoantibody; IQR, interquartile range; IVCY, intravenous cyclophosphamide.

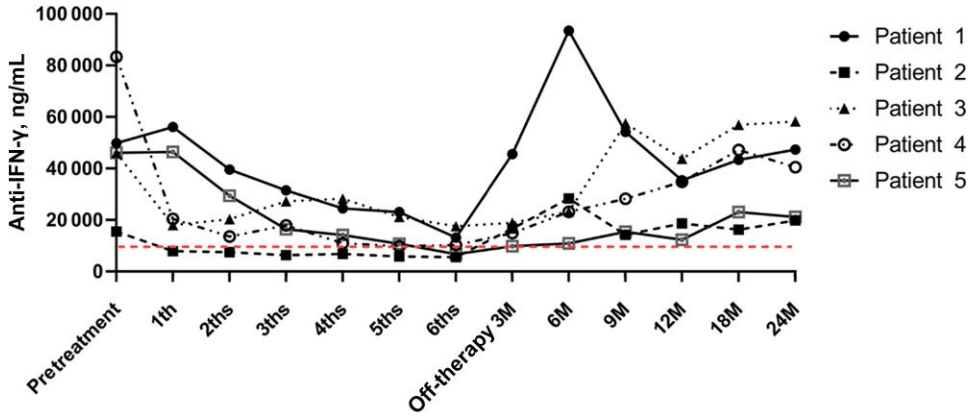

Figure 2. Anti-IFN-γ autoantibody titer changes in plasma from 5 patients treated with IVCV: There was a significant decrease in AIGA titers before and after receiving IVCY therapy. The AIGA titers in serum after 3, 4, 5, and 6 months were significantly different from those before pulse IVCY ($P < .05$). After 3 months of follow-up, the median AIGA titers of all patients began to rise gradually. The AIGA titers monitored after 12 months of follow-up were significantly different from those after completion of the sixth IVCY therapy session ($P < .05$). Abbreviations: AIGAs, anti-IFN-γ autoantibodies; IFN, interferon; IVCY, intravenous cyclophosphamide.

The median hemoglobin concentration and total bilirubin level (IQR) were 129 (109–136) g/L and 7.7 (7.3–10.4) μmol/L, respectively. Serum biochemical analysis showed a median serum albumin concentration and globulin concentration (IQR) of 38 (36.4–37.3) g/L and 31.8 (28.9–32.8) g/L, respectively. The median concentrations of aspartate aminotransferase, alanine aminotransferase, and creatinine (IQR) were 27 (21–28) U/L, 32 (22–35) U/L, and 78 (60–85) μmol/L, respectively. The median ESR, CRP concentration, and procalcitonin (IQR) were 27 (15–40) mm/H, 9.93 (2.59–15.94), and 0.066 (0.053–0.08) ng/mL, respectively. The autoantibody titer test showed decreased antibody titers or autoantibody negativity in 3 patients: patient 2: ANA (−); patient 3: ANA (−), anticardiolipin antibody (−); patient 4: ANA 1:100, anti-SSA (±), anti-SSB (+) (Table 7).

Five patients continued to use antibiotics or antifungal agents to treat primary infections after completing IVCY therapy, with durations of 6, 3, 3, 8, and 3 months for antifungal treatment from patients 1–5 and of 12, 6, and 8 months for anti-NTM treatment for patients 1, 3, and 4, respectively. Patient 1 required itraconazole for maintenance treatment of TM infection until 6 months after IVCY discontinuation and a combination of moxifloxacin and clindamycin for maintenance treatment of NTM infection until 12 months after IVCY discontinuation. Patient 2 continued TM therapy with voriconazole until 3 months after completion of IVCY therapy. Patient 3 remained on TM treatment with itraconazole until 3 months after completion of IVCY and on NTM treatment with a combination of moxifloxacin and clindamycin until 6 months after completion of IVCY therapy. Patient 4 required itraconazole for maintenance therapy of TM infection until 8 months after IVCY discontinuation and a combination of moxifloxacin and clindamycin for maintenance therapy of NTM infection until 8 months after IVCY discontinuation. Patient 5 needed voriconazole to maintain treatment of TM infection until 3 months after completing IVCY therapy. All patients continued to be followed for 24 months after discontinuation of the 6 pulses of IVCY and achieved complete remission without relapse, except patient 3. Patient 3 had a relapsed TM infection at the 18th month of follow-up, and the median titers of AIGAs detected in the serum of the patient rose to 58 321 ng/mL.

