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Role of nuclear factor-κB (NF-κB) on mind body interventions (MBIs) in patients with systemic lupus erythematosus (SLE)

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ABSTRACT

Mind body interventions (MBIs) are exercise that emphasizes the use of brain and body to assist the healing process and to manage symptoms in order to improve wellbeing. The MBIs are expected to be a supporting therapy for patients with autoimmune disease such as systemic lupus erythematosus (SLE), to improve patients' activities, reduce fatigue, stress, and depression. One type of MBIs that could be potentially applied in Indonesia is *latihan pasrah diri* (LPD). Studies showed that MBIs can affect the expression of pro- and anti-inflammatory mediators. Nuclear factor-κB(NF-κB) is a transcription factor that controls gene expression related to many physiological responses including inflammation, proliferation, cell differentiation, and apoptosis. NF-κB can be activated through canonical and alternative pathway. This literature review aimed to identify the role of NF-κB as consequence of practicing MBIs in SLE patients. We searched for relevant publications in the MEDLINE/Pub Med and Google Scholar with no date restriction. This review revealed that abnormal NF-κB could mediate autoimmune condition in SLE pathogenesis. MBIs are expected to be a supportive treatment that can help to control NF-κB expression in SLE patients. LPD as an Indonesian original MBI is expected as a suitable techniques that can be applied in patients with SLE in Indonesia. Further studies on the effect of LPD on NF-κB expression in patients with SLE need to be further explored.

ABSTRAK

Intervensi pikiran-tubuh (IPT) adalah latihan yang menekankan penggunaan otak dan tubuh untuk membantu proses penyembuhan serta untuk mengelola gejala dan meningkatkan kesejahteraan hidup. Intervensi pikiran-tubuh diharapkan menjadi terapi pendukung untuk pasien dengan penyakit autoimun seperti *systemic lupus erythematosus* (SLE), untuk meningkatkan aktivitas pasien, mengurangi kelelahan, stres, dan depresi. Salah satu jenis IPT yang berpotensi diterapkan di Indonesia adalah latihan pasrah diri (LPD). Penelitian menunjukkan bahwa IPT dapat mempengaruhi ekspresi mediator pro-dan anti-inflamasi. *Nuclear factor*-κB (NF-κB) adalah factor transkripsi yang berperan mengontrol ekspresi gen yang terkait dengan banyak respon fisiologis tubuh termasuk peradangan, proliferasi, diferensiasi sel, dan apoptosis. NF-κB dapat diaktifkan melalui jalur kanonik dan alternatif. Tinjauan pustaka ini bertujuan untuk mengidentifikasi peran NF-κ Bakibat praktek IPT pada pasien SLE. Publikasi yang relevan di MEDLINE/PubMed dan Google Cendekia tanpa batasan tanggal dikumpulkan. Ulasan ini mengungkapkan bahwa NF-κB yang abnormal dapat memediasi kondisi autoimun dalam patogenesis SLE. IPT diharapkan menjadi pengobatan suportif yang dapat membantu mengendalikan ekspresi NF-κB pada pasien SLE. LPD sebagai IPT asli Indonesia diharapkan sebagai teknik yang cocok yang dapat diterapkan pada pasien SLE. Studi lebih lanjut tentang efek LPD pada ekspresi NF-κB pada pasien SLE perlu dieksplorasi lebih lanjut.

Keywords:
mind body interventions;
Latihan Pasrah Diri;
NF-κB;
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therapy;

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INTRODUCTION

Mind body interventions (MBIs) has been broadly defined as a group of therapies that emphasize on the use of brain in conjunction with the body to assist healing process, and is widely used to manage symptoms and improve wellbeing. Hopefully, MBIs can be usedas supporting therapy in patients with autoimmune disease such as systemic lupus erythematosus (SLE) to improve patients' activities and to reduce fatigue, stress, and depression. Several methods inMBIsare*tai chi*, *qigong*, yoga, meditation, and *latihan pasrah diri* (LPD).[1,2] Several studies showed that MBIs could affect expression of many pro- and anti-inflammatory mediator.[1,3,4]

Nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB) controls the expression of many genes that regulates immune response, cell growth, and proliferation; survival and apoptosis; embryogenesis and stress response; and also development of many stimuli.[5]Disturbance of NF-κB could lead to several autoimmune and inflammatory disorder, or cancer. MBIs therapy in patients with SLE is expectedto affect NF-κB regulation. This review discussesthe potential ofMBIs in improving the condition of patients with SLE through NF-κB regulation based on existing studies.

