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Effects of Tissue Inhibitor Metalloproteinase-1 on Allergic Responses in Ovalbumin-induced Allergic Rhinitis Mice Model

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ABSTRACT

The prevalence of allergic rhinitis (AR) is increasing globally. However, the role of tissue inhibitor of metalloproteinases-1 (TIMP-1) in allergic diseases remains unclear. While some studies have found a positive correlation between TIMP-1 and allergic conditions, others suggest that TIMP-1 may have a protective effect. The aim of this study was to examine the effects of TIMP-1 on allergic responses in an ovalbumin (OVA)-induced allergic rhinitis mouse model. The mice were divided into four groups: a control group, an AR group, a TIMP-1 10 µg/kg group, and a TIMP-1 20 µg/kg group. Nasal symptoms (sneezing and nasal rubbing), serum OVA-specific immunoglobulin E (IgE) levels, and eosinophil counts in the nasal mucosa were measured. The AR group showed significantly higher nasal symptoms, serum OVA-specific IgE levels, and eosinophil counts compared to the control group. Nasal symptoms, such as sneezing and nasal rubbing, were significantly reduced after intranasal administration of TIMP-1 at a dose of 20 µg/kg. Both 10 µg/kg and 20 µg/kg doses of TIMP-1 also lowered IgE levels and eosinophil counts significantly. These findings suggest that TIMP-1 may play a protective role in an allergic rhinitis mouse model by reducing nasal symptoms, OVA-specific IgE levels, and eosinophil infiltration in the nasal mucosa.

Keywords: Allergic rhinitis, Tissue inhibitor metalloproteinase-1, Ovalbumin, Immunoglobulin E, Oosinophil

Introduction

Allergic rhinitis (AR) is one of the most common diseases worldwide.[1] It is characterized by nasal symptoms such as sneezing, itching, runny nose, and nasal congestion. These symptoms result from inflammation mediated by immunoglobulin E (IgE) in response to allergen exposure.[1,2] Allergic rhinitis has a major impact on quality of life, emotional stability, sleep, daily activities, and productivity.[2] Several studies have shown that the rising prevalence of allergic rhinitis (AR) is not limited to developed countries but is also occurring in developing countries, particularly in urban areas where the prevalence was once low.[1] A contributing factor to the increasing prevalence of allergies, particularly in developed countries, is the "hygiene hypothesis" proposed by Strachan.[3] Some studies supporting this hypothesis have shown that reduced prevalence of allergic diseases in population living in remote tropical areas of developing countries may be associated with the protective effects of intestinal worm infections.[4,5]

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The excretory-secretory (ES) product of intestinal worms is considered to have a preventive effect against allergies. Several studies have identified many recombinant proteins from parasitic worms that exhibit potential as therapeutic targets for immunological diseases, including allergies.[6,7] One of these proteins has a sequence homologous to a family of mammalian proteins known as tissue inhibitor metalloproteinase (TIMP).[8] Tissue inhibitor of metalloproteinases (TIMP) constitutes approximately 6% of the total ES product produced by adult hookworms. This protein plays an important role in helminth therapy due to its immunosuppressive effects can be utilized to help treating allergic and autoimmune diseases.[9]

Tissue inhibitor of metalloproteinases (TIMP) is an endogenous protein that functions as a natural inhibitor of metalloproteinases (MMPs). This protein is present in mammals, including humans. Initially recognized for their role as endogenous protease inhibitors, TIMPs are now understood to also play a role in immunological responses and inflammatory processes, particularly TIMP-1. The activity of TIMPs varies across the body, —exhibiting elevation in some tissues and reduction in others—during the progression of certain diseases. Among the four members of the TIMP family, TIMP-1 is distinctive as it can exert its effects not only by interacting with different forms of MMPs but also through other mechanisms. TIMP-1 binds to its receptor and activates signaling pathways in various immune cells, including T cells, B cells, NK cells, neutrophils, and macrophages. [10,11]

The exact role of TIMP-1 in allergic diseases is still not fully understood. However, several studies using mouse models of asthma triggered by ovalbumin have shown that TIMP-1 is actively involved in allergic airway inflammation.[11] In one study, mice that did not have TIMP-1 experienced stronger airway hyperresponsiveness and more severe eosinophilic inflammation. They also showed increased levels of T2 cytokines. These results suggest that TIMP-1 might actually help

