



## REVIEW ARTICLE

## EOSINOPHILS IN SICKLE CELL ANEMIA: EMERGING MOLECULAR MECHANISMS AND CLINICAL IMPLICATIONS

Emmanuel Ifeanyi Obeagu

Department of Biomedical and Laboratory Science, Africa University, Zimbabwe.

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#### \*Address for Correspondence:

Dr. Emmanuel Ifeanyi Obeagu, Department of Biomedical and Laboratory Science, Africa University, Zimbabwe. Tel: +234 803 736 9912; E-mail: [emmanuelobeagu@yahoo.com](mailto:emmanuelobeagu@yahoo.com)

### Abstract

Sickle cell anemia (SCA) is a genetic hemoglobinopathy characterized by defective hemoglobin S, which results in sickle-shaped red blood cells. Chronic inflammation, endothelial dysfunction, and repeated vaso-occlusive crises (VOC) characterize the condition, all of which contribute considerably to morbidity and mortality. The purpose of this paper is to elucidate potential molecular pathways and interactions involving eosinophils in the context of SCA severity. A thorough literature analysis was done to collect existing evidence on the molecular interactions of eosinophils in inflammatory disorders, with an emphasis on their probable involvement in SCA. The findings indicate that eosinophils may contribute to SCA severity via several routes. Eosinophil degranulation produces cytotoxic proteins such as major basic protein (MBP) and eosinophil peroxidase (EPO), which can increase oxidative stress and endothelial damage. Furthermore, eosinophils interact with adhesion molecules, causing vascular inflammation and aiding in the attachment of sickled red blood cells to the endothelium. Eosinophils appear to play multiple roles in the pathogenesis of SCA, including inflammation, oxidative stress, and endothelial dysfunction. While direct studies on eosinophils in SCA are sparse, the molecular insights gained from this review indicate their possible role in disease severity.

**Keywords:** Sickle cell anemia, eosinophils, inflammation, molecular mechanisms, vaso-occlusive events, immune modulation.

### INTRODUCTION

Sickle cell anemia (SCA) is a model of hematological complexity, with a wide range of clinical symptoms ranging from moderate to severe and frequently unpredictable results. Despite progress in understanding its genetic foundation and pathophysiology, the mechanisms driving the varying severity of SCA remain unknown. Recent study has given light on how eosinophils, which have previously been seen as effector cells in allergy responses, contribute to the pathophysiology of SCA. Eosinophils, traditionally thought to be passive bystanders in hemoglobinopathies, have emerged as active actors in the complex molecular landscape of SCA<sup>1</sup>. The connection between eosinophils and SCA severity is a complex network of molecular interactions that includes inflammation, immunological dysregulation, and vascular dysfunction.

Understanding the role of eosinophils in SCA pathophysiology is critical for clarifying disease causes and discovering new treatment targets. By thoroughly examining the literature on eosinophil biology and its relevance to SCA, this study seeks to provide insights

into the molecular mechanisms driving disease severity and inform the development of tailored therapies<sup>2</sup>.

Vaso-occlusive crises (VOCs) are central to the pathogenesis of SCA, which are characterized by sickle-shaped red blood cells occluding tiny blood arteries, resulting in tissue ischemia and infarction. Eosinophils have been linked to vascular inflammation and endothelial dysfunction, raising the risk of VOCs and organ damage in SCA. Furthermore, eosinophils interact with other immune cells, such as neutrophils and platelets, which exacerbates the inflammatory response and contributes to the persistence of vascular injury. In addition to their role in inflammation and vascular disease, eosinophils influence the hemolytic process associated with SCA via a variety of methods. Eosinophil-derived mediators can directly or indirectly affect red blood cell (RBC) membrane integrity and enhance RBC adherence to endothelial cells, aggravating hemolysis and contributing to the etiology of anemia in SCA. Furthermore, eosinophils may have a role in the control of immunological responses to RBCs, which could influence the pace of hemolysis and illness severity<sup>3</sup>.

Genetic investigations have revealed important information about the genetic factors of eosinophil function and their implications for SCA severity. Polymorphisms in genes involved in eosinophil activation and cytokine signaling pathways have been related to variations in illness phenotype, emphasizing the role of genetic factors in regulating eosinophil-mediated processes in SCA. Furthermore, developing therapeutic methods that target eosinophils have significant opportunities for reducing disease severity and improving clinical outcomes in SCA patients<sup>3</sup>.