MATERIALS AND METHODS

A literature searching from MEDLINE/PubMed and Google Scholar database was performed. Keyword used in this strategy were 1) "mind body intervention" OR "latihan pasrah diri", 2) NF-κB, 3) lupus OR "systemic lupus erythematosus". Manual searching was also performed as a supplemental approach to identify additional primary references. Literature searching was limited to publications in English or Bahasa Indonesia with no date restriction.

RESULTS AND DISCUSSION

Mind body interventions

Several commonly used MBI techniques include *tai chi*, *qigong*, yoga, meditation, and LPD. *Tai chi* and *qigong* are traditional Chinese therapy that combines mental focus, coordinated breathing, and specific posture. *Tai chi* movements can provide self defence and are externally focused, while *qigong* is internally focused. Yoga is originated from ancient Indian philosophy. As practiced in the west, it typically includes physical postures, coordinated breathing, and meditation or relaxation, though there are considerable variability across different schools of yoga with specific interventions. Meditation refers to a broad range of practices that involve training the mind, particularlyto focus on attention. In particular, mindfulness meditation teaches individuals to bring attention to present moment experiences with openness, curiosity, and non judgment.[1] LPD use relaxation and dzikr method that done independently and could activate relaxation response. LPD consist of three parts including relax position (tense-relax muscle) that could be done in a seated position or lying down, and not concentrating or consciously regulate breathing. This method is conducted for 15-20 minutes, thus it can be done easily anywhere.[2]

MBIs can be combined with other approaches and cause additional or synergistic effects on overcome inflammation. In particular, the combination of MBIs with pharmacological therapies that target inflammation may enhance the anti-inflammatory effects. Effects of MBIs may initially be reflected on the alterations of gene expression profiles and pro-inflammatory signalling. Alterations of inflammatory gene expression can be identified after relatively short interventions and generally seen asthe reduction of pro-

inflammatory gene expression in monocyte population. A critical step in research on MBIs is to determine how to maintain the practices and to examine the effects on inflammation and health in longer period.

NF-κB as inflammatory mediator

NF-κB is a transcription factor that controls gene expression related to many physiological responses such as inflammation, proliferation, cell differentiation, apoptosis, response to stress, embryogenesis, and development in response of various stimuli.[5,6] NF-κB is activated by many inflammatory stimuli including growth factor and infectious agents.[5] NF-κB is crucial for health maintaining. The disturbance of NF-κB expression could lead to many autoimmune disorders, malignancies, arthritis, atherosclerosis, and tumors.[7]

Inflammatory response is activated by various signalling pathway that regulate pro- and anti-inflammatory mediator produced by cells ontissue and recruited leukocytes. Previous study showed that inflammatory signalcan be provided by IL-1, TNF receptors and Toll-like microbial pattern, microbial recognition receptor included in IL-1R group. IL-1 and TNF-α represent basic pattern of pro-inflammatory cytokines. It released immediately byinfected or injured tissue. Tool like receptors (TLRs) recognize microbial molecular pattern known as pattern recognition receptor (PRR).[8] However, endogenous ligand could possibly stimulate TLRs during tissue injury or conditions that stimulate inflammation without infection.[9] Although structurally different, those receptors use similar mechanism signalling pathway, which include activation of several IκB kinase (IKK) and NF-κB.[10]

Recently, two different pathways for NF-κB activation has been recognized, which are canonical and alternative pathway. Canonical pathway is induced by microbial products and pro inflammatory cytokines such as TNFα and IL-1. Canonical pathway triggers activation of Rel A or cRelcontaining complex.[11] Alternative pathway is activated by TNF-limphotoxin β (TNFSF3) cytokine family,[12] B cell activating factors (BAFF and TNFSF13B),[13] and NF-κB ligand receptor activator (RANKL dan TNFSF11),[14] but not TNFα.[13,15,16] The activation by those factors in alternative pathway will lead to the activation of RelB/p52 complex.[13] The canonical and alternative pathways are distinguished by the different IKK sub unit that activate them. IKK complex consists of IKKα (IKK1) and IKKβ (IKK2) sub units; and a regular IKKγ sub unit (NEMO). IKKβ regulates the activation of canonical pathway through phosphorylation of IκBs that need sub unit IKKγ.[17] IKKα is needed for the activation of alternative pathway through phosphorilation and processing of p100as the precursor of p52,[12] and it is IKKβ and IKKγ independents.[10]