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protect the airways and reduce asthma severity.[12] Other study, however, has reported different results. In that experiment, mice that were given TIMP-1 actually showed more eosinophil infiltration and a shift in macrophages toward the M2 phenotype. This change may play a role in promoting type 2 (T2) inflammation in asthma.[13]

Research on the role of TIMP-1 in allergic rhinitis remains limited. Previous findings have shown a positive correlation between TIMP-1–positive cells and mast cells in the nasal mucosa of patients with allergic rhinitis 30 minutes after exposure to house dust mite (HDM) allergen. Six hours after exposure, the MMP/TIMP-1 ratio was found to be higher in HDM-exposed mucosa. These findings suggest that relatively low TIMP-1 levels may enhance the activity of MMP-2, MMP-9, and MMP-13, which are involved in cell migration during the late phase of allergic reactions.[14]

The role of TIMPs, particularly TIMP-1, in allergic diseases remains controversial, and research on their involvement in allergic rhinitis is still limited. Therefore, this study evaluated the role of TIMP-1 in allergic rhinitis.

Materials and Methods

Animals

This study used male Balb/c mice aged 6–8 weeks, weighing 20–25 g. The mice were acclimatized for 7 days under standard laboratory conditions before induction. Food and water were provided *ad libitum*. The experimental protocol was approved by the Ethics Committee of the Faculty of Medicine, University of Andalas, Padang, Indonesia (certificate no. 438/UN.16.2/KEP-FK/2024). The mice were randomly divided into four groups, with six mice in each group, making a total of 24 mice. The groups were as follows:

Group 1 (G1) : control group, mice were not induced ovalbumin and given phosphate- buffered saline (PBS) 10 µl/kg intranasally

Group 2 (G2) : allergic rhinitis group, mice were induced ovalbumin and given PBS 10 µl/kg intranasally

Group 3 (G3): treatment group 1, mice were induced ovalbumin and given recombinant protein of TIMP-1 10 µg/kg intranasally

Group 4 (G4): treatment group 2, mice were induced ovalbumin and given recombinant protein of TIMP-1 20 µg/kg intranasally

Establishment of AR model and treatment procedures

Sensitization began with an intraperitoneal injection of 50 µg of ovalbumin (OVA) (chicken egg albumin grade V, Sigma-Aldrich) and 1 mg of aluminum hydroxide [$Al(OH)_3$] dissolved in 200 µl PBS as systemic sensitization. The injections were administered on days 0, 7, and 14. On day 21, the local sensitization phase began. The mice were challenged intranasally using a micropipette with 30 µl of PBS containing 500 µg OVA for seven consecutive days, ending on day 27. On day 23 (the third day of challenge), groups G1 and G2 received 10 µl/kg of PBS intranasally, while group G3 received 10 µg/kg of rhTIMP-1, and group G4 received 20 µg/kg of rhTIMP-1 intranasally. These treatments were given once daily for five consecutive days (days 23–27). All mice were sacrificed 24 hours after the final challenge (day 28) as seen in Figure 1.

Nasal Symptoms

After the final allergen exposure on day 27, the mice were monitored for 15 minutes to record signs and symptoms of allergic rhinitis, such as sneezing and nasal rubbing.

Blood samples

Blood samples were collected via intracardiac puncture while the mice were under anesthesia. The mice were anesthetized by intraperitoneal injection of 0.03 ml ketamine (120 mg/kg) and 0.01 ml xylazine (5 mg/kg). The samples were then centrifuged at 3000 rpm for 10 minutes to separate the serum. The collected serum was stored at −80 °C for later use.

Measurement of OVA-specific IgE Level

Serum samples were used to measure OVA-specific IgE levels with an enzyme-linked immunosorbent assay (ELISA) kit (FineTest, Wuhan, China), following the manufacturer's instructions.

Histological examination

The head of each mouse was decapitated and fixed in 10% paraformaldehyde for 24 hours. Nasal mucosal tissues were then collected and embedded in paraffin blocks. Tissue sections with a thickness of 5 µm were prepared and stained with hematoxylin and eosin. The slides were examined under a Leica optical microscope at 400× magnification across ten different fields to count eosinophils. Eosinophils were identified based on their characteristic morphology, including a bilobed nucleus and eosinophilic granules in the cytoplasm.[15]

Statistical Analysis

Data are presented as mean ± standard deviation. Statistical comparisons between groups were performed using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test with GraphPad Prism software version 10. A p-value of < 0.05 was considered statistically significant.