Given the increased awareness of eosinophils as significant participants in SCA pathophysiology, there is an urgent need for additional study to determine the particular processes underpinning their contributions to disease severity. Integrating insights from fundamental science research with clinical observations is critical for improving our understanding of eosinophil-mediated processes in SCA and converting these discoveries into useful treatment strategies. This thorough review seeks to summarize existing understanding on the molecular interplay of eosinophils in SCA severity, laying the groundwork for future research efforts aimed at better therapy of this complicated hematological illness<sup>4</sup>.

The purpose of this review is to thoroughly understand the molecular interactions of eosinophils in sickle cell anemia (SCA) severity.

#### **Eosinophils**

Eosinophils are a type of white blood cell (leukocyte) that has many functions in the immune system, including protecting against parasites and moderating inflammatory responses. These cells are distinguished by their multilobed nuclei and cytoplasmic granules that contain a variety of enzymes, proteins, and mediators<sup>4</sup>. Eosinophils are primarily responsible for battling parasite illnesses, particularly helminths. They use poisonous proteins stored in their granules to fight and eliminate parasites<sup>5</sup>. Eosinophils, in addition to battling parasites, help to regulate inflammatory reactions. They emit cytokines, chemokines, and lipid mediators, which influence immune cell and tissue responses. Eosinophils are linked to allergic reactions, especially in allergic asthma and other allergic disorders. They accumulate in tissues during allergic reactions, producing inflammatory mediators that cause tissue damage<sup>6</sup>. In addition to immunological tasks, eosinophils participate in tissue repair; wound healing, and tissue homeostasis.

#### **Eosinophils in Sickle Cell Anemia (SCA)**

Eosinophils have received attention in the context of sickle cell anemia due to the chronic inflammatory condition seen in SCA patients. While there have been few direct investigations on eosinophils in SCA, their role in immunological regulation and inflammation implies that they may have an impact on disease severity<sup>7-9</sup>. When Eosinophils are activated; they release cytokines, chemokines, and other inflammatory mediators. Chronic inflammation in SCA contributes to disease severity. Eosinophils' ability to release these mediators may aggravate the inflammatory cascade in SCA<sup>10</sup>. SCA is characterized by vaso-occlusive crises, which occur when sickled red blood cells block small

blood veins. While eosinophils' direct role in these events is unknown, their interactions with endothelial cells and the production of cytotoxic chemicals may contribute to endothelial dysfunction, exacerbating vaso-occlusive crises<sup>11-15</sup>.

Eosinophils, while usually connected with parasite defense and allergy responses, have complicated functions that go beyond these traditional responsibilities<sup>16</sup>. While direct evidence in sickle cell anemia is sparse, their participation in immune regulation and inflammation implies possible implications to disease development. Further research is needed to understand their unique role and mechanisms in SCA, which will pave the way for possible therapeutic approaches aimed at reducing disease severity and consequences. Eosinophils, a type of white blood cell known for its role in allergy responses and immunological control, have sparked attention in sickle cell anemia (SCA) due to the disease's chronic inflammatory condition. While direct investigations on eosinophils in SCA are scarce, their possible roles and interactions within this hemoglobinopathy are worth investigating<sup>17</sup>. Chronic inflammation is a defining feature of SCA and contributes considerably to disease severity. Eosinophils, which are known to release cytokines and chemokines, may contribute to the inflammatory environment in SCA, thereby aggravating the inflammatory cascade<sup>18</sup>.

#### **Immune activation and vaso-occlusive events**

These crises, which are characterized by the blockage of blood vessels by sickled red blood cells, are fundamental to SCA problems. While the role of eosinophils in these events is unknown, their interactions with endothelial cells and the possible release of cytotoxic chemicals may contribute to endothelial dysfunction, altering the frequency or severity of vaso-occlusive crises<sup>19-25</sup>. Eosinophils express adhesion molecules such as P- and L-selectin. Investigating their interactions with endothelial cells in the setting of SCA may uncover potential roles in vascular adhesion and endothelial dysfunction<sup>26</sup>. Eosinophils produce reactive oxygen species (ROS) when activated. Oxidative stress is a crucial factor in SCA pathogenesis. Understanding eosinophil-derived ROS and their effects on red blood cell physiology or endothelial function may shed light on their role in disease severity<sup>27</sup>. Eosinophils communicate with other immune cells. Investigating their connections and the potential modification of the immune landscape in SCA may reveal unexpected interactions that influence disease development<sup>28</sup>. While direct data is lacking, investigating the potential involvement of eosinophils in SCA represents a viable route for better understanding disease complexity. Unraveling eosinophil relationships and functions within the SCA environment could shed light on their contributions to disease severity and consequences, potentially guiding future therapeutic options.

