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PENELITIAN UNGGULAN PERGURUAN TINGGI (U)

PENGEMBANGAN KEBIJAKAN PENATALKSANAAN PENYAKIT LUPUS ERITEMATOSUS SISTEMIK MENGGUNAKAN KOMBINASI VITAMIN D DENGAN CURCUMIN SEBAGAI AGEN IMUNOMODULATOR UNTUK MENINGKATAN KEBERHASILAN TERAPI

Tahun ke 1 dari rencana 5 tahun

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ABSTRAK

Lupus Eritematosus Sistemik (LES) merupakan suatu penyakit autoimun sistemik yang bersifat kronis dan melibatkan multi organ dengan angka harapan hidup yang masih cukup rendah yaitu 70% untuk jangka waktu 5 tahun dan 50% untuk jangka waktu 10 tahun untuk pasien LES di Indonesia. Patogenesis LES disebabkan oleh respon imun hiperaktif yang berakibat pada peningkatan produksi autoantibodi patogenik terhadap antigen tubuh yang menjadi penyebab timbulnya keradangan sitemik dan kerusakan jaringan. Abnormalitas respon imun inlah yang menyebabkan progresifitas penyakit pasien LES menjadi semakin parah. Salah satu agen yang mampu meregulasi respon imun ini adalah vitamin D dan curcumin. Penelitian ini merupakan penelitian pohon yang dilakukan selama 5 tahun. Pada tahun pertama, diuji pengaruh pemberian metabolit aktif vitamin D dalam berbagai dosis dalam meregulasi aktivitas respon imun (sel limfosit Th1, Th2, Th17, Treg, dan sel dendritik) pasien LES secara *in vitro*. Pada tahun kedua, dilakukan pengembangan hewan coba model LES dengan metode induksi Pristane. Selanjutnya pada tahun ketiga, diuji pengaruh pemberian vitamin D dengan dosis yang telah diperoleh pada penelitian tahun pertama dalam meregulasi aktivitas respon imun, autoantibiodi (ANA test, Anti-Sm, Anti ds-DNA), indeks keradangan (CRP, LED, IL-6) secara *in vivo* pada hewan coba model LES. Selain itu, tim peneliti lain telah mulai menguji efek curcumin terhadap aktivasi respon imun secara *in vitro* pada tahun pertama. Sehingga harapan nya pada tahun ketiga nanti dapat dilakukan uji pemberian kombinasi vitamin D dan curcumin secara *in vivo* pada hewan coba model LES. Pada tahun keempat dan kelima, dibuktikan pengaruh pemberian vitamin D dan curcumin sbagai terapi komplementer dengan uji klinik *double blind* pada pasien LES yang akan melihat dua parameter utama yaitu dari segi *safety* (efek terapi dan efek samping) dan dari segi *efficacy* (manifestasi klinis, keluhan sistemik, indeks aktivitas penyakit yang diukur dengan skor SLEDAI, kadar autoantibodi, kimia darah yang menunjukkan aktivitas keradangan dan fungsi organ, serta perbaikan respon imun). Dengan demikian, diharapkan pada akhir penelitian ini dapat ditetapkan suatu kebijakan penatalaksanaan LES menggunakan kombinasi vitamin D dan curcumin sebagai agen imunomodulator untuk meningkatkan keberhasilan terapi dan meningkatkan harapan hidup pasien LES.