DISCUSSION

Immunodeficiency in HIV-negative patients caused by AIGAs was defined as adult-onset immunodeficiency (AOID) in 2012. In 2019, the International Union of Immunological Societies Expert Committee updated the classification of innate/primary immunodeficiencies. Adult-onset immunodeficiency associated with interferon-γ autoantibody (IGA) belongs to the autoimmune phenotype of primary immunodeficiency [12]. AIGAs have been reported to be associated with severe disseminated NTM infection in previously healthy hosts [4, 5]. However, current studies have found that AIGAs are closely related to TM infection in HIV-negative hosts, especially in the epidemic area of TM in Southwest China. AIGAs are the most common form of immunodeficiency in HIV-negative hosts infected with TM. TSM patients with positive AIGAs are more likely to have relapsed, severe, and refractory infections and are more likely to have coinfections with other opportunistic pathogens [1, 5, 6].

Specific human leukocyte antigen class II haplotypes (HLA-DRB1 16:02 and HLA-DQB1 05:02) have been reported to be explicitly associated with AIGAs, especially in Southeast Asia. Furthermore, the production of this antibody might be related to the stimulation of pathogen infection [12, 13]. However,

Table 5. T Lymphocyte and Natural Killer Cell Changes in Plasma From 5 Patients Treated With IVCY

			Treatment Duration, mo						Post-treatment Duration, mo					
…	Patient No.	Pretreatment	1	2	3	4	5	6	3	6	9	12	18	24
$CD3^+$ T lymphocyte count, /μL	1	1522	1387	729	1231	1029	821	924	1084	1478	1297	1136	1191	1204
	2	955	1829	777	671	891	811	932	1543	1021	1231	1443	1321	1211
	3	2845	3578	2467	2571	1941	1625	1731	2455	1625	2935	2030	2725	2111
	4	1941	834	582	1668	1044	917	953	1156	1234	1275	917	953	538
	5	1432	1321	1516	1093	1102	783	982	1201	1124	1342	994	1432	876
$CD4^+$ T lymphocyte count, /μL	1	676	538	354	510	478	342	453*	493	623	525	389	498	501
	2	597	900	259	321	231	342	432	558	689	652	590	602	634
	3	1268	1562	1197	1297	942	689	673	1043	689	1339	860	1558	1101
	4	1127	434	235	803	717	487	486	706	655	675	487	486	273
	5	873	653	768	621	542	412	491	665	662	764	543	698	478
$CD4^+$ T lymphocyte cell, %	1	34	28	38	31	36	30	39	35	32	30	24	31	31
	2	47	39	23	37	15	31	36	26	38	35	30	35	38
	3	35	33	38	40	32	29	28	32	32	35	32	39	42
	4	42	42	30	38	41	32	34	41	38	38	41	40	37
	5	46	39	40	37	39	35	36	35	40	36	37	38	44
$CD8^+$ T lymphocyte count, /μL	1	824	776	361	686	532	381	443	621	843	754	717	672	602
	2	332	859	393	220	473	384	453	459	432	444	465	421	390
	3	1463	1858	1172	1169	934	889	832	1311	889	1514	1124	1100	892
	4	744	348	287	735	360	415	348	402	492	524	360	415	231
	5	463	563	717	401	390	221	432	402	394	453	387	664	256
$CD8^+$ T lymphocyte cell, %	1	34	34	39	45	38	26	27	37	37	37	43	36	40
	2	24	36	29	22	23	27	28	19	22	22	22	21	22
	3	31	31	27	25	28	34	28	23	24	21	25	20	22
	4	28	32	29	24	24	25	26	24	29	31	29	23	22
	5	22	32	27	26	25	18	33	23	25	23	28	26	19
Natural killer cell, %	1	14.64	34.96	13.2	24.24	12.1	8.3	10.2	18.8	13.2	17.16	32.48	16.3	14.2
	2	15.35	13.44	9.8	17.73	13.3	11.54	13.86	8.9	30.07	22.01	9.1	7.3	15.6
	3	13.44	15.35	17.73	13.86	14.75	9.8	13.3	15.6	30.07	22.01	29.74	9.53	7.3
	4	4.23	9.78	25.72	14	7.8	15.3	12.9	18	16.03	12.3	38.1	11.8	9.3
	5	21.1	10.3	36.71	12.4	15.2	11.2	9.93	17.4	19.2	14.5	14.3	12.5	16.21
Natural killer cell, /μL	1	223	485	96	298	125	68	94	204	195	223	369	194	171
	2	147	246	76	119	119	94	129	137	307	271	131	96	189
	3	382	549	437	356	286	159	230	383	489	646	604	260	154
	4	82	82	150	2342	81	140	123	208	198	157	349	112	50
	5	302	136	557	136	168	88	98	209	216	195	142	179	142

