



Organoruthenium 9E1 and APL Altered Collagen II263-272 Peptide as Therapy for Autoimmune Diseases

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Abstract

Therapy for autoimmune diseases such as rheumatoid arthritis and multiple sclerosis (MS) is currently available in symptom management, pain-relieving, and mitigation of disease. Currently, prescribed drugs for patients with the disease work in specific mechanisms, regardless of failure to determine the most effective medication. We use a literature review to highlight two newly examined substances: organoruthenium 9E1 and APL altered collagen II263-272 peptide, and elaborate substances mentioned above' potential to be used in rheumatoid arthritis and MS therapy. Several studies show positive effects from 9E1 and altered CII263-272 peptides on experimented mice. Altered CII263-272 peptide can elicit Th cells to produce neurotrophic factors, decrease the body amount of pro-inflammatory T cells, increase the body amount of anti-inflammatory T cells, and alleviate collagen-induced arthritis symptoms. Meanwhile, 9E1 can inhibit Mst1 kinase effectively (IC₅₀=45nM), giving consequences of decreasing Th1 cells' cytokines, increasing Th2 cells' cytokines, decreasing body amount's IgG1 and IgG2a, slowing down EAE and collagen-induced arthritis' manifestation, increasing IL-10 and IL-4-producing T cells. Organoruthenium and altered CII263-272 peptide possess positive and multiple effects as therapies for EAE and collagen-induced arthritis, hence potential to be prescribed to patients with rheumatoid arthritis and MS. This literature review suggests further research concerning 9E1 and altered CII263-272 peptide usage in the community to examine their effectivity, side effects, and suitable dose.

Keywords: 9E, APL, autoimmune, EAE, collagen-induced arthritis

Introduction

Autoimmunity is a disorder that occurs due to the body's inability to maintain immunological tolerance. One type of drug to reduce malignancy in autoimmune diseases works by shifting the number of T cells from pro-inflammatory T cells to anti-inflammatory T cells (Elkhalifa et al., 2018) (Klöß et al., 2020). Th1 cells are a type of pro-inflammatory

cytokine-producing cell (Interferon, IL-2, IL-12), and Th2 cells are anti-inflammatory cytokine-producing cells (IL-4, IL-5, IL-6, IL-13). In multiple sclerosis (MS) patients, High Th1 cells will infiltrate brain lesions and exacerbate degeneration of myelinated nerve cells, while Th2 cells act as immunomodulators, preventing the expansion of lesions. Several studies have shown that the change from infiltrating and pro-inflammatory trigger cells to regulatory cells or Th2 cells inhibits the symptoms of various autoimmune diseases (Rocamora-Reverte et al., 2021) (Sabatos-Peyton et al., 2010).

This review article will discuss two substances that are thought to be associated with symptomatic improvement in collagen-induced arthritis and EAE. The first substance is the altered collagen II263-272 peptide. This substance is another form of CII263-272, a predominant antigenic collagen type II (CII) peptide that can induce T cell activation when attached to MHC and interact with T-cell receptors (TCR). The altered CII263-272 peptide differs from CII263-272 in that a specific amino acid substitution can attach to HLA-DR4/1-associated RA without a T-cell stimulatory effect and can inhibit T-cell activation in RA (Zhao et al., 2008). Another study showed that altered CII263-272 peptides could suppress Th17 cell counts and induce regulatory T cell differentiation in the early stages of collagen-induced arthritis (R. Li et al., 2009) (Zhang et al., 2020). With this definition, the altered CII263-272 peptide belongs to the altered peptide ligand (APL) class.

