International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Role of Leflunomide in Vitiligo

Sherif Shoukry Awad, Maha hussain Ragaie, Mira Abdelfatah Ahmed

Dermatology&STDs; Faculty of Medicine; Minia University; Egypt

Abstract

Vitiligo is characterized by the death of melanocytes in the skin. This is associated with the presence of T cell infiltrates in the lesional borders. Leflunomide (LF) is an immunomodulator and a member of the disease-modifying antirheumatic family of drugs (DMARDs). This study was designed to investigate the efficacy and safety of Leflunomide in treatment of vitiligo patients. Sixteen vitiligo patients were treated with leflunomide, and evaluation was done clinically. Results: Evaluating the clinical outcome of vitiligo patients in this study after treatment with leflunomide, revealed significant regimentation indicated by improvement of VASI score. Once daily leflunomide is an effective and convenient treatment to stop vitiligo progression with tolerability and a favourable safety profile.

Keywords: Vitiligo, leflunomide, DMARDs, leflunomide, T cell infiltrates

Short communication **Corresponding Author*, e-mail: mera.ahmed@mu.edu.eg

1. Introduction

Vitiligo is a chronic pigmentary skin disease characterized by the selective loss of melanocytes resulting in white, hypopigmented macules and patches. It is the most common cause of cutaneous depigmentation affecting 0.5%-2% of the population worldwide. Half of the cases develop before the age of 20 years, but the disease may appear during any time of life. Males and females are equally affected regardless of race or skin phototype [1]. It has a deep psychological impact on patients and their quality of life because of cosmetic disfigurement, social stigma, unpredictable course, and variable response to treatment [2]. Two major subtypes of vitiligo are well recognized: non-segmental (NSV) and segmental (SV). Non-segmental vitiligo (NSV) is the more common subtype [3]. Several theories have been put forward to explain the pathogenesis of vitiligo and mechanisms that finally lead to the loss of functional melanocytes from the epidermis. The important ones include a genetic predisposition, autoimmune destruction of melanocytes, altered redox status, free radical mediated melanocyte damage, heightened sympathetic response, and catecholamines / neurotransmitter mediated melanocyte damage, and impaired melanocyte adhesion or melanocytorrhagy. The combination of all these effectively explains the vitiligo pathogenesis (the combination theory) [4]. Vitiligo is a multi-genetic disease with a complex pathogenesis. The familial clustering of vitiligo cases in 6–8% of first-grade relatives supports this view; also, the concordance of vitiligo in monozygotic twins is approximately 23% [5]. The theory of vitiligo development due to oxidative stress (OS) suggests that ROS production would be induced by multiple intrinsic factors (such as inflammation and protein synthesis), as well as extrinsic ones, such as exposure to ultraviolet radiation pollutants, and phenolic compounds. In parallel, a failure in the antioxidant mechanism would occur, disrupting cell homeostasis and culminating in cell damage [6]. Evidence for the participation of the innate immune system in the pathogenesis of vitiligo is very consistent, with the latter being considered the link between oxidative stress and the adaptive immune response. First, dendritic cells, macrophages, and NK (natural killer) cells are found in the lesional and perilesional skin of patients with vitiligo, characterizing an activation of the innate immune response [7]. Cytotoxic CD8 cells are considered the first accused of melanocytes destruction in vitiligo. They are increased in the blood and skin of the patients and can be seen invading the epidermis in close vicinity to melanocytes of the affected skin [8-9]. Adhesion defects between cell components of the epidermis have also been implicated in the pathogenesis of vitiligo. E-cadherin is a protein that assists in anchoring between keratinocytes, and its low expression has been identified in melanocytes in vitiligo [10]. The possible involvement of viruses [i.e., Hepatitis C virus (HCV), hepatitis B virus (HBV), Epstein-Barr virus (EBV), *Cytomegalovirus* (CMV), and *Human immunodeficiency virus* (HIV)] in the aetiopathogenesis or deterioration of vitiligo has been suggested by several studies [11]. The neural theory of vitiligo is based on the clinical observation of lesion distribution: on dermatomes in the segmental type and symmetrical in non-segmental vitiligo, alluding to the neuroimmunology influence in vitiligo. There are also anecdotal cases of vitiligo appearing in delimited areas after nerve injury [12].

2. Materials and Methods

This study was conducted on 16 active non-segmental vitiligo patients. All patients were subjected to Full history taking, Full general clinical and dermatological examination. The diagnosis was made by dermatological examination and wood's light and all lesions were photographed. All patients received leflunomide at a dose of 100mg for three days then 20 mg daily for 1month.