Normal range: $CD3^+$ T lymphocyte count: 690–254/μL; $CD4^+$ T lymphocyte count: 410–1590/μL; $CD4^+$ T lymphocyte cell: 30.1%–40.4%; $CD8^+$ T lymphocyte count: 190–1140/μL; $CD8^+$ T lymphocyte cell: 20.7%–29.4%; natural killer cell: 9%–15%.

Abbreviation: IVCY, intravenous cyclophosphamide.

The 6-month $CD4^+$ T lymphocyte count compared with pretreatment ($P < .05$)

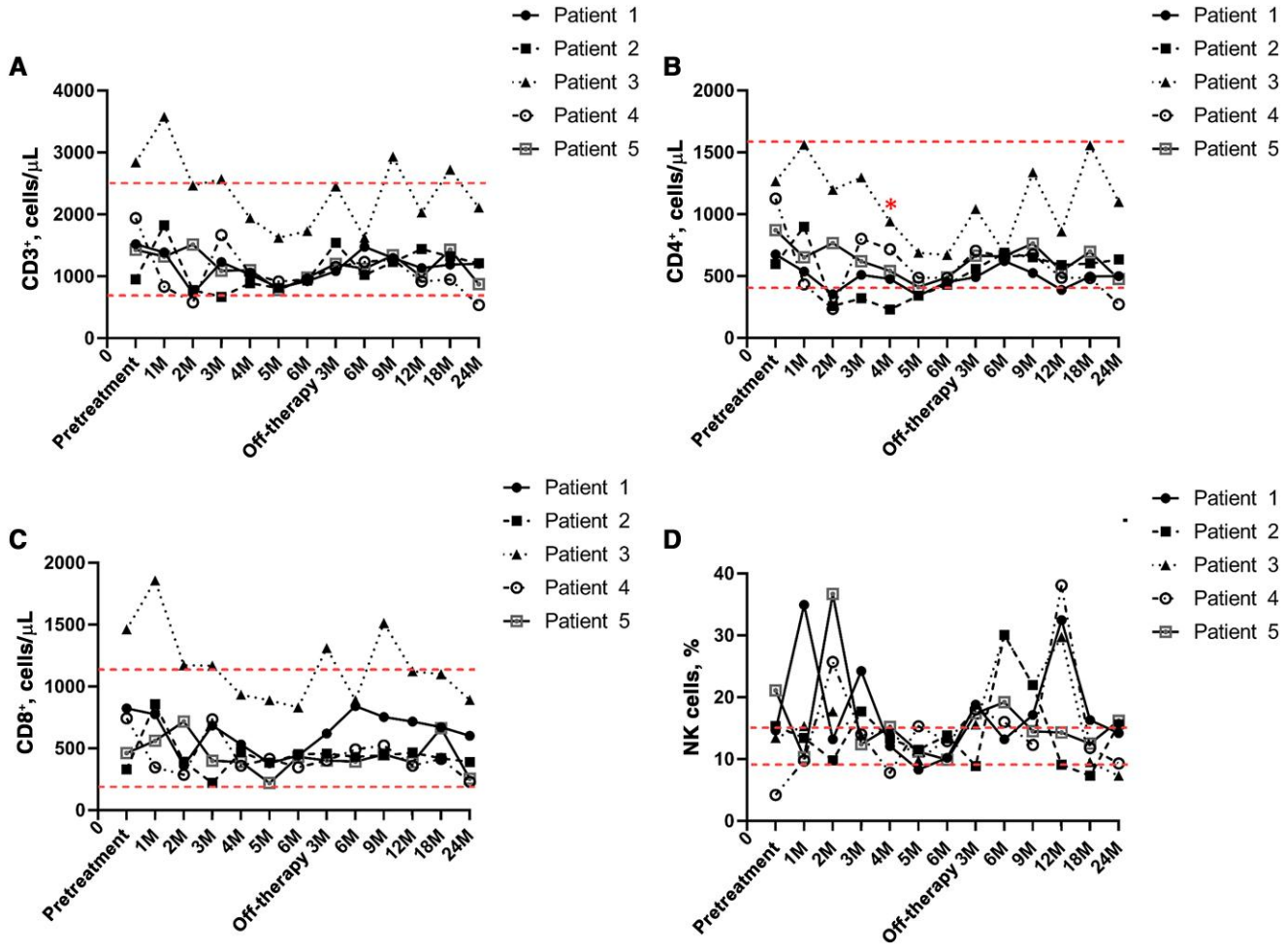

Figure 3. T lymphocyte and natural killer cell changes in plasma from 5 patients treated with IVCV: $CD3^+$ T lymphocyte count (*A*), $CD4^+$ T lymphocyte count ($P < .05$) (*B*), $CD8^+$ T lymphocyte count (*C*), and natural killer cell (*D*) decreased after completion of IVCY therapy. All the relevant laboratory values of lymphocytes gradually increased after IVCY therapy. Abbreviations: IVCY, intravenous cyclophosphamide; NK, natural killer.

the relationship among the expression of HLA-DRB1 16:02 and HLA-DQB1 05:02, pathogenic species, and AIGA titers remains unclear. Studies have demonstrated that AIGAs target the binding activity of synthetic IFN-γ peptides (amino acid residues 121–131) in patients, including inhibition of IFN-γ-mediated immunocidal effects of macrophages against nontuberculous mycobacteria, and IFN-γ-regulated production of chemokines and cellular inflammatory factors is also blocked [14]. However, one investigator found that stimulating serum-intervened peripheral blood mononuclear cells from AIGA-positive patients using recombinant human IFN-γ (EE-IFN-γ) with a