An altered peptide ligand (APL) is an analog of an antigen-specific to a particular T cell. Because several residues are different from the analog, APL can stimulate that T cell with the same or even a different response from the analog. APL can be classified into agonists, subagonists, superantagonists, partial agonists, and antagonists based on their ability to stimulate antigen-specific T cells. An example of APL circulating in the community as a reducer of malignancy in relapse-remitting MS is Glatiramer acetate. Glatiramer acetate, whose structure resembles the essential myelin protein, was initially used in the laboratory to induce EAE in mice and was found to decrease the susceptibility of these mice to EAE (Pul et al., 2011). Treatment with APL with an appropriate substitution of Th1 recognition residues can inhibit Th1 cell differentiation and simultaneously increase Th2 cell numbers. An increase in the number of Th2 will trigger the body's response to immunosuppression (Anderton, 2001). Another substance that will be discussed in autoimmune therapy is 9E1. 9E1 is organoruthenium that selectively inhibits sterile mammals 20 (MST1) kinase, a proapoptotic cytosolic kinase that plays an essential role in various biological processes, including cellular responses to oxidative stress (Anand et al., 2009). Researchers predict a link between the Mst1 gene and Th1 cell development. It is also known that Mst1 controls Ag receptor-associated nave T cell activation (Praskova et al., 2008) (C. Li et al., 2017).

The challenge in finding therapeutic drugs for autoimmune diseases is to find drugs that are most effective in prolonging the patient's life and drugs that are most effective in reducing degenerative symptoms of autoimmune diseases. Research to find new drugs continues to be carried out, and some research that seems irrelevant may significantly influence the advancement of knowledge about the treatment of autoimmune and immunodegenerative diseases. Reviewing the literature hopes that further and detailed discussion about the

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multifunctionality of altered collagen II263-272 peptide and organoruthenium 9E1 as a treatment for rheumatoid arthritis and MS is expected.

Literature Review

The most common autoimmune disease in the world is rheumatoid arthritis, followed by psoriasis, Crohn's Disease, type 1 diabetes, Multiple Sclerosis (MS), and systemic lupus erythematosus (SLE) (Centers for Disease Control and Prevention (CDC), 2009) (Fugger et al., 2020). The incidence of rheumatoid arthritis in Indonesia alone (aged 15 years and over) ranges from 0.2% to 0.3% (Darmawan et al., 1993). A study we reviewed used a mouse model of collagen-induced arthritis as an autoimmune model of rheumatoid arthritis, and a mouse model of experimental autoimmune encephalomyelitis (EAE) as an autoimmune model of MS (Constantinescu et al., 2011) (Williams, 2004). Neurotrophins are factor proteins that control synaptic function, preservation, and survival of neuronal cell morphology and differentiation. Neurotrophins have been shown to have neuroprotective effects in neurodegenerative diseases, (S. Skaper, 2008). The neurotrophic factor found in the brain is the brain-derived neurotrophic factor (BDNF) (Krabbe et al., 2007)v. Drugs that increase the potential of target cells or brain paracrine cells to secrete BDNF regularly have been shown to reduce the destructive effects of autoimmune diseases (MS) and brain immunodegenerative diseases (Alzheimer's disease) (S. D. Skaper, 2012) (Naegelin et al., 2020).

Research Methods

The method of writing a review of this article is based on the search of the relevant literature to the main problem of the review. Literature comes from textbooks or journals obtained online, then selected according to relevance to the theme and title, and feasibility. The literature search was conducted using PubMed and Google Scholar Database until the latest references in 2022.

Reference eligibility categories include (one reference does not necessarily cover all categories): (1) discuss treatment for rheumatoid arthritis and MS, (2) discuss drugs that have the potential to prolong the lifespan of brain nerve cells, reduce immune cell infiltration into the brain, or reduce erosion of bone and cartilage, (3) discusses brain-derived neurotrophic factor, Th1/Th2/Th17 cells, immunotherapy, Mst1, and Mst1 kinase genes, and IL-10, (4) discusses altered peptide ligands that can be used to treat rheumatoid arthritis or MS, (5) discusses the performance of autoimmunity drugs widely used today, such as glatiramer acetate, and (6) discusses organoruthenium 9E1 and altered collagen II263-272 peptide and their relationship with the body's immune system.

In this case, the authors use five leading research journals that form the basis for the theory of 9E1 and altered collagen II263-272 peptide as a drug for treating encephalomyelitis and collagen-induced arthritis, plus other supporting journals.

