CASE REPORT

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Introducing the tolerogenic macrophage therapy as an alternative approach to manage systemic lupus erythematosus: a case series

Terawan Agus Putranto[1,2*], Djoko Wibisono[2], Nyoto Widyo Astoro[2], Martina Lily Yana[2], Endra Tri Prabowo[2], Denny Irwansyah[2], Nurhadiyanta[2], Yudo Rantung[1], Taruna Ikrar[1,2,3], Fred Fandrich[2]

ABSTRACT

Introduction: Systemic Lupus Erythematosus (SLE) has been quite an enigma in medicine. The possibility of the host own defense mechanism attacking itself is still quite difficult to understand. Patients who suffer from this disease tend to have a problem in their qualities of life, especially as the majority affect female in their productive ages. Conservative therapy to manage this disease is widely developed and implemented. Since the known therapies have several side effects and limitation, a need to develop a new strategy that can re-establish the "tolerance" mechanism of our immune system is increasingly needed. Immunotherapy is already a promising field in the strategy against autoimmune cases. In our facility, we developed immunotherapy called ToM (Tolerogenic Macrophage) which similar to Mreg (Regulatory Macrophage) in order to utilise the "tolerance" ability of this immune apparatus.
Case: In this study, we present 2 cases of female patients who suffer from SLE, which underwent ToM Therapy in our Cellcure facility in RSPAD Gatot Soebroto Jakarta-Indonesia. After the procedure the patient was monitored one month and one year. Clinical and control parameter such as ANA (IF) and ANA profile was examined again in both patients to measure the effect of this therapy**.** The ANA titer and the titer of specific antibodies such as dsDNA, Nucleosomes and Histones results show significant reduction, accompanied by the improvement of the symptoms.
Conclusion: ToM Therapy seems to have a good efficacy as immunotherapy for SLE. Further study needed to establish this approach.

Keywords: Tolerogenic Macrophage, Systemic Lupus Erythematosus, Immunotherapy
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[1]The Indonesia Army Medical Science Institute, Jakarta, Indonesia
[2]Department of Cellcure, RSPAD Gatot Soebroto, Jakarta, Indonesia
[3]Pacific Health Sciences University, California, United States of America

*Correspondence to:
Terawan Agus Putranto; Department of Cellcure, RSPAD Gatot Soebroto, Jl.Abdul Rahman Saleh, No.24, Central Jakarta 10410, Indonesia.
terawan@rspadgs.net

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INTRODUCTION

Klemperer, Pollack and Baehr in 1941, were among the first who described the term systemic lupus erythematosus (SLE) as one of the Connective Tissue Disease.[1] In general, it is characterised by the loss of tolerance toward the host or self-antigens and the induction of destructive immune responses which eventually leads to tissue damage. Until now, most of the patients who suffer from autoimmune diseases are treated with immunosuppressive drugs that induce a generalised immune suppression, which has the possibility to increases the risk of infectious diseases and cancer.[2]

For all we know, the autoimmune diseases are emerging worldwide problems which affect the daily life of the diseased. It is widely known that in majority SLE tend to affect female, a study shows that SLE affects one out of every 700 white females and one out of every 245 black females. In the adult population, females are affected nine to 13 times more often than males, while in paediatrics population, males are affected two to three times more often. The peak age of onset is around second to fourth decades of life.[3] Apparently, this case is higher in African, Asian, and Hispanic population rather than in white population and also apparently tend to develop lupus earlier and have more severe and more active form of the disease, with long-term damage and increased mortality.[4,5]

The mechanism of the disease remains unclear although several theories have been developed, it involves a combination of the complex interaction between gene susceptibility, hormonal influences, and specific environmental triggers which induce autoantibody production, formation of immune complexes, activation of T-lymphocytes, dysregulation of apoptosis, and production of proinflammatory cytokines.[6] In general the pathogenesis of SLE can be divided into 2 stages. First, loss of tolerance to self-antigens

and generation of auto-antibodies. The second is the pathogenic autoantibodies and immune complexes that cause inflammation and disease.[7] This autoimmune response could originated from the increased rate of apoptosis in SLE that will increase the chance of intracellular antigens leakage that may either trigger an autoimmune response or participation in the formation of immune complexes. Several studies showed that UV light especially UVB is an essential trigger in many patients with SLE. There is good evidence that UV exposure to the skin will alter the location and/or the chemistry of DNA that will probably enhance their immunogenicity.[8] By inducing the apoptosis process in human keratinocytes, leading to the formation of clusters containing both nuclear and cytoplasmic antigens.[9,10] Under optimal physiologic condition, apoptotic cells are engulfed by macrophages in the early phase of apoptotic thus avoid trigger inflammation or immune response. Recent studies support this theory as the clearance of apoptotic cells by macrophages in patients with SLE are impaired.[11] However, the primary reasons for this is still unknown.