deletion in the P121–131 region of the C-terminus of IFN-γ EE-IFN-γ, while stimulating pSTAT1 and IL-12 production, restored only 40% of normal levels. Meanwhile, clinical attempts at immunomodulatory therapy using recombinant human IFN-γ to neutralize AIGAs did not improve patient prognosis [15, 16]. That AIGAs neutralize and block IFN-γ was just one of the reasons for immunodeficiency, and there are other more important immunomodulatory mechanisms of AIGAs that affect the impaired clearance of pathogens by the organism. Therefore, we suggested that not only the AIGA titer but also its combined neutralizing effect of the antibodies should be monitored for a more intuitive judgment in AIGA-positive patients infected with TM. AIGA measurement can use direct titers or IFN-γ neutralization. Measuring directly is more convenient and more widely accepted [1, 3, 6, 17]. But there is still no universally accepted standard for positivity of AIGA. In our study, all 5 patients had at least 1 relapse even with aggressive antifungal therapy. Patient 1 had 3 relapses during a 19-month course of TM infection. Four of the 5 patients had coinfections with other opportunistic pathogens, the most common of which was NTM infection. Before IVCY therapy, inflammatory markers were tested in 5 patients, showing an increase in ESR, CRP, procalcitonin, and white blood cell count. Moreover, high titers of AIGAs in serum also indicated that the patients remained in a state of persistent infection. Therefore, in the presence of