Results and Discussion

The average number of sneezing episodes was 6.67 ± 5.82 in the control group, 15.50 ± 3.78 in the AR group, 8.17 ± 5.49 in the TIMP-1 10 µg/kg group, and 5.00 ± 2.97 in the TIMP-1 20 µg/kg group. The average number of nasal rubbing episodes was 11.83 ± 6.05 in the control group, 22.50 ± 7.01 in the AR group, 14.17 ± 8.52 in the TIMP-1 10 µg/kg group, and 11.33 ± 3.27 in the TIMP-1 20 µg/kg group. We found a significant difference in sneezing ($p = 0.018$) and nasal rubbing ($p = 0.046$) between the control and AR groups (Figure 2). In this study, we recorded symptoms for 15 minutes on the final day after the ovalbumin nasal challenge. Although different studies may use varying

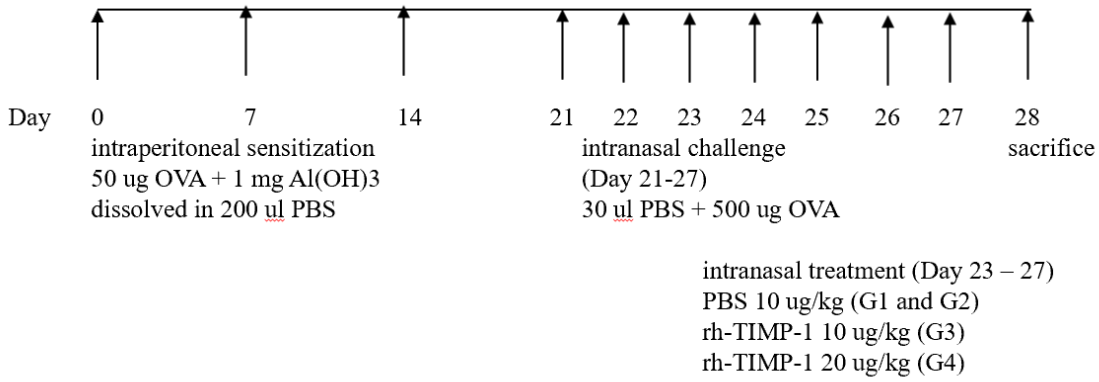

Figure 1: Schematic of the establishment of allergic rhinitis model and treatment procedures

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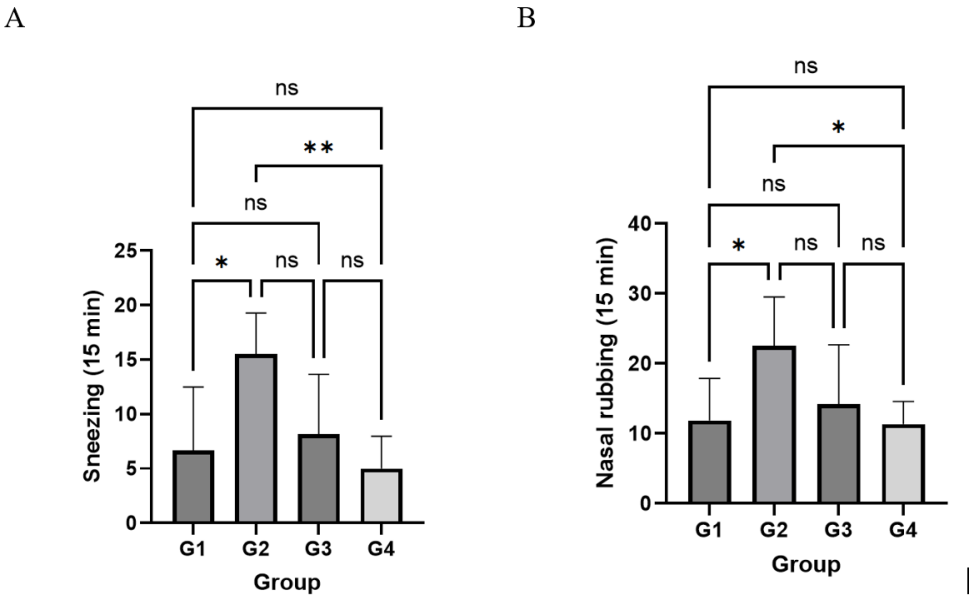