ANA (anti-nuclear antibodies) is widely recognised as one of the SLE-related biomarkers. It is included as key biomarker and the entry criterion for the EULAR–ACR SLE classification.[12] This specific autoantibody can assist in the diagnosis and determine the prognosis of an autoimmune disease.[13,14] Ana has shown a quite good performance as a blood-based biomarker.[12,15] It has the ability to bind to and destroy the structures in the cell and subcellular nucleus as well as organelles, including cell surface, cytoplasm, nucleus and nucleolus. If the ANA result of the test is positive, ANA profile test can be performed to determine the specific subtype of antibodies.[16,17] The ANA-profile test consists of set of different antibodies that target nuclear and cytoplasmic antigens. From where these antigens are present in all nucleated cells and have a role in transcription or translation, in the cell cycle or as structural proteins.[18] The source of the appearance of these autoantibodies that presents in SLE is the insufficient clearance of cell fragments from dying cells, which makes autoantigens available for the immune system.

The main goal to achieve the most efficient and best results of SLE therapy is focused on the optimal outcome which can be seen as improvement in disease activity, prevention of damage and disability, and a reduction in mortality rate.[19] As the origin for SLE development is, as yet still studied, the treatment of the disease is mainly aimed at the suppression of symptoms and autoimmune inflammatory response.[20] Management of SLE patients usually begins with the basic recommendations of prevention such as avoidance to the prolonged sunlight exposure and counselling for modifiable risk factors such as smoking. The utilisation of corticosteroids (CS) in SLE management began in the 1950s and was a major important therapeutic breakthrough.[21] Corticosteroids acts by controlling the inflammation associated with lupus and suppress the immune system. As times went by, corticosteroids stand as the most effective short-term therapy for SLE.[22] The antimalarial drug hydroxychloroquine was also found to exert protective effect on survival point of view. In addition to controlling flares and disease activity, antimalarial drugs usually have anti-inflammatory and antithrombotic properties. Therefore, it is added to the medical regimen to reduce the dosages of other required medications. Another recent course of therapy that developed and chosen for SLE includes belimumab (10 mg/kg every 4 weeks) which approved by the US Food and Drug Administration and European Medicines Agency in 2011.[23,24] Belimumab acts by inhibits the B-lymphocyte stimulator, a pathological factor in patients with SLE.[25–27]

Besides the mentioned conservative therapy of SLE, in recent development a new therapeutic strategy starts to emerge, it is called immunotherapy which basically utilising the patient own immune system to manage the affected systems caused by the disease. Professional Antigen-presenting cells such as Dendritic cells (DC), macrophages and B-cells critical for initiating, maintaining and shaping the T-cell mediated immune responses.[28,29] This tolerance ability naturally demonstrated in the gastrointestinal tract which is in contact with a vast amount of antigens, including a diverse commensal microbiota, food antigens and also potentially pathogenic microbes. In the gastrointestinal system, the tolerance is shown against the commensal microorganisms that play important role in digestive function.[30] As effector cells of both innate and adaptive immune responses, DC, Macrophage and B-cells are central to not only maintaining protective immunity against pathogens but also preventing inflammatory intestinal immune responses against the microbiota and food antigens. Specifically, macrophage maintaining tolerance in our gastrointestinal system by constitutively producing the anti-inflammatory cytokine interleukin (IL)-10.[31,32]

So far, a wide variety of in vitro protocols based on immunotherapy has been established. Among them were the generation of immune tolerance-inducing DC or tolerogenic DC (tolDC) and regulatory macrophages (Mreg) that being