Table 6. B Cell and Serum Immunoglobulin Changes in 5 Patients With IVCY

			Treatment Duration, mo						Post-treatment Duration, mo					
…	Patient No.	Pretreatment	1	2	3	4	5	6	3	6	9	12	18	24
$CD19^+$ B cell, %	1	7.08	7.62	8.9	12	5.2	7.4	6.4	12.07	12.3	10.92	9.08	10.8	13.1
	2	10.2	7.2	9.2	8.1	7.3	6.9	9.1	9.9	10.9	8.9	11.9	10.9	12.1
	3	8.22	7.12	7.66	6.55	6.68	5.62	8.3	7.95	3.52	7.23	8.99	13.4	11.6
	4	21.86	15.92	9.65	7	10	8.1	6.5	10	4.99	11.2	17.5	10.7	9.89
	5	13.2	10.2	7.13	6.32	6.22	5.45	6.01	6.54	8.88	7.49	8.9	9.09	9.98
$CD19^+$ B cell, /μL	1	108	106	65	148	54	61	59	131	182	142	103	129	158
	2	97	132	72	54	65	56	85	153	111	110	172	144	147
	3	234	255	189	168	130	91	144	195	57	212	183	365	245
	4	424	133	56	118	104	74	62	116	62	143	160	102	53
	5	189	135	108	69	69	43	59	79	100	101	88	130	87
IgG, g/L	1	19.2	19.9	20.47	25.97	23.85	24.05	18.21	24.05	25.26	26.53	35.81	23.85	24.04
	2	12.61	11.93	11.14	10.75	12.9	9.9	8.9	10.75	12.9	14.2	11.2	9.7	10.7
	3	12.1	12.45	12.65	13.13	10.97	12.45	9.45	9.45	10.57	10.58	12.02	43.43	37.02
	4	10.77	10.81	10.54	9.86	9.89	8.21	7.54	10.73	9.9	11.98	13.46	14.58	17.79
	5	15.79	16.12	14.17	15.52	13.39	14.22	13.7	15.3	15.92	16.34	15.98	14.38	15.34
IgA, g/L	1	1.47	1.55	1.58	1.86	1.76	1.52	1.43	1.53	1.84	2.25	2.64	2.11	1.98
	2	1.67	1.7	1.69	1.54	1.41	1.21	1.09	1.54	1.67	1.65	2.43	2.11	1.98
	3	1.62	1.54	1.59	1.63	1.57	1.58	1.45	1.45	1.38	1.21	1.56	2.11	1.86
	4	1.5	1.71	1.66	1.5	1.49	1.34	1.31	1.42	1.27	1.49	1.53	1.57	1.63
	5	2.3	2.11	2.34	2.53	2.1	2.04	1.93	1.98	2.11	2.53	2.31	2.22	2.32
IgM, g/L	1	1.21	1.3	1.14	1.02	0.93	0.96	0.89	1.09	1.34	1.66	1.42	1.23	1.19
	2	1.07	1.17	1.27	1.2	1.01	1.04	0.91	1.11	1.21	1.23	1.29	1.22	1.17
	3	1.77	1.76	1.76	1.8	1.65	1.81	1.48	1.55	1.71	1.71	1.9	1.65	1.27
	4	1.82	1.9	1.87	1.57	1.55	1.48	1.4	1.73	1.54	2.36	2.03	2.26	3.45
	5	1.52	1.56	1.46	1.43	1.29	1.54	1.62	1.47	1.57	1.55	1.34	1.45	1.62

Normal range: $CD19^+$ B cell: 9.02%–14.1%; IgG: 8–18.0 g/L; IgA: 2.01–2.69 g/L; IgM: 0.84–1.32 g/L.

Abbreviations: Ig, immunoglobulin; IVCY, intravenous cyclophosphamide.

high-titer AIGAs in serum, it is difficult to eradicate intracellular pathogens such as TM even with maintenance therapy with antimicrobials, and it is of great significance to start a therapeutic regimen that can effectively reduce AIGA titers to better control the infection in patients at this time.