Kata kunci: *vitamin D, curcumin, respon imun, LES*

ABSTRACT

Systemic Lupus Erythematosus (LES) is a systemic autoimmune disease that is chronic and involves multiple organs with life expectancy is still quite low at 70 % for a period of 5 years and 50 % for a period of 10 years for patients LES in Indonesia . Pathogenesis LES is caused by a hyperactive immune response that results in increased production of pathogenic autoantibodies against antigens of the body which cause systemic inflammation and tissue damage . Abnormality of the immune response that causes disease progression inlah LES patients become more severe . One agent who is able to regulate the immune response is vitamin D and curcumin . This research was conducted tree for 5 years . In the first year , tested the effect of the active metabolite of vitamin D in regulating the activity of various doses of the immune response (Th1 lymphocytes , Th2 , Th17 , Treg , and dendritic cells) in vitro LES patients . In the second year , made the development of animal models of LES with Pristane induction method . Later in the third year , tested the effect of vitamin D at a dose that has been gained in the first year of research activity in regulating immune responses , autoantibiodi (ANA test , anti - Sm , anti ds - DNA) , inflammatory indices (CRP , ESR, IL - 6) in vivo in animal models of LES . In addition , other research teams have begun to examine the effects of curcumin on the activation of immune responses in vitro in the first year . So that his hopes for a third year to do a test later administration of the combination of vitamin D and curcumin in vivo in animal models of LES . In the fourth and fifth years , demonstrated the effect of vitamin D and curcumin sbagai complementary therapies with a double-blind clinical trials in patients with LES that will see the two main parameters , namely in terms of safety (therapeutic effects and side effects) and in terms of efficacy (clinical manifestations , complaints systemic disease activity index as measured by the SLEDAI score , levels of autoantibodies , blood chemistry showed inflammatory activity and organ function , and improved immune response) . Thus , it is expected by the end of this study can be defined policy management LES using a combination of vitamin D and curcumin as immunomodulatory agents to increase therapeutic efficacy and increase the life expectancy of patients LES .

Keywords : vitamin D , curcumin , immune response , LES

RINGKASAN

Penurunan kadar vitamin D dalam darah telah dikaitkan dengan gangguan fungsi sel imunyang meningkatkan resiko respon autoimunitas yang lebih tinggi. Pasien Lupus Eritematosus Sistemik (LES) dengan hipovitamin-D memiliki skor aktivitas penyakit yang lebih tinggi dibanding pasien LES normovitamin-D. Mekanismenya dikaitkan dengan peningkatan maturasi dan fungsi sel dendrit, peningkatn sintesis interleukin-6 (IL-6) yang a menurunkan rasio *transforming growth factor* β (TGF-β) sitokin tersebut (TGF-β:IL-6). Hal ini akan menghambat perkembangan sel T regulator dan meningkatnya sel T helper 17 (Th17) yang inflamatorik. Keseimbangan sel Th1/Th2 juga terganggu dengan aktivitas Th2 yang lebih tinggi *mencetuskan pembentukan autoantibodi*. Diharapkan pemberian metabolit aktiv vitamin D dapat memperbaiki gangguan tersebut.

Berdasarkan latar belakang tersebut di atas, maka dilakukan penelitian *in vitro* pengaruh pemberian vitamin D $\{1,25(OH)_2D_3\}$ dalam regulasi sistem imun pasien LES, khususnya penurunan diferensiasi dan fungsi sel dendrit, penurunan fungsi dan jumlah sel Th17 dalam kaitan dengan sel Treg dan perbaikan keseimbangan Th1 dengan Th2.

SUMMARY

Decreased levels of vitamin D in the blood have been associated with impaired cell function imunyang increase the risk of autoimmunity higher response . Systemic Lupus Erythematosus Patients (LES) with hipovitamin - D scores higher disease activity than patients normovitamin LES - D . The mechanism associated with increased dendritic cell maturation and function , peningkatn synthesis of interleukin - 6 (IL - 6) that a lowered ratio of transforming growth factor β (TGF - β) cytokine (TGF - β : IL - 6) . This will hamper the development of regulatory T cells and helper T cells increased 17 (Th17) are inflammatory . Th1/Th2 cell balance is also disturbed by the activity of Th2 higher trigger the formation of autoantibodies . It is expected that the provision of active metabolites of vitamin D can correct the disorder.

Based on the background mentioned above , it is done in vitro study the effect of vitamin D [1,25 (OH) 2D3] in immune system regulation LES patients , particularly the decline in the differentiation and function of dendritic cells , a decrease in the function and the number of Th17 cells in terms of cell Treg and improved balance of Th1 to Th2 .

DAFTAR PUSTAKA

Abbas, A., Lichtman, A.H. 2006. Basic Immunology: Functions and Disorders of the Immune System, Updated Edition 2006-2007, 2nd ed. Philadelphia, Elsevier.