Figure 2: Effect of TIMP-1 on nasal symptoms in allergic rhinitis mice: A.sneezing, B. nasal rubbing in 4 treatment groups (G1: control; G2: AR; G3: TIMP-1 10 µg/kg; G4: TIMP-1 20 µg/kg). Statistical analysis was performed by one-way ANOVA followed by Post Hoc test; *p<0.05, **p<0.01, ns:not significant; AR: allergic rhinitis; TIMP: Tissue inhibitor metalloproteinase.

methods and time intervals to count sneezing and nasal rubbing episodes, the results are generally consistent. [16] Piao et al,[17] Nguyen et al,[18] Liu et al,[19] and Kang et al,[20] in their studies also counted for 15 minutes found that the AR group showed higher frequency of nasal rubbing and sneezing compared to the control group. This result is consistent with the typical symptoms of allergic rhinitis, where exposure to allergens triggers the immune system and causes these common reactions.[21]

In this study, we used ovalbumin as the allergen. Ovalbumin is one of the most commonly used allergens in allergy research involving experimental animals.[22] Beside ovalbumin, histamine can be used as allergen to induce allergic responses in animals model. [23] When an allergen enters the body, it is processed and triggers a strong Th2 cell response. Th2 cells produce cytokines like IL-4, IL-5, and IL-13, which then trigger B cells to release IgE antibodies. These IgE antibodies circulate in the blood and attach to receptors on basophils and mast cells. When an allergic reaction begins, the mast cells break down and release histamine along with other inflammatory substances, such as leukotrienes and prostaglandins. These substances cause typical nasal allergy symptoms, including sneezing, itching, runny nose, and congestion.[21,24]

Allergic rhinitis mice treated with TIMP-1 (10 and 20 µg/kg) showed fewer sneezing and nasal rubbing episodes compared to the AR group. Our results showed that giving a 20 µg/kg dose of TIMP-1 was much more effective at reducing sneezing and nasal rubbing ($p = 0.005$ and $p = 0.035$, respectively) compared to the 10 µg/kg dose (Figure 2). This suggests that TIMP-1 has strong potential as a treatment to ease allergic rhinitis symptoms. The decrease in these symptoms indicates that TIMP-1 may help control the inflammatory pathways involved in allergic reactions. These findings support by one study that found when TIMP-1 is activated at the beginning of inflammation, it can help lower hypersensitivity. In contrast, when TIMP-1 is absent, the hypersensitivity at the inflammation site develops more quickly and lasts longer. Administering recombinant TIMP-1 may therefore help lessen inflammatory hypersensitivity.[25] That research showed that TIMP-1 plays an important role in regulating inflammation.

The average serum levels of OVA-specific IgE were 1.86 ± 0.48 ng/ml in the control group, 138.00 ± 5.13 ng/ml in the AR group, 77.00 ± 49.82 ng/ml in the TIMP-1 10 µg/kg group, and 65.74 ± 50.32 ng/ml in the TIMP-1 20 µg/kg group. AR mice showed a significant increase in OVA-specific IgE levels compared to normal mice ($p < 0.0001$) (Figure 3). Some studies using ovalbumin as allergens to induce AR also showed the same results. [17,19,20] This is in line with the pathophysiology of allergic rhinitis where the increase in IgE is caused by a strong T-helper type 2 (Th2) immune response.[24] TIMP-1 at both doses (10 and 20 µg/kg) significantly reduced OVA-specific IgE levels in AR mice ($p = 0.035$ and $p = 0.010$, respectively) (Figure 3). This decrease suggests that TIMP-1 may help control the immune response that cause allergic rhinitis. It might work by suppressing B cell activity and IgE production or by bringing the Th2 immune response back into balance.

The average number of eosinophils in the nasal mucosa was 1.33 ± 1.21 in the control group, 6.00 ± 2.19 in the AR group, 1.33 ± 1.75 in the TIMP-1 10 µg/kg group, and 1.00 ± 1.09 in the TIMP-1 20 µg/kg group. Mice with OVA-induced allergic rhinitis had a significant increase in eosinophil counts in their nasal tissue compared to the control group ($p = 0.0004$) (Figure 5). The increase in eosinophils reflects the typical pattern of allergic inflammatory cell infiltration, which is strongly associated with the clinical symptoms seen in this study. In the late phase of an allergic reaction, basophils, neutrophils, monocytes, and eosinophils are recruited to the affected area. At the same time, various mediators such as cytokines, prostaglandins, and leukotrienes are released. Together, these factors help maintain and intensify the inflammatory response.[24]