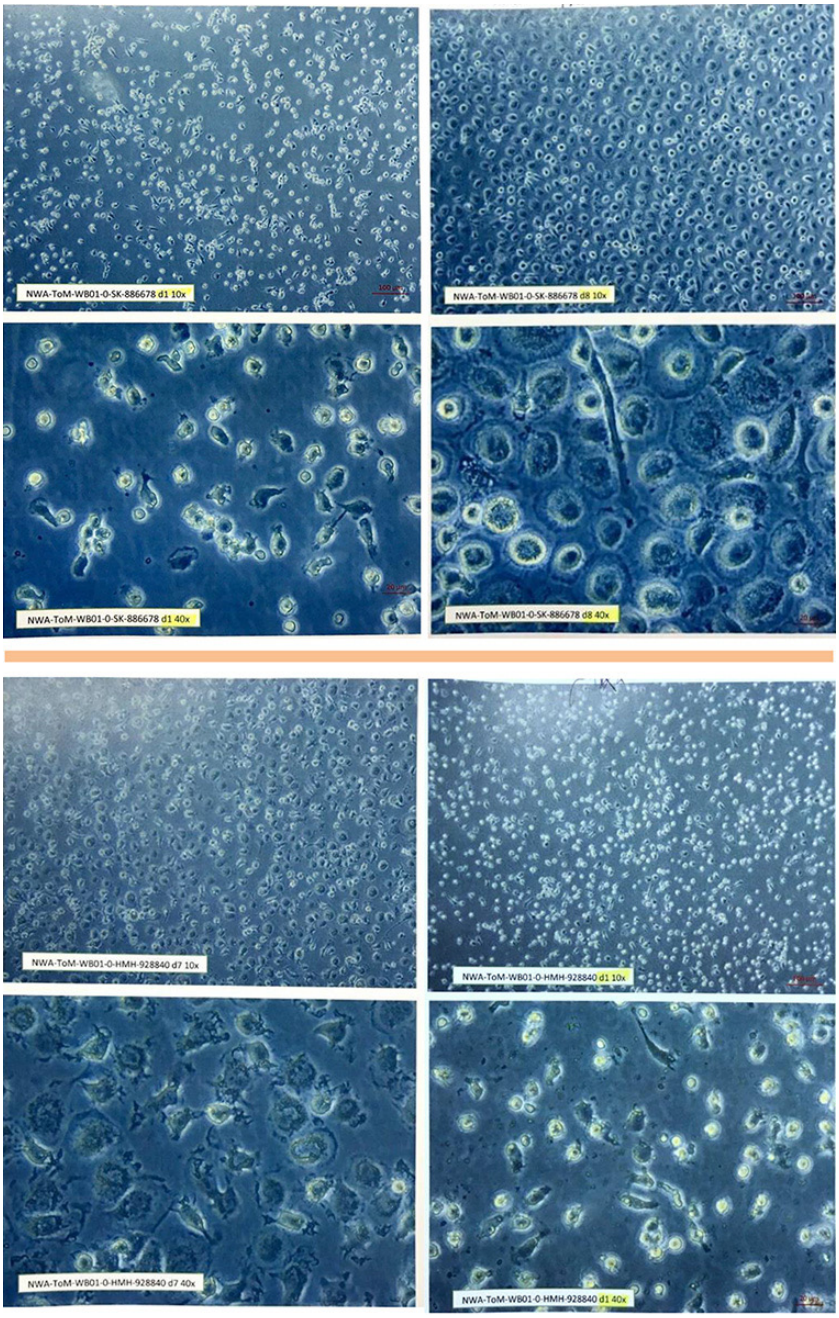

Figure 1. Macrophage morphology before culture (left) and 7 days after culture (right) for the patient in case 1 (Above) and case 2 (below).

tested in Phase I clinical trials in patients with autoimmune diseases such as type 1 diabetes, rheumatoid arthritis or Crohn's disease as well as, kidney transplantation, demonstrating in all cases that tolerogenic cell therapies are safe and well-tolerated, without relevant side effects.[33–37] This ability of tolerance in macrophage is ideal to utilise for immunosuppressive therapies, such as shown in Mreg in solid organ transplantation.[33,38] Based on these features, the main idea of tolerance immunity is a process that prevents the induction of immunity to innocuous or harmless antigens, both self and non-self antigens. In this article, we present two cases of female patient who suffers from Systemic Lupus Erythematosus which undergo the Tolerogenic Macrophage (ToM) therapy in Cellcure Facility in RSPAD Gatot Soebroto Jakarta-Indonesia.