Results and Discussion

A research found that the ability of glatiramer acetate to induce Th1, Th1/Th0, and Th2 cells to produce BDNF. Glatiramer acetate (GA) is an altered peptide ligand of myelin essential protein (MBP) studied in mice infected with EAE. After GA-specific T cells were stimulated, BDNF secretion and GA-specific T-cell proliferation were calculated. The irradiated APCs did not proliferate, even though GA triggered them. There was a quantifiable small proliferation when GA-specific T cells were augmented in untriggered APCs. The graph shows that the irradiated APCs produced small amounts of BDNF, although the APCs did not proliferate. All GA-specific T cells produced more BDNF after incubation with GA-triggered APCs. RT-PCR and flow cytometry (not shown) showed that BDNF expression in mRNA to protein levels increased after treatment with GA. This study can be extrapolated for altered peptide ligands in general, thus proving that altered CII263-272 peptides can trigger Th1 and Th2 cells in mice with collagen-induced arthritis to produce BDN (Ziemssen et al., 2002).

A study was carried out with the procedure of giving altered collagen II263-272 peptide, wild type peptide, or phosphate-buffered saline (PBS) in three groups of experimental rats with collagen-induced arthritis (R. Li et al., 2009). After the 24th day, the group of rats given altered collagen was observed for arthritis scores and the results were significantly lower (95%CI 2.50 ± 2.43) than the group of rats treated with wild-type peptide (95%CI 4.50 ± 2.23) and PBS (6.33 ± 2.73 , $P < 0.05$). Subsequent observations were made by paying attention to Th17 cells as a variable. Th17 cells produce a proinflammatory cytokine, namely IL-17. The three groups of mice had higher serum levels of IL-17 than normal mice (CI95% 6.06 ± 1.31), with serum on altered CII263-272 peptide, wild-type peptide, and PBS 21.65 ± 5.50 , 27.82 ± 3.01 , and respectively. 24.09 ± 5.94 (calculations were made on the 17th day). Serum levels of IL-17 in the altered CII263-272 peptide-treated rats were significantly lower than in the other two groups ($P < 0.05$). On day 30, there was no difference in serum IL-17 levels between the three groups. These results indicate that the altered CII263-272 peptide can suppress Th17 cell activity in the early stages of collagen-induced arthritis. Another observation about the effect of altered CII263-272 peptides on regulatory/anti-inflammatory T cells showed that mice in the altered CII263-272 peptide treatment group had a higher ratio of Foxp3+CD4+CD25+ T cells to CD4+CD25+ T cells ($64.81 \pm 9.73\%$). significantly compared to wild-type peptide treatment mice ($48.02 \pm 5.33\%$) and PBS treatment mice ($41.77 \pm 7.51\%$) ($P < 0.01$), counting was carried out on day 17. On day 30, the ratio in the three groups decreased and did not differ significantly. These results indicate that altered CII263-272 peptides can increase regulatory T cells in the early stages of collagen-induced arthritis. Subsequent observations were made to evaluate the ability of the altered peptide in influencing the humoral immune response in rats infected with collagen-induced arthritis. ELISA was used to calculate the levels of anti-CII IgG antibodies and their subtypes (IgG1 and IgG2a) in the three groups. The results showed that there was no difference in the levels of anti-CII IgG and IgG1 in the three groups. However, the levels of IgG2a in the altered CII263-272 peptide treatment rats were significantly reduced compared to the PBS treatment rats (OD = 0.56 ± 0.19 to 0.95 ± 0.29 , $P < 0.05$). This suggests that the altered CII263-272 peptide can inhibit Th1 cell-dependent autoimmunity symptoms in vivo.

Research proves that altered CII263-272 peptide inhibits collagen-induced arthritis, 35 days after immunization, the mice were infected with collagen-induced arthritis (immunization with altered CII263-272 peptide), the mice were killed and the ankle joints were dissected, fixed with 10% buffered formalin, decalcified with ethylenediaminetetraacetic acid, and embedded in paraffin, then sliced for 4 μm preparation. Histological assessment was carried out on the following scale: 0 normal synovium, 1 – synovial membrane hypertrophy and cell infiltration, 2 – cartilage erosion and pannus, 3 – severe erosion of cartilage and subchondral bone, 4 – loss of joint integrity and ankylosis. The results showed that PBS-treated rats showed cartilage and bone erosion as well as a lot of inflammatory cell infiltration, with a mean histological value of 3.18 ± 0.85 . In altered CII263-272 peptide treated mice, moderate synovial hyperplasia and arthritis severity were significantly reduced compared to wild type peptide and PBS (1.27 ± 1.20 against 2.45 ± 1.52 , $P < 0.05$; 1.27 ± 1.20 against 3.18 ± 0.85 , $P < 0.01$) (R. Li et al., 2009).