3. Results and discussion

Evaluating the clinical outcome of vitiligo patients in this study after treatment with leflunomide, revealed significant regimentation indicated by improvement of VASI score. Leflunomide (LF) is an immunomodulator and a member of the disease-modifying antirheumatic family of drugs (DMARDs). LF is used effectively in solo or as combined therapy in autoimmune arthritis. LF was first launched at the end of 1998. In the early 2000s, FDA labelled LF with a precautionary regular hepatic function monitoring throughout the therapeutic regimen [13]. LF acts through the inhibition of dihydroorotate dehydrogenase (DHODH), an inner mitochondrial membrane enzyme that catalyzes the rate-limiting step of the *de novo* pathway of pyrimidine biosynthesis. Cellular regeneration and growth can be fulfilled through a salvage pathway with a two-fold coverage of pyrimidine nucleotide cellular requirements; however, the active proliferation of cells such as lymphocytes clonal expansion requires up to eightfold increase of pyrimidine nucleotides with a mandated dependence on the *de novo* pathway. We can expect that Leflunamide may interfere the pathogenesis of vitiligo through several mechanisms. Immune-mediated disorders are associated with the active expansion of autoimmune lymphocytes and innate immune cells such as monocytes and macrophages. The main and early characterized mode of action of LF is the cellular depletion of the pyrimidine nucleic acid building blocks with a milieu-dependent outcome such as inhibition of autoimmune lymphocyte expansion and, consequently, inhibition of immunokine and immunoglobulin production [14].

Manipulating innate immune responses is considered the anti-inflammatory gateway of LF. In a mouse model of lupus nephritis, LF inhibited the destructive tissue inflammatory pathway mediated through Toll-like receptor 9 (TLR9) signaling pathway with a reduction in the autoantibody production and immune complex deposition in the renal tissue [15]. Anti-inflammatory activity of LF can be undertaken through the suppression of the *trans*-endothelial migration of blood mononuclear cells and the inhibition of the expression of adhesion molecule CD44 [16]. LF acts through the inhibition of the tyrosine kinase activity responsible for the signal transduction of many vital pathways in the immune response. For instance, the inhibition of immunoglobulin class switching of IgM to IgG1, which is mediated through IL4-activated JAK3/STAT6 pathway [14], [17]. Similarly, the activation of T-cell proliferation by the T-cell growth factor IL2 was also inhibited with a deficiency of clonal expansion [18]. LF inhibits signal transduction of the T-cell receptors stimulated by anti-CD3 mAb in Jurkat cells; this finding supports tyrosine phosphorylation inhibition as a mechanism of the immuno-suppressive function of LF [14]. In addition, LF anti-inflammatory activity is reported in a clinical study of patients with active rheumatoid arthritis. The main findings in this study are the reduction of inflammatory joint destruction. IL1β and matrix metalloproteinases (MMP) such as MMP1 are reduced upon treatment with LF [19]. This may be explained by the inhibition of the TNF-α-dependent activation of NF-κB [20]. In a rat model of lung fibrosis-induced by bleomycin, LF reduced lung tissue expression of the inflammatory cytokines IL6, TNF-α, and NF-κB [21]. LF was reported as being an inhibitor of neuroinflammatory events associated with HIV infection independent of viral replication which is attributed to the inhibition of the secretion of the proinflammatory mediators IL6, CXCL10, and CCL2 [22].

4. Conclusion

Once daily leflunomide is an effective and convenient treatment to stop vitiligo progression with tolerability and a favorable safety profile.

References

[1] C. Bergqvist, K. Ezzedine. (2020). Vitiligo: a review. Dermatology. 236 (6) 571-592.

[2] K. Ezzedine, V. Eleftheriadou, H. Jones, K. Bibeau, F.I. Kuo, D. Sturm, A.G. Pandya. (2021). Psychosocial effects of vitiligo: a systematic literature review. American Journal of Clinical Dermatology. 1-18.

[3] A. Zailaie, K. Abdul-Aziz, I.A. Messaad. (2017). Effects of Acute Exposure of Diazinon on the Ovarian Steroidogenesis in Chicken, Gallus gallus. Egyptian Academic Journal of Biological Sciences, B. Zoology. 9 (1) 1-11.

[4] K. Boniface, C. Jacquemin, A.S. Darrigade, B. Dessarthe, C. Martins, N. Boukhedouni, J. Seneschal. (2018). Vitiligo skin is imprinted with resident memory CD8 T cells expressing CXCR3. Journal of Investigative Dermatology. 138 (2) 355-364.

[5] X. Sun, A. Xu, X. Wei, J. Ouyang, L. Lu, M. Chen, D. Zhang. (2006). Genetic epidemiology of vitiligo: a study of 815 probands and their families from south China. International journal of dermatology. 45 (10) 1176-1181.

[6] K. Oyarbide-Valencia, J.G. van den Boorn, C.J. Denman, M. Li, J.M. Carlson, C. Hernandez, I.C. Le Poole. (2006). Therapeutic implications of autoimmune vitiligo T cells. Autoimmunity reviews. 5 (7) 486-492.