Adam, J.S., Hewison, M. 2008. Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. *Nat Clin Pract Endocrinol Metab*. **4**(2):80-90

Adorini, L., and G. Penna. 2009. Dendritic cell tolerogenicity: a key mechanism in immunomodulation by vitamin d receptor agonist. *Human Immunol*. **70**(5): 345-52.

Akahoshi M, Nakashima H, Tanaka Y, Kohsaka T, Nagano S, Ohgami E, Arinobu Y,Yamaoka K, Niiro H, Shinozaki M, Hirakata H, Horiuchi T, Otsuka T, & Niho Y. (1999) Th1/Th2 balance of peripheral T helper cells in systemic lupus erythematosus. *Arthritis and Rheumatism* Vol 42 No 8 (Aug 1999) pp 1644–8.

Almoallim h. Ed , Cytokine roles in the pathogenesis of SLE, Systemic Lupus Erythematosus, InTech Janeza Trdine 9, 51000 Rijeka, Croatia. 65-82,2012

Anolik, J.H. 2007. B cell biology and dysfunction in SLE. *Bulletin of the NYU hospital for joint diseases*. **65**(3): 182-6.

Arikunto, S. 2002. Prosedur Penelitian. Jakarta: Rineka Cipta.

Bacon, C.M., McVicar, D.W., Ortaldo, J.R., Rees, R.C., *et al*. Interleukin-12 (IL-12) induces tyrosine phosphorylation of JAK2 and TYK2: differential use of Janus family tyrosine kinases by IL-2 and IL-12. *J Exp Med* 1995;**181**(1): 399–404.

Baeke, F., Etten, E. V., Overbergh, L., Mathieu, C. 2007. Vitamin D3 and the immune system: maintaining the balance in health and disease. *Nutrition research reviews*, **20**(1), 106-18.

Baeke, F., Takiishi, T., Hannelie, K., Conny, G., Chantal, M. 2010. Vitamin D: modulator of the immune system. *Cuurent Opinion in Pharmacology*. **10**:482-496.

Bikle, D. 2009. Nonclassic actions of vitamin D. *J. Clin. Endocrinol. Metab*. **94**(1): 26–34,

Borigini, M.J., Zieve, D. 2009. Systemic lupus erythematosus. A.D.A.M., Inc

Callen J.P. Lupus Erythematosus, Discoid. *e Medicine*. 2007.

Carlson, M.J., West, M.L., Coghill, J.M., Panoskaltsis-Mortari, A., Blazar, B.R., Serodi, J.S. 2009. In vitro-differentiated Th17 cells mediate lethal acute graft-versus-host disease with severe cutaneus and pulmonary pathologic manifestations. *Blood Journal*, **113**: 1365-1374

Carroll, M.C. 2004. A protective role for innate immunity in systemic lupus erythematosus. *Nature Reviews Immunology*. **4**(10):825-831.

Cella, M., Scheidegger, D., Palmer-Lehmann, K., *et al*. 1996. Ligation of CD40 on dendritic cells triggers production of high levels of interleukin-12 and enhances T cell stimulatory capacity: T–T help via APC activation. *J Exp Med*. **184**(2):747–52.

Chan R.W.-Y., Lai F.M.-M., Li E.K.-M., Tam L.-S., Chow K.-M., Li P.K.-T., & Szeto C.. (2006). Imbalance of Th1/Th2 transcription factors in patients with lupus nephritis. *Rheumatology (Oxford, England)* Vol 45 No 8 (Aug 2006) pp 951-957.

Chen, S., Sims, G.P., Chen, X.X. *et al*. 2007. Modulatory effects of 1,25-dihydroxyvitamin D 3 on human B cell differentiation. *J. Immunol*. **179**:1634-1647.

Chang DM, Su WL, & Chu SJ. (2002)The expression and significance of intracelluiar T helper cytokines in systemic lupus erythematosus. *Immunological Investigations* Vol 31 No 1 (Febr 2002) pp 1-12

Comabella, M., Montalban, X., Munz, C., Lunemann, J.D. 2010. Targeting dendritic cells to treat multiple sclerosis. *Nat. Rev. Neurol*. **6**(9): 499-507.