A study found that organoruthenium compounds 9E1 and 9E2 were formed, differing in that 9E1 in the form of an R-configuration and 9E2 in the form of an S-configuration were tested against the kinases of the Ste-20 group, namely Mst1, PAK1, PAK4, and TAO2 (Anand et al., 2009)(Anand et al., 2009). Myelin basic protein is used as a substrate for all four proteins. The result is that compound 9E1 showed the highest selectivity to Mst1 than other kinases, with IC₅₀ shown in table 1. Compound 9E1 was concluded to have submicromolar potency with a preference for Mst1 10 times higher than TAO2 and 20 times higher than PAK1 and PAK4. 9E2 shows a potential greater preference for TAO2 than 9E1.

Table 1. IC₅₀ values of 9E1 and 9E2 inhibitors against four kinases, the Ste-20 group (Anand et al., 2009).

No	Kinase	Value of IC ₅₀ for 9E1 inhibitor	Value of IC ₅₀ for 9E2 inhibitor
1	PAK1	1.9 μM	0.7 μM
2	PAK4	1.2 μM	0.7 μM
3	TAO2	0.3 μM	130 nM
4	Mst1	45 nM	212 nM

Mammalian sterile 20 (MST1) kinase is a proapoptotic cytosolic kinase that plays an important role in various biological processes, including cellular responses to oxidative stress (Anand et al., 2009). Although no studies have found a physiological substrate for Mst1 kinase, it is known that the caspase-activated by Mst1 kinase phosphorylates histone H2b in the 14th amino acid serine (Praskova et al., 2008). The result is chromatin condensation that leads to apoptosis. Several studies have also suggested an association between the Mst1 gene and Th1 cell development. It is also known that Mst1 controls Ag receptor-associated nave T cell activation (Salojin et al., 2014). The Mst1 gene deletion procedure in experimental mice

through homologous recombination, followed by germline transmission of the mutant gene to Mst1 gene heterozygous mice (Mst1^{+/-}) and homozygous mice (Mst1^{-/-}) (Tomiya et al., 2013). There were fewer CD8⁺ and CD4⁺ T-cell counts in peripheral blood counts in Mst1^{-/-} mice compared to wild-type (WT) mice. Mst1^{-/-} also showed significantly reduced levels of B lymphocytes. Mst1^{-/-} mouse B cells had a decreased response-ability, while the production of IL-2, IFN- γ , and TNF- α in Mst1^{-/-} mouse T cell culture with stimulation through the CD3/CD28 pathway was significantly decreased (Table 2). Th2 cytokine levels (IL-4, IL-5, IL-13) were increased in the same T cell culture, indicating that Mst1^{-/-} T cells were more motivated to become Th2 cell subtypes.

Table 2. Cytokine production in CD4⁺ T cells from WT and Mst1^{-/-} mice (n=5 per genotype), was observed 48h after stimulation with mAbs on CD3 and CD28 (1 g/ml) (Salojin et al., 2014)

No	Group of Rats	Level of IL-4 (ng/ml)	Level of IL-5 (ng/ml)	Level of IL-10 (ng/ml)	Level of IL-13 (ng/ml)
1	Mst1 ^{+/+}	12 \pm 1	15 \pm 1	31 \pm 6	26 \pm 1 m
2	Mst1 ^{-/-}	37 \pm 1	42 \pm 2	105 \pm 15	63 \pm 4
3	p value	3 x 10 ⁻⁷	1 x 10 ⁻⁵	2 x 10 ⁻³	4 x 10 ⁻⁵
No	Group of Rats	Level of TNF- α (ng/ml)	Level of IFN- γ (ng/ml)	Level of IL-2 (ng/ml)	
4	Mst1 ^{+/+}	1769 \pm 83	2393 \pm 198	16416 \pm 2371	
5	Mst1 ^{-/-}	725 \pm 25	920 \pm 35	1871 \pm 227	
6	p value	2 x 10 ⁻⁶	8 x 10 ⁻⁵	3 x 10 ⁻⁴	