#### **Eosinophils: Functions and roles**

Eosinophils are a specialized type of white blood cell that plays diverse roles in the immune system. Their functions extend beyond their historical association

with parasitic infections and allergic responses. Eosinophils are characterized by their bilobed nucleus and granules containing various proteins, enzymes, and mediators within their cytoplasm<sup>29</sup>. Eosinophils are integral in combating parasitic infections, especially against helminths (parasitic worms). They release toxic granule proteins and enzymes to target and kill parasites, playing a crucial role in host defense against these organisms<sup>29</sup>. Eosinophils are involved in regulating inflammatory responses. They secrete cytokines, chemokines, and lipid mediators that modulate immune cells and tissue responses. However, their exact role in promoting or controlling inflammation can vary in different contexts.<sup>30</sup> Eosinophils are prominently associated with allergic conditions, such as allergic asthma and allergic rhinitis. They accumulate in tissues during allergic reactions and release inflammatory mediators that contribute to tissue damage and inflammation<sup>29</sup>. Besides their immune functions, eosinophils also participate in tissue repair, wound healing, and maintaining tissue homeostasis. They can regulate aspects of tissue remodeling and repair processes. Eosinophils are heavily involved in allergic conditions and can contribute to tissue damage and exacerbation of symptoms during allergic reactions<sup>28</sup>. Eosinophils' ability to release inflammatory mediators implicates them in chronic inflammatory diseases. Their presence and interactions with other immune cells can contribute to the perpetuation of inflammation in various conditions<sup>30</sup>. In the context of sickle cell anemia, while direct studies specifically focusing on eosinophils are limited, their involvement in modulating inflammatory responses and their potential role in chronic inflammation might suggest implications for disease severity. Investigating their interactions and functions within the inflammatory milieu of SCA could provide insights into their contributions to the pathophysiology of the disease. Eosinophils exhibit diverse functions in immunity, inflammation, and tissue homeostasis.<sup>31</sup> While primarily known for their roles in parasitic defense and allergic responses, their involvement in chronic inflammation suggests potential implications for various disease conditions, including sickle cell anemia. Further research into their specific roles and interactions within the context of SCA may offer valuable insights into disease mechanisms and potential therapeutic interventions.

#### **Involvement in inflammatory responses**

Eosinophils, a type of white blood cell, are involved in modulating inflammatory responses through the release of various mediators and interactions with other immune cells. While traditionally associated with combating parasitic infections and allergic reactions, eosinophils play a multifaceted role in regulating inflammation in different physiological and pathological conditions<sup>28</sup>. Eosinophils produce and release cytokines such as interleukins (IL-4, IL-5, IL-13), tumor necrosis factor alpha (TNF- $\alpha$ ), and others. These cytokines can influence the function of other immune cells, regulate inflammation, and contribute to tissue responses<sup>32</sup>. Eosinophils also secrete chemokines, including eotaxins (e.g., CCL11) that

attract and recruit other immune cells, particularly eosinophils themselves, and certain subsets of T cells. This chemotactic activity is crucial in the recruitment of immune cells to sites of inflammation<sup>33</sup>. Upon activation, eosinophils release lipid mediators like leukotrienes, prostaglandins, and platelet-activating factor (PAF). These lipid mediators play diverse roles in regulating inflammation, vascular permeability, and immune cell activation.

