



# Safety of lymphocytes immunotherapy during the COVID-19 outbreak in Wuhan, China

Tianli Chang<sup>1</sup> · Su Song<sup>2</sup> · Donghui Huang<sup>1,2</sup> · Ping Su<sup>1,2</sup> · Xianjin Xiao<sup>1,2</sup> · Honggang Li<sup>1,2</sup> · Aihua Liao<sup>1,2</sup> · Wenpei Xiang<sup>1,2,3</sup>

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## Abbreviations

COVID-19	Coronavirus Disease-2019
SARS-CoV-2	2019 Novel coronavirus
RM	Recurrent miscarriage
LIT	Lymphocyte immunotherapy

Dear editor,

We read with great interest the informative review article by Cavalcante et al. [1], “Lymphocyte immunotherapy in the treatment of recurrent miscarriage: systematic review and meta-analysis.” We pay close attention to the “Safety of immunotherapy with lymphocytes” in the review. Immune dysregulation was an important aspect among multiple etiologies of miscarriage. Lymphocyte immunotherapy was a therapeutic method gained acceptance for clinical application for women suffering from alloimmune recurrent miscarriage. Paternal lymphocyte immunotherapy was attributed to the high expression of anti-paternal cytotoxic antibodies (APCAs), anti-idiotypic antibody (Ab2), mixed lymphocyte reaction blocking antibody (MLR-Bf) and blocking antibody (BAb), these antibodies increased the resistance to the

compatibility of human leukocyte antigens (HLA) between father and mother and protected the fetus from toxic effects of the mother’s immune system [2, 3], suppressed the over-activity of natural killer (NK) cells and T helper-1 (Th-1) pattern of cytokines to induce maternal immune tolerance to fetal allotransplantation in women with alloimmune cause of recurrent pregnancy loss [4, 5]. The objective of this clinical follow-up is to clarify the security of lymphocytes immunotherapy during the COVID-19 outbreak in Wuhan, China and to provide guidance for subsequent active immunotherapy during the COVID-19 outbreak in the future.

## Participants

To contribute data, our center had to be able to enroll patients treated with allogeneic leukocyte immunization following uniform standards. The inclusion criteria for participants included: (1) the diagnosis was “alloimmune recurrent miscarriage”; (2) alloimmune antibody “blocking antibody” was negative; (3) autoimmune antibody “anti-nuclear antibody, antineutrophil cytoplasmic antibody, rheumatoid factors” were negative; (4) chromosome of couples was normal; and (5) patients were conducted LIT during November 1, 2019 to January 17, 2020 in Center of Reproductive Medicine, Tongji Medical College, Huazhong University of Science and Technology. Exclusion criteria included: (1) patients with endocrine system diseases were excluded including but not limited to luteal phase deficiency, thyroid disorder, polycystic ovarian syndrome, premature ovarian failure, hyperprolactinemia and diabetes; (2) genital abnormalities such as genital malformation, myoma of uterus, intrauterine adhesion, tubal adhesion, uterine cervical incompetence; and (3) patients with autoimmune disease.

Tianli Chang and Su Song contributed equally to this work.

✉ Wenpei Xiang  
wpxiang2010@gmail.com

- <sup>1</sup> Institute of Reproductive Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
- <sup>2</sup> Center of Reproductive Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
- <sup>3</sup> Institute of Reproductive Health, Center of Reproductive Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

## The study plan

Through the case management system in the Center of Reproductive Medicine, Tongji Medical College 203 patients were selected as subjects. Clinical 4-month follow-up were conducted every other week by telephone during February, 2020 to May, 2020. We received 187 complete pieces of feedback (187/203). The follow-up information was demonstrated in Table 1.

## Discussion

Safety of LIT for recurrent miscarriage has not been entirely investigated, although most of the researchers have claimed no side effects on mother and the infants. However, studies regarding the safety of LIT showed that there was a possibility of maternal complications about autoimmunity and the virus susceptibility such as human immunodeficiency viruses, cytomegalovirus and hepatitis virus was increased [1]. Therefore, the risk of infectious disease transmissions was the point of concern. The SARS-CoV-2 infection has become an urgent public health challenge all over the world.

Most of the infected people could recover after 2–3 weeks. However, once infected patients develop severe acute respiratory distress syndrome (ARDS), more than 10% of patients may deteriorate within a short time and die from multiple organ failure [6]. Recently, a study found that the hyperfunction of CD4 + and CD8 + T cells was associated with the pathogenesis of extremely severe SARS-CoV-2 infection [7]. Th1 and Th2 cells are the main subgroups of fully differentiated CD4 positive T cells. Some noteworthy alterations of T-lymphocyte after LIT, including reduction in the Th1/Th2 ratio increased CD4 +/CD8 + ratio and decreased CD8 + T cell percentage, made a combined effect on regulation of maternal tolerance and prevention of fetus rejection, which could consequently increase the pregnancy success [8, 9]. However, whether these changes in the immune system were predisposing factors to SAR-COV-2 infection was not clear. The demographic characteristics in Table 1 indicated that all the patients were not suffered from COVID-19 during the COVID-19 outbreak in Wuhan while Wuhan's overall infection rate is 0.55% (50,340/9,080,000, data cutoff on June 24, 2020). It seemed that lymphocyte immunotherapy was safety for all the patients who had a residential history of Wuhan or potential COVID-19 exposure in the early stage of epidemic of Wuhan, while patients' awareness of protection might

**Table 1** Demographic characteristics of study participants (*n* = 187)

Characteristics	Lymphocyte immunotherapy (LIT)
Residence	Wuhan
Age, (years) (mean ± SD)	31.35 ± 0.3418
Blocking antibody positive conversion*, <i>n</i> (%)	124 (66.31%)
Pregnancy, <i>n</i> (%)	70 (37.4%)
Type of Lymphocyte immunotherapy (LIT)	Paternal LIT
Therapeutic schemes	2–8 times before the planned pregnancy with 2 weeks of intervals
Time of infusion within 10 weeks*, <i>n</i> (%)	
≤ 4 times with 2 weeks of intervals	89 (47.5%)
4 times with 2 weeks of intervals	96 (51.4%)
≥ 4 times with 2 weeks of intervals	2 (1.1%)
Dose of lymphocyte per treatment	2–5 × 10 <sup>7</sup> lymphocyte/mL (NS)
Injection site	Intradermal injection of the forearms
Immunosuppressive medication history, <i>n</i> (%)	
Prednisone	18 (9.6%)
Dexamethasone	3 (1.6%)
Cyclosporine	2 (1.1%)
Complications	
Autoimmune disorders (Hyperthyroidism, Hepatitis, Purpura, Systemic lupus erythematosus, Rheumatoid arthritis, Chronic urticaria), <i>n</i> (%)	1**
Alloimmune disorders (Viral Transmission, Flu-like symptoms, Transfusion reaction), <i>n</i> (%)	0
Diagnosis of COVID-19, <i>n</i> (%)	0

\*The antibody detection and treatment were discontinued due to city lockdown

\*\*One patient suffered from chronic urticaria when she was at 11 gestational weeks. Oral low-dose cyclosporine and antiallergic drugs were applied for 2 weeks

not be sufficient at that time. In consideration of factors such as insufficient sample size, effectiveness of protective measures and inconsistency of exposure risk, we need long-term follow-up, multicenter trials with larger sample size, case–control or prospective studies to confirm the security and risk of lymphocyte immunotherapy.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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