Crispin, J.S. Varela, J.A. 2007. The role myeloid dendritic cells play in the pathogenesis of systemic lupus erythematosus. *Autoimmunity reviews*. **6**(7): 450-456.

Cutolo, M. 2009. Vitamin D and autoimmune rheumatic diseases. *Rheumatology*. **48**: 210-212.

Ding, D., Mehta, H., McCune, J., Kaplan, M.J. 2006. Aberrant phenotype and function of myeloid dendritic cells in systemic lupus erythematosus. *J. Immunol*. **177**: 5878-5889.

Dusso, A.S., Brown, A.J., Slatopolsky, E. 2005. Vitamin D. *Am J Physiol Renal Physiol*. **289**: p F8-28.

Esche, C., Shurin, M.R., Lotze, M.T. 2000. IL-12 Receptor. In: Oppenheim JJ, Feldmann M, editors. Cytokine reference. *San Diego: Academic Press*; p. 189–201.

European Assosiation of Oral Medicine. Oral Lupus Erythematosus. *School of Dental Medicine University of Zagreb*. 2005.

Ferreira, G.B., Manthieu, C., Overbergh, L. 2010. Understanding dendritic cell biology and its role in immunological disorders through proteomic profiling. *Proteomics Clin. Appl*. 4: 190-203.

Fransen, J.H., Vlag, J.V.D., Ruben, J., Adema, G.J., Berden, J.H., Hilbrands, L.B. 2010. The role of dendritic cells in the pathogenesis of systemic lupus erythematosus. *Arthritis Research & Therapy*. **12**: 207.

Gee. K., Guzzo, C., Che Mat, N.F., *et al*. 2009. The IL-12 Family of Cytokines in Infection, Inflammation and Autoimmune Disorders. *Inflamm Allergy Drug Targets*. 8:40-52.

Ginanjar, E., Sumariyono, Setiati, S., Setiyohadi, B. 2007. Vitamin D and autoimmune disease. *Acta Med Ind. J. Intern. Med.* **39**(3): 133-141

Greenberg, M.S., Michael, G. 2003. Burket's Oral Medicine Diagnosis & Treatment. 10th ed. *Hamilton: BC Decker Inc.*

Hackstein, H., Thomson, A.W. 2004. Dendritic cells: emerging pharmacological targets of immunosuppressive drugs. *Nat Rev Immunol.* **4**(1):24-35.

Hanafiah, K.A. 2008. Rancangan Percobaan teori dan aplikasi, Edisi Ketiga. Jakarta: PT RajaGrafindo Persada.

Handono, K., *et al*., 2011. Role of Vitamin D in Healthy and Rheumatic Autoimmune. *Faculty of Medicine* - Brawijaya University.

Handono, K., Daramatasia, W., Pratiwi, *et al*., 2012. Low Level of Vitamin D Increased Dendritic Cell Maturation and Expression of Interferon-γ and Interleukin-4 in Systemic Lupus Erytematosus. *IORSJPBS*. **2**(4): 37-43.

Handono, K. 2000. HLA klas II dan kerentanan genetik terhadap LES di Indonesia. *Acta Med Ind.* **32**: 11-15.

Hewison, M., Freeman, L., Hughes, S.V., *et al*. 2003. Differential Regulation of Vitamin Receptor and Its Ligan in Human Monocytes-Derived Dendritic Cells. *J Immmunol.* **170**(11): 5382-5390.

Holick, M.F. 2007. Vitamin D deficiency. *Med Pro.* **357**:266-281.

Irastorza, G.R., Egurbide, M.V., Olivares, N., *et al*, 2008. Vitamin D deficiency in systemic lupus erythematosus: prevalence, predictors and clinical consequences. *Rheumatology*. **47**:920-923.

Jacobson, N.G., Szabo, S.J., Weber-Nordt, R.M., *et al*. 1995. Interleukin-12 signaling in T helper type 1 (Th1) cells involves tyrosine phosphorylation of signal transducer and activator of transcription (STAT)3 and STAT4. *J Exp Med.* **181**(5):1755–62.