In addition, IL-10 production in Mst1^{-/-} T cells was markedly increased (as previously noted, IL-10 is synthesized by Th2 and T regulatory CD4⁺CD25⁺Foxp3⁺). In observing IgG1 and IgG2a levels, Mst1^{-/-} mice produced less IgG1 and IgG2a than WT (Wild-Type) mice when both were stimulated with chicken OVA on CFA (containing *Mycobacterium tuberculosis*). Histological observations in Mst1^{-/-} mice showed a lower incidence and severity than WT mice when both groups of mice were immunized with CII on CFA. Both groups of mice were immunized with myelin oligodendrocyte glycoprotein peptide 35-55 in CFA. Both groups showed EAE symptoms, although the manifestation in Mst1^{-/-} mice was slower than in others (p = 0.0098, by Kaplan-Meier log-rank test). Furthermore, histological observations were made on the brain and bone marrow preparations. The results showed a lower severity of inflammatory and degenerative lesions in Mst1^{-/-} mice than in WT mice (8.1 \pm 3.6 against 31.8 \pm 2.5, p = 0.00017). In addition, more IL-10 and IL-4-producing T cells were found in the bone marrow of Mst1^{-/-} mice, suggesting that Mst1 deletion in the CD4⁺ T-cell compartment is sufficient to relieve CNS inflammation when infected with EAE. It should be noted that Mst1

deficiency did not affect the growth and development of mice, and no endocrine abnormalities were seen when compared with wild-type mice (Anand et al., 2009).

Conclusion

In this literature review, it was emphasized that 9E1 and altered collagen II263-272 peptides have the potential to treat symptoms of patients with autoimmune diseases, especially rheumatoid arthritis and MS. The two substances differ in their mechanism for reducing malignancy. However, both can reduce the number of pro-inflammatory T cells, increase regulatory T cells' levels, decrease the production of Th1 cytokines (IL-2, IL-12), and increase the production of Th2 cytokines (IL-4, IL-5, IL-6, IL-13). Altered peptide ligand (APL) specific for Th1 and Th2 cells can trigger specific cells to produce BDNF. BDNF is an essential factor that helps maintain brain nerve cells and prevents damage from MS disease. For APL therapy to be effective, it should be noted that the anti-APL Th1 and Th2 cell reactions are not encephalitogenic. The altered CII263-272 peptide is an ideal APL that induces a non-encephalitogenic Th2 reaction that facilitates local immunosuppression and neuroprotection. Th1 may also contribute to the therapeutic effect by acting as a producer of neurotrophic factors. 9E1 is a more effective Mst1 kinase inhibitor than 9E2 and the most effective Mst1 kinase inhibitor with an IC₅₀ value of 45 nM. Given its inhibitory effect, 9E1 was able to reduce the impact of EAE, reduce the response of CD4⁺ T cells to encephalitogenic antigens and protect against collagen-induced arthritis.

An essential effect of 9E1 is helping to increase the levels of IL-10 cytokines, wherein the increase of this cytokine is a self-limiting mechanism that can shift the concentration of T cells from effector T cells to the IL-10-dependent regulatory T cell population. There is the potential to combine the two substances as one medication, considering a more optimal impact on increasing levels of regulatory T cells and decreasing inflammatory T cells, and other effects in the form of triggering the production of neurotrophic factors by altered CII263-272 peptide. In addition, the increase in neurotrophic factors is expected to prevent other neurodegenerative diseases, such as Alzheimer's disease. Further research needs to be done to determine the effectiveness, side effects, and appropriate dosage of these two substances when given as a medication to society.

Declarations of Competing Interest

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Contribution for authorship

Khairu Zein - conception and design; analysis and interpretation of the data; drafting of the article; **Ardhin Martdana** - drafting of the article , critical revision of the article for important intellectual content; **Fenska Seipalla**- drafting of the article, critical revision of the article for important intellectual content, final approval of the article; **Tirza Sosanta** - drafting of the article, critical revision of the article for important intellectual content

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