CASE

Case 1

Forty-one-year-old female, present with several complaints including recurrent syncope, insomnia, joint pain, and spontaneous bruises. The patient vital signs are within the normal range as well as normal body mass index (BMI). The patient had a previous history of CAD (Coronary Artery Disease) which already treated with PCI (Percutaneous Coronary Intervention) and benign breast neoplasm measured around 3.4 x 4.0 cm which already treated with excision of the tumour. The patient already treated for SLE with Plaquenil (Hydroxychloroquine), vitamins D3 and Calcium supplementation, each at single daily dose. After a thorough examination by our hematologic consultant, the patient was then screened through complete blood works to measure the patient overall condition if she was suitable for this therapy. The patient also screened for previous disease, previous medical procedure, recent infection status including hepatitis and HIV, recent transfusion, recent vaccination, obstetric and gynaecological status, and recent medication. After the patient passed the first checkpoint of screening, the patient explained and asked to sign the informed consent. At the next day, the patient blood collected and cultured in our laboratory. Then the patient will be scheduled for the re-injection of the produced ToM products one week after the blood collection.

Before the ToM therapy, the patient level of ANA titer was 1:1000 (September 23rd, 2017). About a year after the therapy (October 9th, 2018), the patient came back to our facility for a routine examination, and the ANA titer decreased to 1:320. It is a quite significant regression of ANA titer value. The patient also describes the overall symptoms and their quality of life is improved significantly after the therapy.

Case 2

Twenty-years old female patient admitted to our hospital with several complaints including intermittent knee pain, hair loss, and intolerance to sun exposure which will cause erythema in her skin. No history of any previous disease, no familial history of similar symptoms, also unremarkable allergy history. Patient vital signs are within the

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normal limit at the time of admission. The ANA Profile test results before (March 15th, 2019) and one month after ToM therapy (April 25th, 2019) showed a significant reduction in the titer of specific antibodies such as dsDNA, Nucleosomes and Histones one month after the ToM therapy (suppl. fig 1).

Besides the ANA titer, we also want to show the readers the Macrophage cells morphology before and after culture process, which we used to execute the ToM Therapy (figure 1). On the left is the morphology of cultured macrophage cells prior and seven days after the culture process, before injected back into the patient's body. The cultured cells should pass several parameters checkpoint that included in our protocol, should the cultured cell passed these parameters then it can finally be allowed to be injected back into the patients through intravenous access as ToM therapy.

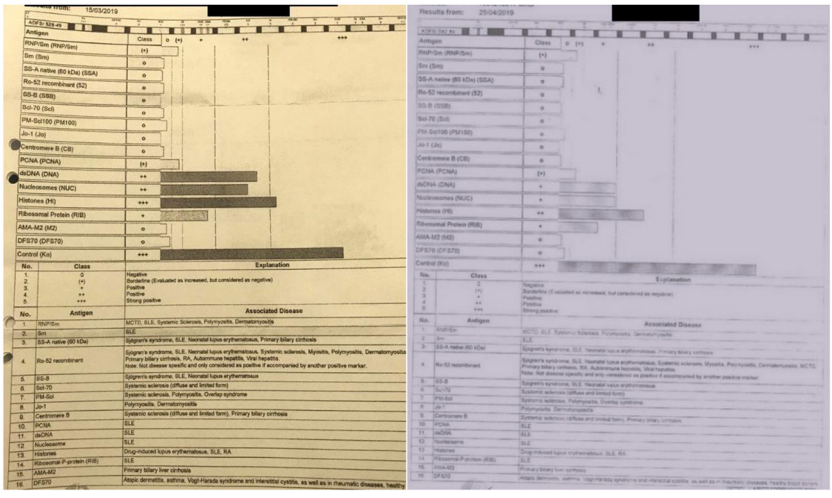
DISCUSSION

SLE is widely known tend to affect woman, especially in childbearing age. It makes SLE quite a haunting issue for the female population. Since its unclear pathomechanism, it makes the applicable therapeutic approach merely on suppressing the emerging symptoms, and preventive measures halt the disease progression. Immunotherapy itself is not an entirely new approach. Several diseases already approached with similar strategies. However, its potential was significantly supported by the emergence recent technological advance. Choosing to manage the disease in cellular level sure have the pros and cons. In these cases, we try to accentuate the applicability of "tolerance" in the macrophages, as it is the critical component in the autoimmunity against the host self-antigen. Macrophages play a major role in SLE pathogenesis, therefore by inducing its tolerance ability, we expect to see positive results.