James, W.D., Berger, T.G., Elston, D.M. 2006. Andrew's Disease of thr Skin Clinical Dermatology. 10th ed. *Philadelphia: Saunders Elsevier*.

Kamen, D.L., Cooper, G.S., Bouali, H., *et al.* 2006. Vitamin D deficiency in systemic lupus erythematosus. *Autoimmune. Rev.* **5**(2):114-117.

Kapsenberg, M.L. 2003. Dendritic cell control of pathogen driven T cell polarization. *Nat immunol.* **3**: 984-993.

Kristin, K.D., Donald, L., Trump, *et al.* 2007. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. *Nat Rev Cancer.* **7**:684-700

Kumar, V., Abul, K.A., Nelson, F. 2005. Pathologic Basis of Disease. 7th ed. *Philadelphia: Elsevier saunders*.

Kuwano, Y., Prazma, C.M., Yazawa, N., *et al.* 2007. CD83 influences cell-surface MHC class II expression on B cells and other antigen-preenting cells. *Int Immunol.* **19**(8): 977-992.

Lebeer, S., Vanderleyden, J., De Keersmaecker, S.C. 2010. Host interactions of probiotic bacterial surface molecules: comparison with commensals and pathogens. *Nat Rev Microbiol.* **8**:171-184.

Levings, M.G., Gregori, S., Tresoldi, E., *et al.* 2005. Differentiation of Tr1 cells by immature dendritic cells requires IL-10 but not $CD25^+CD4^+$ Tr cells. *Blood.* **105**(3): 1162-1169.

Lichtenegger, F.S., Mueller, K., Otte, B., *et al.* 2012 CD86 and IL-12p70 Are Key Players for T Helper 1 Polarization and Natural Killer Cell Activation by Toll-Like Receptor-Induced Dendritic Cells. *PLoS ONE* **7**(9): e44266.

Lizee, G., Laszlo, G., Radvanyi, *et al.* 2006. Improving antitumor immune responses by circumventing immunoregulatory cells and mechanisms. *Clin Cancer Res.* **12**: 4794-4803.

Lonza. 2009. Optimized Protocol for Human Dendritic Cells. Amaxa® Human Dendritic Cell Nucleofector® Kit. Lonza Cologne AG. All rights reserved DPA-1004 08/09.

M. Rossi, M., Young, J.W. 2005. Human dendritic cells: potent antigen-presenting cells at the crossroads of innate and adaptive immunity. *J Immunol.* **175**(3):1373–1381.

Ma, X., Neurath, M., Gri, G., *et al.* 1997. Identification and characterization of a novel Ets-2-related nuclear complex implicated in the activation of the human interleukin-12 *p40* gene promoter. *J Biol Chem.* **272**(16):10389–95.

Maddur, M.S., Vani, J., Dimitrov, J.D., *et al.* 2010. Dendritic cells in autoimmune diseases. *The Open Arthritis Journal*. **3**: 1-7.

Manzi, S. 2001. Epidemiology of Systemic Lupus Erythematosus. *The American Journal of Managed Care*. 7(16).

Marco, E.C., Varela, M.M.M.S, Vila, A.M., *et al.* 2010. Serum 25-hydroxyvitamin D levels in patients with cutaneous lupus erythematosus in a mediterranean region. *Lupus*. 1-5.

Marks, J.G., Miller, J.J. 2006. Lookingbill and Marks Principles of Dermatology. 4th ed. *Philadelphia: Elsevier inc.*

Masutani K, Akahoshi M, Tsuruya K, Tokumoto M, Ninomiya T, Kohsaka T, Fukuda K, Kanai H, Nakashima H, Otsuka T, & Hirakata H. (2001) Predominance of Th1 immune response in diffuse proliferative lupus nephritis. *Arthritis and rheumatism* Vol 44 No 9 (Sept 2001) pp 2097–106. Toubi, E., and Y. Shoenfeld. The role of vitamin D in regulating immune responses. IMAJ 2010; 12:174-175.
Monrad, S.U., Desch, K.C., Kaplan, M.J. 2008. Role of dendritic cells in the pathogenesis of systemic lupus erythematosus. *Future Rheumatol*. **3**(3): 269-279.