NF-κB canonical pathway

Nuclear factor-κB canonical pathway occurs inresponse to TNFα and IL-1 signals.TNFα and IL-1 are pro-inflammatory cytokines that has an important role in pathogenesis of chronic inflammatory diseases such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), asthma, and chronic obstructive pulmonary disease (COPD).[18,19] Activation of NF-κB has wide implication on inflammatory diseases,[20] therefore a lot of interest in developing anti-inflammatory drugs that target NF-κB.[6]

Other than the association with canonical pathway, the activation of NF-κB is related to existence of Rel-A or cRel-containing complex in inflamed tissue. Several studies showed that the production of pro-inflammatory cytokines and chemokine in disease

tissue depend on NF-κB. The trial using fibroblast-like synoviocytes from RA patients could be used as an example.[21] However, NF-κB activation does not always turn into pro-inflammatory and have a complex role in inflammatory response. The role of RelA as a critical effectors of canonical pathway has already been shown in a study using RelA and IKKβ knockout mice.[22] Another study using gene knockout has shown that NF-κB protein has both pro- or anti-inflammatory roles. Homodimer of NF-κB p50 subunit inhibited NF-κB target gene and inflammation.[23] The complex ofp50 homodimer was also found in resting T-cell and the reduced expression could be seen after T-cell activation. Over expression of p50 could also inhibit IL2 expression in T-cell,[24] although increased p50 expression was also reported to suppress TNFα production.[23] Another study also showed that anti-inflammatory role of p50 homodimer in septic shock targets of canonical pathway through IKKβ.[25] Anti-inflammatory role of NF-κB directly inhibitedthe expression of pro-inflammatory genes and manipulated anti-inflammatory cytokines expression or activation such as IL-10.

Apoptosis is an important mechanism to inhibit prolonged inflammation. Neutrophil apoptosis happened during inflammation. Activation induced cell death (AIDC) from specific T-cell antigen is important mechanisms that limit inflammation and immune response.[26] NF-*κ*B palys a role in neutrophil pro-apoptosis during inflammation,[27] which could in volve in anti-inflammatory mechanism of NF-κB during acute inflammation. Nevertheless, NF-κB also playa role in mechanism to prevent pathogen-induced apoptosis in macrophage.[28] In this context, NF-κB possibly has pro-inflammatory effect by extending macrophage active phase.

Alternative pathway

Alternative pathway is characterized by phosphorilation of p100 by IKKα that will activate RelB or p52 heterodimer. Other kinase that activate IKKα has been identified as NF-κB inducing kinase (NIK).[12] Genetic study in mice showed an important role of alternative pathway in lymphoid organogenesis and lymphocyte B cell functions.[12,13] NF-κB inducing kinase(NIK) activation triggers phosphorylation and proteosomal process ofNF-κB2 p100 precursor into mature p52 subunit through an IKKα dependant process.[13] Sub sequently, p52 undergo dimerization with Rel-B that shows up as nuclear RelB/p52 DNA binding activity and regulates different class of genes.[29] Recent study showed that synthesis of alternative pathway constituent, RelB and p52, are controlled by IKKβ-IκB-RelA: p50 canonical pathway signalling.[14] Cell differentiation or development that being stimulated by the activation of BAFF, RANKL or lymphotoxin-α activates alternative pathway.[30]

NF-κB in systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease with immune response abnormalities in B-cell, T-cell, andmonocyte. These abnormalities cause polyclonal B-cell activation, increased antibody producing cells and antibody production, hypergammaglobulinemia, and immune complex formation. The main pathway is through auto antibody activation and B cell differentiation due to uncontrolled help of T-cell. B-cell activation is increased in active SLE. T-cell abnormality in SLE decreased T-cell number, possibly due to anti-lymphocyte antibody that will lead to the disruption of B-cell and cause increased antibody production.[31]