Eosinophils interact with various immune cells, including mast cells, T cells, and macrophages, through direct cell-cell contact or via secreted factors. These interactions can influence the activation, function, and recruitment of other immune cells, thereby modulating inflammatory responses<sup>29</sup>. In the context of sickle cell anemia, chronic inflammation is a hallmark feature contributing significantly to disease severity and complications. While direct studies specifically focusing on eosinophils in SCA are limited, their potential involvement in immune modulation and inflammatory responses suggests that they might contribute to the inflammatory milieu observed in SCA patients. Understanding the specific mechanisms by which eosinophils modulate inflammatory responses in the context of SCA could provide insights into their contributions to disease severity. Further investigations focusing on the interactions between eosinophils and other immune cells, their cytokine/chemokine profiles, and their influence on the inflammatory cascade in SCA may uncover potential therapeutic targets for managing the inflammatory aspects of the disease<sup>34-37</sup>. Eosinophils, through their ability to release cytokines, chemokines, lipid mediators, and interactions with other immune cells, play a significant role in modulating inflammatory responses. While their exact contributions to sickle cell anemia remain to be fully elucidated, exploring their involvement in the inflammatory milieu of SCA may provide valuable insights into disease pathogenesis and potential therapeutic interventions<sup>38</sup>.

#### **Potential contributions to vaso-occlusive events**

Eosinophils express adhesion molecules such as P-selectin and L-selectin, which facilitate their adhesion to endothelial cells. Interactions between eosinophils and endothelial cells might contribute to endothelial activation or injury, potentially influencing the initiation or perpetuation of vaso-occlusive events in SCA<sup>39-43</sup>. Upon activation, eosinophils can release cytotoxic molecules, including reactive oxygen species (ROS) and other granule contents. These molecules might induce endothelial dysfunction or contribute to the inflammatory microenvironment, affecting the endothelium and potentially exacerbating vaso-occlusion<sup>44</sup>. Eosinophils, through their release of cytokines, chemokines, and lipid mediators, might influence the inflammatory milieu. This inflammatory environment, when dysregulated, could impact endothelial function and vaso-occlusive processes in SCA<sup>45</sup>. While direct evidence on the involvement of eosinophils in vaso-occlusive events in SCA is limited, understanding their interactions with endothelial cells and potential contributions to the inflammatory microenvironment could offer insights into their

hypothetical roles in influencing disease severity. Further research delineating the specific mechanisms and functional implications of eosinophils in vaso-occlusion might provide a clearer understanding of their involvement in SCA complications, potentially paving the way for targeted therapeutic strategies<sup>46-53</sup>.

#### **Eosinophils as modulators of immune responses**

Eosinophils, traditionally known for their role in defending against parasitic infections and contributing to allergic responses, also serve as modulators of immune responses by interacting with various immune cells and releasing immunomodulatory molecules<sup>38</sup>. Eosinophils interact with different immune cells, including mast cells, T cells, B cells, and macrophages. These interactions can influence immune cell activation, proliferation, and cytokine production<sup>37</sup>. Eosinophils release various cytokines (e.g., IL-4, IL-5, IL-13) and chemokines (e.g., eotaxins) that modulate the functions of other immune cells. For instance, eosinophil-derived cytokines can regulate the activity of T cells and influence the polarization of macrophages<sup>39</sup>. Eosinophils contribute to tissue inflammation by releasing inflammatory mediators. In certain contexts, they can dampen inflammation by releasing anti-inflammatory cytokines or by regulating the functions of other immune cells<sup>30</sup>. Eosinophils are heavily involved in allergic reactions, where they release mediators that contribute to tissue damage and inflammation. However, they also play roles in modulating immune responses during allergic diseases, potentially influencing disease severity<sup>54</sup>. In the context of sickle cell anemia, chronic inflammation and immune activation significantly contribute to disease severity. While direct studies specifically focusing on eosinophils in SCA are limited, their involvement in immune modulation and interactions with other immune cells suggest potential contributions to the inflammatory milieu observed in SCA patients. Eosinophils, known for their diverse roles in immune responses, possess the ability to modulate the functions of other immune cells and release immunoregulatory molecules<sup>55</sup>. While their direct involvement in sickle cell anemia remains to be fully elucidated, investigating their interactions and immunomodulatory functions within the inflammatory milieu of SCA might provide valuable insights into their potential contributions to disease pathogenesis.