A previous study reported that anti-CD20 monoclonal antibody therapy achieved good clinical efficacy in patients with positive AIGAs who were coinfected with refractory infections [5, 7, 18]. However, this high-cost treatment is unlikely to be considered in resource-limited settings and has not been proven to be effective in all patients in the literature. The use of an immunosuppressant with cyclophosphamide has been reported in the literature to be effective in reducing AIGA titers of patients with AIGA-associated NTM infection, but no clinical study data are available in patients with AIGA-associated TM infection. Cyclophosphamide is an alkylating agent that reduces the production of pathogenic autoantibodies by depleting B cells and affecting the differentiation of T cells. Currently, IVCY is used as a standard regimen for treatment, especially for for severe autoimmune and autoinflammatory diseases, such as systemic lupus erythematosus and antineutrophil cytoplasmic antibody-associated primary vasculitis syndrome [19, 20]. Previous studies have found no significant differences between 6 monthly pulses of IVCY and pulses of low-dose IVCY twice a month in the treatment of lupus nephritis [21, 22]. In our study, the serum AIGA titers of 5 patients decreased significantly during IVCY therapy, and the AIGA titers after the third pulse of IVCY were significantly different from those before IVCY. During pulsed IVCY therapy, the T-lymphocyte count, B-lymphocyte count, immunoglobulin concentration, and other related indicators decreased, but all increased after completion of IVCY therapy. Therefore, this was only a temporary decrease, and the T-lymphocyte count was still within the normal range during the decline. With the decline in AIGA titers, the related inhibitory function improved, which restored the body's immune killing function against TM infection. At this time, the combination of antifungal therapy increased eradication of intracellular TM, maybe completely eliminating intracellular pathogens and reducing recurrence. After the fourth pulse of IVCY, the AIGA titers of the 5 patients were relatively stable, with a slight decline. Moreover, considering the adverse side effects of cyclophosphamide, including suppression of T cells and B cells, severe nausea, vomiting, etc., we attempted to discontinue therapy after completing 6 pulses of IVCY and continued to use antibiotics for maintenance therapy, achieving good clinical prognoses.