Natural immune systems also play an important role in autoimmunity. An abnormal stimulation of natural immunity affects SLE immune opathogenesis through TLR. Apoptosis in patients with SLE leads to the introduction and internalization of nucleus self-antigen through B-cell receptor. It also activates TLR7 at B-lymphocyte endosome and support its role in auto antibody production. RNA complex will enter plasmacytoid dendritic cells (pDCs) through Fc receptor, leading to INF-α emergence that affect thedevelopment, progressiveness, and pathogenesis of SLE.[32]

TLR7 and TLR9 induce signal transduction via myeloid differentiation primary response 88 (MyDD88) protein, which expressed in endosomal compartment. This protein will interact with interleukin-1 receptor-associated kinase ¼ (IRAK1/4) and TNF receptor-associated factor 6 (TRAF6), and create a complex. Furthermore, IRAK1 and TRAF6 will detach from the complex and interact with IKKβ kinase (Iκβ kinase), which will activate NF-κB leading to gene expression of pro-inflammatory cytokines and chemokines.[32]

NF-κB has animportant role in immune response towards infection; however, disrupted NF-κB activation could be the initiation factor for inflammatory disease. The activation of NF-κB is crucial in inflammatory mediator production such as ROS and iNOS, and also emergence of symptoms.[33] NF-κB has been known involves in autoimmune disease pathogenesis such as RA (rheumatoid arthritis), type I diabetes, multiple sclerosis, and SLE.[31]

NF-κB targets gene that involved in the development, maturation, activation, and differentiation of lymphocyte, and in inflammatory function of natural immune cells. NF-κB family includes NF-κB1 (p50/p105), NF-κB2 (p52/p100), p65 (RelA, RelB, and c-Rel).[32] NF-κB increase the involvement of T-celland B-cell in SLE pathogenesis.[31] Many evidences showed the important role of NF-κB in maturation and development of dendritic cell and lymphocyte. Abnormal NF-κB signal leads to T-cell autoreactive activation, which is important in SLE and plasma cell development.[32]

Existing studies showed that NF-κB involved in renal inflammation pathogenesis that caused by infection, injury, or autoimmune factors. NF-κB was also known to have an involvement in nephritic lupus pathogenesis, one of the most common complication in SLE and could reduce patients' survival rate. Nephritic lupus is characterized by autoimmune complex deposition in glomerulus that leads to kidney inflammation. Nephritic lupus patients experience increased NF-κB expression and activation in mesangial cells and glomerular endothelial, along with increased inflammatory cytokines.[33]

IKKβ inhibition leads to reduce the inflammatory mediators' induction due to hypoxia at kidney tubular cells. Selective IKK inhibitor, Bay11-7082, improve nephritic lupus in mouse by inhibiting NF-κB and inflammasome NLRP3.[34] Genes that are known to encode 2 negative regulator of NF-κB, A20 (TNFAIP3) and A20-binding inhibitor NF-κB1 (ABIN1/TNIP1), also has correlation with lupus and nephritic lupus diseases.[35] A20 is an enzyme that transforms into ubiquitin and inhibits activation of NF-κB related to immune and inflammation stimuli. ABIN1 is ubiquitin bound protein that inhibit NF-κB signal by facilitating A20 action and disrupting IKK activation. A20 deficiency in human and animal model is correlated with inflammatory and autoimmune disease, including lupus.[36] Genetic studies in human and animal showed the ABIN1 involvement in nephritic lupus. Mouse with inactive ABIN1 showed different NF-κB activation and undergo lupus-like autoimmunity and symptoms similar to nephritic lupus in human.[35]

NF-κBinducing kinase (NIK) mediate non canonical NF-κB cascade from several TNF members, including BAFF, TWEAK, CD40, and OX40 that implies to lupus pathogenesis. Preclinical study showed that NIK inhibition could lead to increase the survival rate, reduce kidney pathology and reduce proteinuria score.[37] Thus, NIK inhibition could be used as a potential therapy approach for lupus.