#### **Potential molecular mechanisms**

Understanding the potential molecular mechanisms involving eosinophils in sickle cell anemia (SCA) severity requires exploration of their cellular functions and interactions in the context of the disease's pathophysiology. While direct studies focusing exclusively on eosinophils in SCA are limited, hypothetical mechanisms might provide insights into their potential contributions: Eosinophils produce and release various cytokines (e.g., IL-4, IL-5, IL-13) and chemokines (e.g., eotaxins) which can modulate the immune response. Investigating their specific roles in the immune dysregulation observed in SCA could reveal potential contributions to disease severity<sup>39</sup>. Eosinophils express adhesion molecules like P-selectin and L-selectin. Exploring their interactions with

endothelial cells in the context of SCA might unveil potential contributions to vascular adhesion and endothelial dysfunction, key factors in SCA pathogenesis<sup>56</sup>. Activated eosinophils produce ROS. In SCA, oxidative stress is a crucial factor. Investigating eosinophil-derived ROS and their impact on red blood cell physiology or endothelial function might elucidate their influence on disease severity<sup>57</sup>. Eosinophils release cytokines, growth factors, and lipid mediators. Understanding the specific molecules released by activated eosinophils and their effects on inflammation, endothelial integrity, and vaso-occlusive events in SCA could offer insights<sup>39</sup>. Eosinophils interact with various immune cells. Investigating these interactions and their influence on the immune response in SCA might reveal their role in modulating disease severity. While direct evidence remains limited, exploring the potential molecular mechanisms of eosinophils in SCA could offer insights into their hypothetical roles in disease severity.

#### **Inflammatory mediators and chemokines**

Eosinophils, known for their involvement in modulating immune responses, release various inflammatory mediators and chemokines that play pivotal roles in immune regulation and inflammation. While their specific contributions to sickle cell anemia (SCA) are not extensively studied, their potential involvement in the inflammatory milieu of SCA could be inferred<sup>39</sup>. Eosinophils release cytokines that can modulate immune responses. These cytokines may influence the polarization of other immune cells, affecting the overall immune landscape in SCA<sup>58</sup>. Eosinophils produce chemokines that attract and recruit immune cells to sites of inflammation. In SCA, understanding their role in immune cell recruitment could provide insights into the inflammatory process. Eosinophil-derived cytokines might contribute to the dysregulation of immune responses observed in SCA, potentially influencing disease severity and complications<sup>58</sup>. These inflammatory mediators could impact endothelial function, exacerbating the inflammatory cascade and endothelial dysfunction observed in SCA, which is crucial in vaso-occlusive events. Eosinophils, through the release of cytokines and chemokines, have the potential to influence immune responses and inflammation. While their specific contributions to SCA are not fully understood, investigating their role in modulating the inflammatory environment and immune dysregulation in SCA could provide insights into disease mechanisms and potential therapeutic targets. Further research focusing on eosinophil-associated inflammatory mediators in SCA may unveil their significance in disease pathogenesis<sup>39</sup>.

#### **Adhesion molecules and endothelial interactions**

Eosinophils express various adhesion molecules that facilitate their interactions with endothelial cells and potentially contribute to endothelial dysfunction, a significant aspect of sickle cell anemia (SCA) pathophysiology. While direct studies on eosinophils' role in SCA are limited, exploring their adhesion properties and interactions with endothelial cells may offer insights into disease mechanisms<sup>57</sup>. Eosinophils express adhesion molecules such as P-selectin

glycoprotein ligand-1 (PSGL-1), L-selectin, integrins, and others. These molecules facilitate their adhesion to endothelial cells and migration to inflamed tissues<sup>57</sup>. Upon adhesion to endothelial cells, eosinophils can induce endothelial activation and release of inflammatory mediators, potentially contributing to endothelial dysfunction seen in SCA. Eosinophils' adhesion to endothelial cells may contribute to the increased adhesion and activation of various immune cells, potentially exacerbating the vascular adhesion observed in SCA<sup>59</sup>. Eosinophil-endothelial interactions might impact endothelial function, contributing to the overall endothelial dysfunction characteristic of SCA, which plays a role in vaso-occlusive events. Eosinophils' expression of adhesion molecules facilitates their interaction with endothelial cells, potentially contributing to endothelial dysfunction and immune cell adhesion observed in SCA. Although direct evidence linking eosinophil-endothelial interactions to SCA pathogenesis is limited, further research exploring these interactions may provide valuable insights into disease mechanisms and potential therapeutic targets aimed at modulating endothelial dysfunction in SCA<sup>57</sup>.