TIMP-1 at both doses (10 and 20 µg/kg) significantly reduced the total number of eosinophils in the nasal tissue of AR mice compared to the AR group ($p = 0.0004$ and $p = 0.0002$, respectively) (Figure 5). An imbalance between MMP and TIMP can make it easier for inflammatory cells like eosinophils and mast cells to move into the nasal mucosa.[14] The findings in this study suggest that in allergic rhinitis, lower levels of TIMP-1 may cause an increase in eosinophils in the nasal tissue, which can contribute to the appearance of allergic symptoms. Guerra et al,[26] showed increased level of MMP-9, MMP-2 and MMP-7 and decreased tissue inhibitors of MMPs level (TIMP-1 less than TIMP-2) in patients with chronic rhinosinusitis with nasal polyps also in allergic rhinitis group.

The histopathological results also showed that eosinophils cell infiltration was higher in the AR group than in the control group, but it decreased after TIMP-1 treatment (Figure 4). Giving TIMP-1 intranasally may help bring the balance between MMP and TIMP back to normal in the nasal mucosa, which can reduce the movement of

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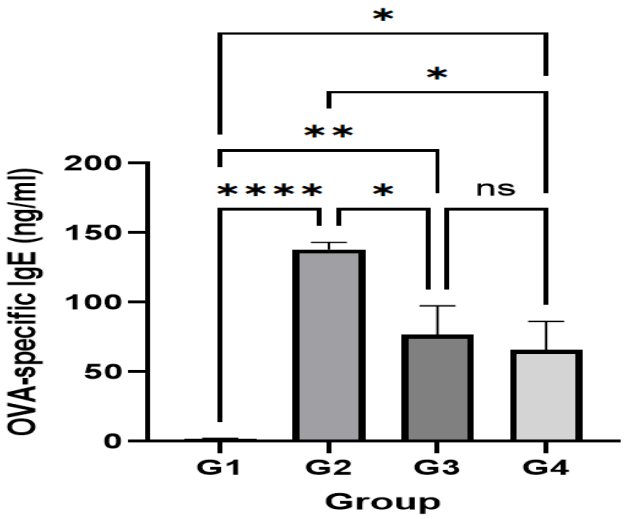

Figure 3: Effect of TIMP-1 on the OVA-specific immunoglobulin-E in the serum of allergic rhinitis mice in 4 treatment groups: (G1: control; G2: AR; G3: TIMP-1 10 µg/kg; G4: TIMP-1 20 µg/kg). Statistical analysis was performed by one-way ANOVA followed by Post Hoc test; *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, ns:not significant; AR: allergic rhinitis; TIMP: Tissue inhibitor metalloproteinase.