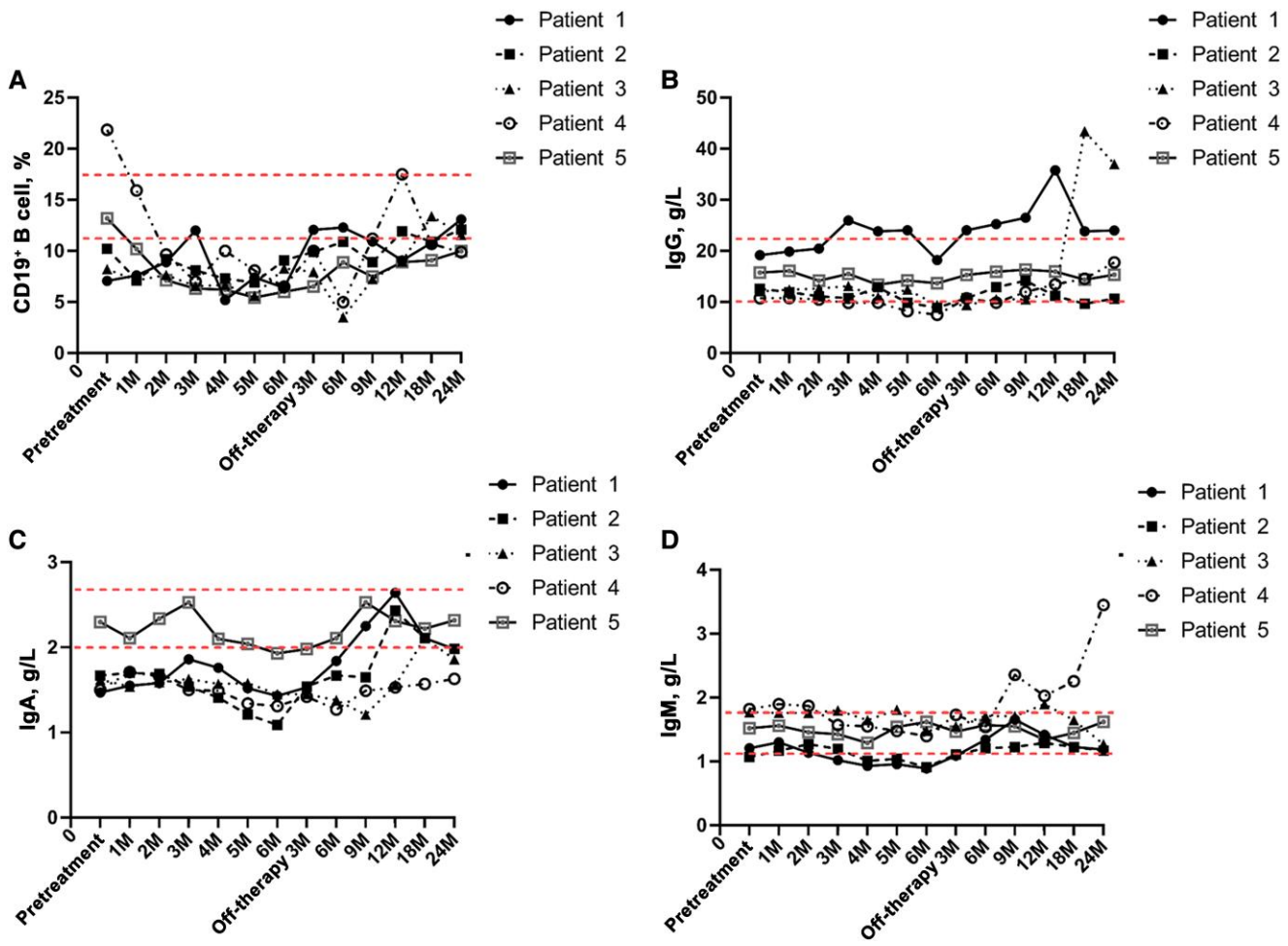

Figure 4. B cell and serum immunoglobulin changes in 5 patients with IVCV: The CD19⁺ B cell count (*A*), serum IgG (*B*), IgA (*C*), and IgM (*D*) decreased after completion of IVCY therapy. All of these titers gradually increased after IVCY therapy. Abbreviations: Ig, immunoglobulin; IVCY, intravenous cyclophosphamide.

Table 7. Clinical Data Before and After Completion of IVCY Treatment in 5 Patients

…	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
…	Before	After	Before	After	Before	After	Before	After	Before	After
WBC, $\times 10^9$/L	10.56	8.84	10.03	5.51	9.66	9.51	6.58	7.66	9.85	8.0
Neutrophil, $\times 10^9$/L	7.87	5.64	7.79	3.72	4.7	5.7	3.35	6.26	6.7	5.03
Lymphocyte, $\times 10^9$/L	1.62	1.94	1.49	1.12	3.6	2.31	2.53	0.83	2.32	1.98
Hemoglobin, g/L	126	137	136	129	111	109	83	90.7	141	136
Platelet, $\times 10^{12}$/L	126	132	231	212	276	209	298	231	298	128
CRP, mg/L	105.7	15.94.	32.5	2.59	16.2	28.7	19.2	2.1	44.7	9.93
ESR, mm/H	49	40	37	27	29	15	47	7	60	66
Procalcitonin, ng/mL	0.16	0.053.	0.26	0.083	0.19	0.066	0.55	0.05	0.88	0.08
Tbil, μmol/L	11.9	13.3	7.6	7.7	8.2	7.3	10.1	10.4	4.3	4.5
Albumin, g/L	36.3	28.1	49.3	36.4	34.3	37.3	35.6	38	36.4	43.9
Globulin, g/L	45.8	44.4	33.3	28.9	37.4	31.8	24.1	24.8	38.4	32.8
AST, U/L	20	27	31	28	12	12	26	28	38	21
ALT, U/L	24	22	43	56	16	18	23	32	36	35
Creatinine, μmol/L	93	90	68	60	66	78	51	53	87	85