#### **Oxidative Stress and Reactive Oxygen Species (ROS)**

Eosinophils, upon activation, are capable of generating reactive oxygen species (ROS) as part of their effector functions. While the direct involvement of eosinophil-derived ROS in sickle cell anemia (SCA) remains understudied, understanding their potential impact on red blood cell physiology and endothelial function could offer insights into disease pathophysiology<sup>60</sup>. Activated eosinophils generate ROS, including superoxide anion (O<sub>2</sub><sup>-</sup>) and hydrogen peroxide, as part of their antimicrobial and immunomodulatory activities. Excessive ROS production can contribute to oxidative stress, causing cellular damage and influencing various cellular processes. Eosinophil-derived ROS might indirectly affect red blood cells in SCA. Oxidative stress can exacerbate red blood cell membrane fragility or influence their susceptibility to sickling<sup>60</sup>. ROS can induce endothelial dysfunction, affecting the integrity of blood vessels. In SCA, this could contribute to vaso-occlusive events and further endothelial damage.

#### **Cytokine and growth factor release**

Eosinophils release various cytokines, growth factors, and lipid mediators, which may have implications in modulating immune responses and inflammation. Although their specific contributions in sickle cell anemia (SCA) are not extensively studied, understanding their cytokine and growth factor release could provide insights into the inflammatory milieu associated with the disease<sup>61</sup>. Eosinophils release cytokines that modulate immune responses and may influence the function of other immune cells. These cytokines can affect inflammation and immune cell activity in various contexts. Eosinophils can produce growth factors such as vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF- $\beta$ ), which play roles in tissue repair, angiogenesis, and immune regulation<sup>62</sup>. Upon

activation, eosinophils release lipid mediators like leukotrienes and prostaglandins, which contribute to inflammatory responses and immune modulation. Eosinophil-derived cytokines and lipid mediators might contribute to the dysregulated inflammatory state observed in SCA, potentially influencing disease severity<sup>61</sup>. Growth factors released by eosinophils could impact tissue repair mechanisms and angiogenesis, which might be relevant in the context of SCA-related tissue damage.

#### **Cellular interactions and immune modulation**

Despite their traditional association with allergy responses and parasitic infections, eosinophils interact with a wide range of immune cells and can influence immunological responses in a variety of ways. Although their precise involvement in sickle cell anemia (SCA) is not well understood, possible interactions and immune regulation may influence disease pathogenesis<sup>63</sup>. Eosinophils can interact with mast cells and basophils, causing allergic reactions and influencing their activation. Eosinophils can alter T cell function by releasing cytokines, which may affect T cell polarization and immunological control. Eosinophils can interact with macrophages, potentially affecting their activation and polarization<sup>63</sup>. Eosinophil interactions with other immune cells may alter the overall immunological landscape in SCA, affecting the inflammatory milieu and disease severity. Eosinophil-mediated actions on immunological cells in SCA may contribute to the disordered immune responses seen in the disease.

#### **CONCLUSIONS**

While the precise involvement of eosinophils in sickle cell anemia (SCA) is unknown, their many functions in immunological regulation, inflammatory responses, and potential interactions within the disease's environment provide exciting areas for investigation. Eosinophils, which have long been associated with parasite infections and allergic reactions, perform a variety of tasks, including the release of cytokines, chemokines, adhesion molecules, and reactive oxygen species. These functions have significant consequences for SCA pathophysiology, including immunological dysregulation, endothelial dysfunction, and inflammatory processes found in the disorder. However, direct evidence indicating the precise role of eosinophils in SCA-specific processes is scarce. Further research into eosinophil-mediated inflammatory responses, cellular interactions, cytokine release, and their impact on disease severity in the setting of SCA is critical. Integrating this knowledge into clinical practice and health policy could improve illness management techniques and drive future SCA research and patient care. As a result, further research into the precise roles of eosinophils in SCA has the potential to advance our understanding of the disease and improve patient outcomes.

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## AUTHOR'S CONTRIBUTION

**Obeagu EI:** conceived the idea, writing the manuscript, literature survey, formal analysis, critical review.

## DATA AVAILABILITY

Data will be made available on request.

## CONFLICT OF INTEREST

There are no conflicts of interest in regard to this project.

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