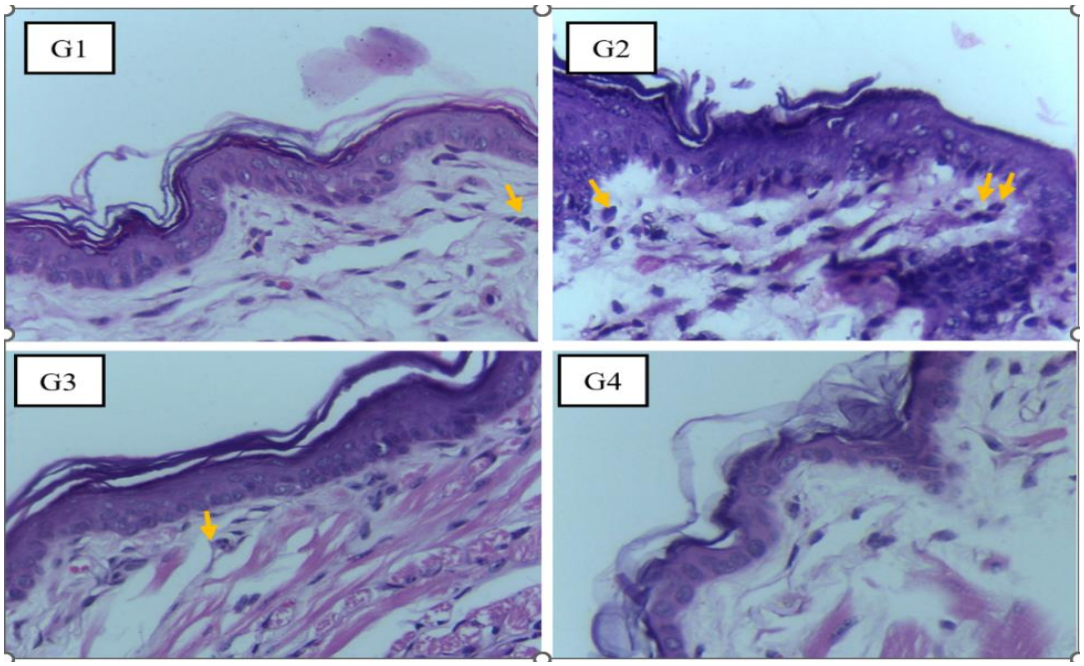

Figure 4: Histopathology of nasal mucosa show infiltration of eosinophils (arrow) (G1. control group, G2. AR group, G3. TIMP-1 10 ug/kg group, G4. TIMP-1 20 ug/kg group) (H&E, 400 x)

eosinophils into the tissue. Navarro et al,[27] also reported that hookworm excretory/secretory products, known as anti-inflammatory protein-2 (AIP-2)—a protein similar to TIMP—can significantly lessen OVA-induced airway inflammation by preventing eosinophils and lymphocytes from infiltrating the airways.

Besides acting as a natural protease inhibitor, TIMP-1 also works like a cytokine that affects how the immune system responds and controls inflammation. It attaches to specific receptors and triggers signaling pathways in different immune cells, such as T cells, B cells, natural killer (NK) cells, neutrophils, eosinophils, and macrophages.[11] Studies in asthma models have shown a protective role for TIMP-1,[12] while others have shown pro-inflammatory effects,[13] indicating the complexity of this molecule's role. So, the results found in this study are probably caused by a combination of TIMP-1's ability to block MMP and its interaction with other cell signaling pathways.

When compared to the relief of nasal symptoms like sneezing and nose rubbing, the impact on the molecular level (IgE) and cellular level (eosinophils) was even more noticeable with both doses of TIMP-1. This shows that TIMP-1 can strongly target the root immune and inflammatory processes that cause allergic rhinitis. Both doses were equally effective in reducing eosinophil buildup in the nasal tissue. This suggests that even lower doses may be enough to control the inflammatory response at the cellular level. The clear drop in eosinophil counts at both doses (10 and 20 µg/kg) shows that TIMP-1 has a strong effect on easing eosinophilic inflammation. This aligns with its known role in regulating the extracellular matrix and controlling the movement of inflammatory cells.[13]

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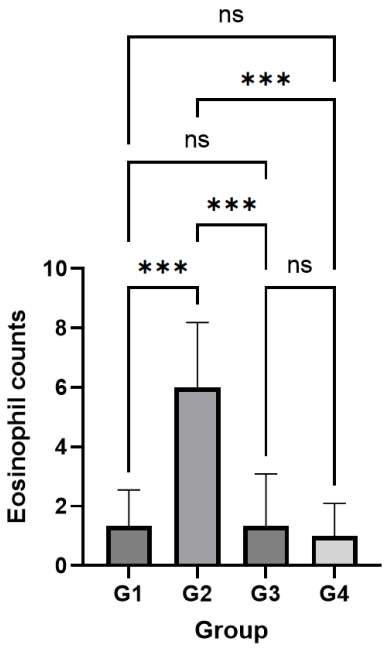

Figure 5: Effect of TIMP-1 on Eosinophil counts in the nasal mucosa of allergic rhinitis mice in 4 treatment groups (G1: control; G2: AR; G3: TIMP-1 10 µg/kg; G4: TIMP-1 20 µg/kg).. Statistical analysis was performed by one-way ANOVA followed by Post Hoc test; ***p<0.001, ns:not significant; AR: allergic rhinitis; TIMP: Tissue inhibitor metalloproteinase.

Even though this study gives promising results, it still has some limitations. Because the research was done on animals, more studies are needed before the findings can be applied to humans. How TIMP-1 actually lowers IgE and eosinophil levels is also not completely clear yet. Future research should look deeper into the molecular mechanisms, especially the roles of specific MMPs and pro-inflammatory cytokines, to better understand the signaling pathways at work.

Conclusion

This study shows that TIMP-1 can help ease allergic reactions in allergic rhinitis induced mice. It does this by lowering the levels of OVA-specific IgE in the blood and reducing the buildup of eosinophils in the nasal tissue. These effects happen at both the molecular and cellular levels, suggesting that TIMP-1 could be a promising target for treating allergic rhinitis.

Conflict of Interest

The authors declare no conflict of interest

Authors' Declaration

The authors hereby declare that the work presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

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