[7] C. Martins, L. Migayron, C. Drullion, C. Jacquemin, F. Lucchese, J. Rambert, K. Boniface. (2022). Vitiligo skin T cells are prone to produce type 1 and type 2 cytokines to induce melanocyte dysfunction and epidermal inflammatory response through Jak signaling. Journal of Investigative Dermatology. 142 (4) 1194-1205.

[8] G.S. Ogg, P. Rod Dunbar, P. Romero, J.L. Chen, V. Cerundolo. (1998). High frequency of skin-homing melanocyte-specific cytotoxic T lymphocytes in

autoimmune vitiligo. The Journal of experimental medicine. 188 (6) 1203-1208.

[9] J.E. Harris. (2015). Melanocyte regeneration in vitiligo requires WNT beneath their wings. Journal of Investigative Dermatology. 135 (12) 2921-2923.

[10] D. Kovacs, E. Bastonini, M. Ottaviani, C. Cota, E. Migliano, M.L. Dell'Anna, M. Picardo. (2018). Vitiligo skin: exploring the dermal compartment. Journal of Investigative Dermatology. 138 (2) 394-404.

[11] S.C. Toker, H. Sarycaoglu, S.K. Karadogan, R. Mistik, E.B. Baskan, S. Tunaly. (2007). Is there any relation between vitiligo and cytomegalovirus?. Journal of the European Academy of Dermatology and Venereology: JEADV. 21 (1) 141-142.

[12] M.S.K. Al'Abadie, H.J. Senior, S.S. Bleehen, D.J. Gawkrodger. (1994). Neuropeptide and neuronal marker studies in vitiligo. British Journal of Dermatology. 131 (2) 160-165.

[13] R.D. Alamri, M.A. Elmeligy, G.A. Albalawi, S.M. Alquayr, S.S. Alsubhi, S.H. El-Ghaiesh. (2021). Leflunomide an immunomodulator with antineoplastic and antiviral potentials but drug-induced liver injury: A comprehensive review. International Immunopharmacology. 93 107398.

[14] C. He, X. Lu, Z. Yan, M. Wu, S. Liu, Y. Yu, P. Luo. (2012). Therapeutic effect of leflunomide on the development of experimental lupus nephritis in mice. Rheumatology international. 32 633-638.

[15] M. Cutolo, S. Capellino, P. Montagna, A. Sulli, B. Seriolo, B. Villaggio. (2005). Anti-inflammatory effects of leflunomide in combination with methotrexate on co-culture of T lymphocytes and synovial macrophages from rheumatoid arthritis patients. Annals of the rheumatic diseases.

[16] K. Siemasko, A.S. Chong, H.M. Jäck, H. Gong, J.W. Williams, A. Finnegan. (1998). Inhibition of JAK3 and STAT6 tyrosine phosphorylation by the immunosuppressive drug leflunomide leads to a block in IgG1 production. The Journal of Immunology. 160 (4) 1581-1588.

[17] C. WW. (1996). A novel mechanism of action of the immunomodulatory drug leflunomide: augmentation of the immunosuppressive cytokine TGF-beta 1, and suppression of the immunostimulatory cytokine IL-2. Transplant Proc. 28 3079-3080.

[18] J.J. Limon, D.A. Fruman. (2012). Akt and mTOR in B cell activation and differentiation. Frontiers in immunology. 3 228.

[19] M.C. Kraan, R.J. Reece, E.C. Barg, E. C., Smeets, J. Farnell, R. Rosenburg, P.P. Tak. (2000). Modulation of inflammation and metalloproteinase expression in synovial tissue by leflunomide and methotrexate in patients with active rheumatoid arthritis: findings in a prospective, randomized, double-blind, parallel-design clinical trial in thirty-nine patients at two centers. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 43 (8) 1820-1830.

[20] S.K. Manna, B.B. Aggarwal. (1999). Immunosuppressive leflunomide metabolite (A77 1726) blocks TNF-dependent nuclear factor-κB activation and gene expression. The Journal of Immunology. 162 (4) 2095-2102.

[21] S. Kayhan, A. Guzel, L. Duran, S. Tutuncu, A. Guzel, M. Gunaydın, M.Y. Selcuk. (2013). Effects of leflunomide on inflamation and fibrosis in bleomycine induced pulmonary fibrosis in wistar albino rats. Journal of thoracic disease. 5 (5) 641.

[22] B. Ambrosius, S. Faissner, K. Guse, M. von Lehe, T. Grunwald, R. Gold, A. Chan. (2017). Teriflunomide and monomethylfumarate target HIV-induced neuroinflammation and neurotoxicity. Journal of neuroinflammation. 14 (1) 1-10.