Normal range: WBC: 4–10 $\times 10^9$/L; neutrophil: 2–6.5 $\times 10^9$/L; lymphocyte: 1.1–3.2 $\times 10^9$/L; hemoglobin: 135–175 g/L; platelet: 100–300 $\times 10^{12}$/L; CRP: <5 mg/L; ESR: 0–20 mm/H; procalcitonin: <0.05 ng/mL; Tbil: 3.4–20.5 μmol/L; albumin: 40–55 g/L; globulin: 20–40 g/L; AST: 15–45 U/L; ALT: 9–60 U/L; creatinine: 59–104 μmol/L.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Tbil, total bilirubin; WBC, white blood cell.

The autoimmune antibodies of patients 2, 4, and 5 declined variously or even became negative at the end of therapy. Sweet's syndrome in patient 2 was also improved at the end of therapy. In previous studies, when patients infected with TM or NTM had positive AIGAs and Sweet's syndrome or ANA 1:320, glucocorticoids were added to the treatment but were not effective in decreasing the AIGA titers [23–25]. Five patients successively discontinued antimicrobial therapy and were then followed up for 24 months. After 3 months of follow-up, the AIGA titers of all patients started to increase gradually. There was a significant difference between AIGA titers after 12 months of follow-up and those after completing 6 pulses of IVCY therapy, which is consistent with prior reports. Five patients successively discontinued TM therapy between 3 and 9 months (median, 4.6 months) after completion of IVCY, and only patient 3 had a relapsed TM infection 18 months after the end of IVCY. Patients still had multiple relapses even with long-term aggressive TM therapy before receiving IVCY; comparatively, the course of TM therapy was significantly shortened after completion of IVCY therapy. We suggested that patients should remain on TM therapy for 6 months after IVCY discontinuation to reduce their physical and economic burdens.

There were some limitations to our study. First, we did not have a large patient population, and a control study was not conducted due to the small sample size. Second, there was no comparative study on the timing of starting IVCY and the course of IVCY, and further studies based on large samples are still needed to determine the timing of initiating IVCY therapy and its dosage, interval time, and course. Third, there is a lack of further basic immunological research to identify other potential antibody-producing cells to further explain the pathogenesis of the disease. Finally, $CD14^+$ monocytes should be measured in these patients, as $CD14^+$ monocytes have the highest responsiveness to IFN-γ. Cyclophosphamide can deplete T cells and affect the differentiation of T cells, and we have been studying the relationship between TM and $CD4^+$ T cells, so we chose to pay attention to $CD4^+$ cells in this study.

CONCLUSIONS

In conclusion, this study performed multisample and exploratory IVCY therapy for patients with AIGA-associated TM infection in the TM epidemic area of mainland China for the first time, and all patients were followed for a long period. In addition, this study demonstrated that pulses of short-term and high-dose IVCY could effectively reduce serum AIGA titers, caused no significant side effects, and may reduce TSM recurrence. Currently, the mechanism of AIGA production is unclear; thus, a pulse IVCY regimen has been shown to have certain clinical value for refractory TM infection at doses of 0.8–1.0 mg/m^2 every 3–4 weeks for a total of 6 cycles, which may serve as a reference standard for the treatment of patients with AIGA-associated TM infections, especially in resource-limited countries.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. All authors: no reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Author contributions. W.Z. and J.Z. contributed to the study conception and design. W.Z., G.F., and M.T. performed the study. S.T. and M.Y. performed data collection and analysis. W.Z. and M.T. contributed to writing and data interpretation. All authors agreed on the journal to which the article would be submitted. All authors reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage. All authors agreed to take responsibility and be accountable for the contents of the article.

Data sharing. All the data are fully available without restriction.

Ethical approval. This study was approved by the Faculty of Medicine at the First Affiliated Hospital of Guangxi Medical University (2021 [KY-E-262]). All patients provided written informed consent. The study was carried out in accordance with the principles of the Declaration of Helsinki. The first author vouches for the completeness and accuracy of the data and for the fidelity of the study to the protocol.

Consent for publication. Signed consent was obtained for the publication of the case details from the participants.

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