Specific stimulating factors and signals can cause Macrophage to undergo extreme changes in transcriptional regulation and assume a specific activation state ranging from highly pro-inflammatory to anti-inflammatory in a process called Macrophage polarisation. Macrophage also influences local inflammation, the dysregulation condition of which is central to the pathology of diseases with inflammatory components, including type 1 diabetes, obesity, non-alcoholic steatohepatitis, atherosclerosis, and Crohn's disease.[39] ToM, specifically in M2c state used as therapeutic component because it is functioning as anti-inflammatory, phagocytic, and tissue remodelling. Therefore, the multiple roles of macrophage appeared to have several benefits that have potentials to be utilised as immunotherapy which proved to be useful as implicated in this study.

Macrophages itself differentiate from monocytes derived from hematopoietic stem cell and embryonic yolk sac macrophages. It exists in all vertebrate tissues and has dual functions in host protection and tissue injury, which are maintained at a delicate balance. Tissue macrophages have heterogeneous phenotypes in different tissue environments. Macrophages have the ability to ingest and degrade dead cells, debris, and foreign materials. It promotes homeostasis by responding to internal and external changes, not only as phagocytes, but also through trophic, regulatory, and repair functions within the body. They can present antigens to T cells and function as effectors for cell-mediated immunity. They are also known for affecting the development of chronic inflammatory diseases.[40,41] Different phenotypes of macrophage can mutually converted under in vitro conditions.[42–44]

This ToM therapy actually similar to the already known human regulatory macrophage (Mreg) which proved to be a promising candidate which is already in its development to be utilised as a cell-based medicinal product.[45] Basically ToM have two important properties after injected back into the patient circulatory system, these include elimination of auto-aggressive T-cells and induce lymphocytes to gain regulatory function. These regulatory cells invade the inflamed tissue components via vessels and capillaries and eliminate or regulate the activated auto-aggressive immune cells. Therefore, the inflammation and auto-aggressive response resolve. The human Mregs is different from macrophages in other activation states. The



Supp Figure 1. ANA Profile for the case 2, before (left) and after (right) ToM Therapy

difference raised from the mode of derivation, cell-surface phenotype, DHRS9 expression and potential suppressor function.[46] Human Mregs developed from macrophage colony-stimulating factor (MCSF, CSF1) which exposed to CD14+ peripheral blood monocytes.[47] Principally, the same technique are applied in our ToM therapy.[48]

In our Cellcure facility, this cellular approach mainly focused on maximising our immune system potentials, not only its immunogenic capability but also its tolerogenic capability. The whole process of ToM therapy could take around a week on average. It starts from the patient first admission, consultation and comprehensive examination performed by the physician in charge. After that, the informed consent was conducted which the physician will explain the type of proposed therapy, the reasoning and the risk and it is anticipative measures if any unwanted response could take place. After the patient signs the informed consent, the process continued with blood collections to measure the patients availability and suitability to perform this therapy. Several particular screenings are performed such as HbsAg and Anti-HIV screening test. This screening test act as suitability measurement to check if the patient own immune system is competent enough to fight the autoimmune process. After the patient passes the screening checkpoint, their white blood cells will be harvested through leukapheresis from the patient peripheral blood. These monocytes were then programmed to gain the regulatory function. This whole process is taking place in our secure and sterile laboratory in Cellcure facility. Within one week, the monocyte would be developed into their tolerogenic state. These cells later will be injected back into the patient circulation system which hopefully will diminish the over-reactive immune response to the host self-antigen.

In this study, we can see from the objective parameters such as IF ANA and ANA Profile that showed a significant reduction of the disease activity represented by the reduced titer value of IF ANA and significant reduction of several specific SLE antibodies such as dsDNA, Nucleosomes and Histones. As we know the significant levels of anti-dsDNA antibodies are considered to be confirmatory in diagnosis establishment of SLE[49,50] and the existence of histones and nucleosome in examination results have been primarily linked to drug-induced lupus.[51,52] It is shown the ToM therapy result in the decrease of the patient IF ANA value and several antibodies in ANA profile which depict subsiding activity of autoimmune process in SLE. The patient also describes that their complaints getting much better and their quality of life is improved significantly even until one year after the therapy. Even though this ToM treatment shows a positive result the authors still realise that there should be further research to be done in order to establish this treatment method as a part of treatment protocol for SLE.

CONCLUSION

Both cases showed that the unconventional approach by utilising the patient own immune arsenals especially macrophages through ToM Therapy showed a promising result. It has the potential roles in managing Systemic Lupus Erythematosus and perhaps the development of the other auto-immune disease.

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AUTHOR CONTRIBUTION

All authors have contributed equally to all process in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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CONFLICT OF INTEREST

The authors declare that there are no conflict of interests or whatsoever regarding the writings of this study.

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