The effects of mind body interventions on inflammatory processes: the role of NF-κB

Alterations of inflammation processes are thought to affectthe symptoms and conditions that responsive to MBIs, including fatigue, depression, and pain. The most common inflammatory markers assessed in MBIs trials are C reactive protein (CRP), a well established marker of inflammatory activity. A previous meta analysis reported that patients treated with various types of MBIs for eight to twelve weeks had decreased circulating level of CRP.[3] Several evidences showed that *tai chi* or *qigong*, and possibly yoga, which incorporate physical activity components, are more likely to reduce the CRP levels, relative to meditation.[1,3]

CRP is partlyregulated by IL-6. Patients who did *tai chi* showed IL-6 reduction at 16 weeks and followed by CRP reductionsat 24 weeks.[38] A total of 12 trials examining the effects of MBTs/MBIs (*tai chi* or *qigong*, yoga, and meditation) on circulating proinflammatory cytokine IL-6found that IL-6 did not consistently change following the practice of these various MBIs. Yoga gave effect in the reduction of IL-6 in patients with heart failure. *Tai chi*/*qigong* or meditation did not affect the IL-6 level in circulation.[3]

The effect of MBIs on the changes of circulating inflammatory markers level might be due to the release of cytokines such as IL-6 from non immunecell for example adipose tissue. Evaluation of the specific effect of MBIs on circulating inflammatory markers secreting immune cells was determined by various cellular assays to measure the production of IL-6, TNF, and IL1 before and after MBI practice. The studies found that the production of IL-6 and TNFα decrease dafter MBI practice. Irwin *et al*.,[39] found that practice of *Tai chi* over 12 or 16 weeks restored the increasing amount (%) of monocyte expressing IL-6, TNF, and co-expressing IL-6 and TNF, significantly.[39] Interestingly, *tai chi* practice induced IL-6 and TNF level reduction after 2 months, and the effect maintained over one year during follow up.

Significant life adversity is associated with alterations of gene transcriptional programs expressed under basal condition in circulating immune cells. Genome wide transcriptional profiling of leukocytes from individuals experiencing a range of life adversities showed a common pattern of increased expression of pro-inflammatory genes, which often accompanied by focal suppression of genes involved in innate antiviral responses. Bioinformatics analyses of these gene expressions identified specific transcription factors as potential mediators of this transcriptional shift, and foundactivation of pro-inflammatory NF-κBs / relfamily transcription factors (TFs) and GATA family TFs, decreased activity of interferon response factors (IRFs) and glucocorticoid receptor that antagonize NF-κB and reduce inflammation. Results of genomic inflammatory markers examination consistently indicated decreased inflammatory gene expression profiles, especially reduction of NF-κB activity.[40] These effects were seen in yoga, *tai chi*, and meditation, and occurred in diverse populations.

Several studies found that MBIs were able to restore leukocyte transcriptional alterations including activation of genes

regulated by the pro-inflammatory NF-κB. Irwin *et al.*[41] showed that *tai chi* caused decreased inflammatory gene expression, similar to the effects of meditation and yoga. A study inolder adult individuals with insomnia showed that *Tai chi* can also induced down regulation of genes transcriptions involved in immunological activation and inflammation (e.g., IL 6, IFNGR 1, CD 69, FOSB, FOS, IFNG, JUNB, IL8, IL18, PTGS2).[41]

MBIs are associated to thedecreasing in sympathetic activity and increasing in parasympathetic activity, reflecting greater sympathovagal balance. Sympathovagal balance is thought to reduce inflammation via decreased adrenergic signalling and lead to reduce the activity of cAMP response element binding protein family transcription factors, which is consistent with reduced sympathetic nervous system signalling through β adrenergic receptors, in conjunction with decrease in NF-κB activity. Similar changes in CREB signalling were found in a yoga trial, which also showed the reduction of NF-κB activity. However, the mediating role of autonomic nervous system in intervention that induces the reduction of inflammation has not been tested. MBIs influence glucocorticoid receptor signalling without affecting cortisol production. It assumed that receptor sensitivity may be modulated by these interventions. Inflammation, in the context of chronic stress, is hypothesized to be due to alterations of glucocorticoid receptor sensitivity. Activity of autonomic nervous system and HPA axis aremodulated by "neural alarm system", which consist of amygdala, dorsal anterior cingulate cortex, anterior insula, and periaqueductal grey (PAG) matter. Neural alarm system regions may be responsive to MBI sand mediate downstream effects of inflammation. MBIs have focused on meditative practices. Mindfulness is associated with alterations in threat related brain regions, including decreased amygdala reactivity and reduced functional connectivity of amygdala. MBIs also influence regulatory areas of brain that modulate activity in threat related regions. MBIs target psychological processes that have been directly and indirectly linked to threat, reward, and regulatory brain regions.[42]