Mora, J.R., Iwata, M., Von Andrian, U.H. 2008. Vitamin effects on the immune system: vitamins A and D take centre stage. *Nat Rev Immunol.* **8**:685-698.

Mouyis, M. 2008. Hypovitaminosis D among rheumatology outpatients in clinical practice. *Rheumatology*. **47**: 1348-1351.

Murphy, T.L, Cleveland, M.G., Kulesza, P., *et al.* 1995. Regulation of interleukin-12p40 expression through an NFk8 half-site. *Mol Cell Biol*. **15**(10):5258–67.

Nair, M., Gerald, E. A., Tedder, T.F. 2012. Isolation and Generation of human Dendritic Cells. *Curr protocol immunol.* 7(32):1-7

Nie, Y.Z., Mok, M.Y., Chan, G.C.F., *et al.* 2010. Phenotypic and functional abnormalities of bone marrow-derived dendritic cells in systemic lupus erythematosus. *Arthtritis Research & Therapy*. **12**: 1-12.

Nishikomori, R., Ehrhardt, R.O., Strober, W. 2000. T helper type 2 cell differentiation occurs in the presence of interleukin-12 receptor _2 chain expression and signaling. *J Exp Med.* **191**(5):847–58.

O'Shea, J.J., Gadina, M., Schreiber, R.D. 2002. Cytokine signaling in 2002: new surprises in the JAK–STAT pathway. *Cell.* **109**(Suppl):S121–131.

Toubi, E., Shoenfeld, Y. 2010. The role of vitamin D in regulating immune responses. *IMAJ*. **12**: 174-175.

Trinchieri, G., Scott, P. 1999. Interleukin-12: basic principles and clinical applications. *Curr Top Microbiol Immunol*. **238**:57–78.

Tuyaerts, S., Aerts, J.L., Corthals, J., *et al*. 2007. Current approaches in dendritic cell generation and future implications for cancer immunotherapy. *Cancer Immunol Immunother*. **56**:1513–1537

Vlad, G., Cortesini, R., Foca, N.S. 2005. License to heal: bidirectionalninteraction of antigen-spesific regulatory Tcells and tolerogenic APC. *J. Immunol*. **174**: 5907-5914.

Wallace, D.J., Hannahs, H.B. 2007. Dubois" Lupus Erythematosus. *Lippincott Williams & Wilkins*. 7th edition.

Wallet, M.A., Sen, P., Tisch, R. 2005. Immunoregulation of dendritic cells. *Clinical Medicine & Research*. **3**(3): 166-175.

Wattford, W.T., Moriguchi M., Akio M., *et al*. 2003. The biology of IL-12: coordinating innate and adaptive immune responses. *Cytokine Growth Factor Rev*. **14** (5): 361–368.

Wolff, K., Goldsmith, L.A., Katz, S.I., *et al*. 2008. Fitzpatrick's Dermatology in General Medicine. 7th ed. New york: *McGraw Hill Medical*. 2008.

Xiaou, J., Vida, H., Xing,L.W., John, L.V.,Qiang, S. 2012. Profound influence of LDL oxidative status and monocyte co-cultures on baboon endothelial activation. *Am J Cardiovasc Dis*. **2**(1): 1–11.

Zittermann, A. 2003. Vitamin D in preventive medicine: are we ignoring the evidence?. *The British journal of nutrition*. **89**(5):552-72.

Zou, J., Presky, D.H., Chang-You, W., *et al*. 1997. Differential associations between the cytoplasmic regions of the interleukin-12 receptor subunits β1 and β2 and JAK kinases. *J Biol Chem*. **272**(9):6073–7.

Zol, L.B., Aranow, C., Mackay, M., *et al*. 2009. The impact of vitamin D on dendritic cell fungtion in patiens with systemic lupus erythematosus. *PLoS ONE*. **5**(2): 1-8.