MBIs also have a role in reducing pro-inflammatory genes expression and NF-κB activity in patients with cancer and other chronic diseases. MBIs practiced by breast cancer patients cause the reduction of depression events and NF-κB level.[43] Another study also showed that NF-κB decreased in breast cancer patients experiencing insomnia.[39] In elderly, MBIs have been proven to reduce loneliness rate and NF-kB level.[44] Even though the NF-κB expression decreased, but IRF1 activity increased in patients practicing MBIs. Not only in patients but also meditation conducted by caregivers of dementia patients can also improve the quality of mental health.[45] MBIs practiced for 9 weeks by patients with inflamatory bowel disease and irritable bowel syndrome could reduce NF-κB expression.[46] Previous study found that MBIs could reduce NF-kB expression. 81% of the studies showed the reduction ofgene transcription factor related to inflammation.[4]

MBIs is ableto fix weak physical condition and mental health, including depression or anxiety disorder. Previous study found that MBIs could reduce stress through inflammation deactivation mechanism involving biological and biomolecular mechanism. Recent study explained that inflammation and antiviral transcription pathway control could induceimmune genes expression. Proper practice of MBIs causethe decreased production of NF-κB and cytokines through down regulation process and lead tostressreduction.[4]

Mind body interventionsas potential supportive therapy in patients withSLE

Psychological disorder and physical limitation in patients with lupus are influenced by several factors such as stress, change in lifestyle, and self point of view to the disease. Until now, studies on the effect of MBIs on systemic lupus erythematous are limited.[47] One of MBIs program in lupus patients was doneon 1982 by Arthritis Center, South west Arizona University. This study was done in 313 patients with lupus from several centres in the United States of America. Patients were followed up within 2 months. Seven weeks after the practice, patients showed a significant reduction in depression score compared to the onebefore treatment. In addition, a significant increasedof relaxation and practice occurred during follow up.[47] A study by Horesh *et al.*[48] On the effect of 8 weeks MBIs therapy in 6 patients with lupus showed the improvement of several aspects, e.g. self point of view to the diseases, including increased of disease acceptance, and decreased of avoidance.[48] Therefore, MBIs canincrease the acceptance of patients to the negative physical and emotional condition.

In order to understand the mechanism of the MBIs effect on the patients condition with Lupus, further studies need to be done, especially the role of NF-κB. In SLE pathogenesis, NF-κB affect the role of B-cell and T-cell through its role in the development and maturation of dendritic cells. Abnormal NF-κB expression could lead to autoreactive T-cell that trigger plasma cell differentiation and lead to several autoimmune disease.[32] From all of previous studies, NF-κB is activated in patients with Lupus, therefore, it can be used as a potential targetfor Lupus therapy.

The potential of MBIs in reducing NF-κB levelin patients with Lupus open an opportunity for further study. *Latihan pasrah diri* is one of MBIs developed and often being used in Indonesia. This technique was developed by a clinician and involving Islamic spiritual element. Majority of Indonesian citizens are moslem, thus this technique might be suitable to be used in Indonesia. In the future, a study onthe effects of LPD as original MBIs from Indonesia in patients with lupus could be done.

CONCLUSION

Disturbance in NF-κB level in the body may facilitate various autoimmune diseases and inflammatory disorders. Abnormal NF-κB signal leads to autoreactive T-cell, which is important in SLE and plasma cell development thus exacerbating autoimmune condition. MBIs are considered to reduce the production of NF-κB and inflammatory cytokines. *Latihan pasrah diri* as Indonesian original MBIs could bepotentially used in SLE patients in Indonesia. Further study on the potential of LPD as a supportive treatment for patients with SLE needs to be done.

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