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Monoclonal Antibodies for Asthma Management

Dolly V. Rojas, Diana L. Silva and Carlos D. Serrano

Abstract

Asthma is a multifactorial and complex disease, with different degrees of risks and severity, as well as the response to treatment. Medications currently available are most effective in severe asthma; nonetheless, there is a percentage of patients that have no response to the treatment that guidelines suggest in their recommendations. In the last years, there have been new insights in inflammatory molecules that contribute to asthma physiopathology and a lot of them have been considered to be possible targets in the management of severe asthma. As a consequence of this, a few monoclonal antibodies have been developed evidencing their effectiveness in the treatment of the disease. The study of these new therapies has allowed the identification of specific inflammatory pathways. This chapter intends to offer a critical perspective of the current guidelines for the management of severe asthma, as well as to discuss current treatments and the future on new molecules. Through an adequate characterization, different phenotypes will be recognized and associated with a determinate biomarker and should be used to select the treatment that can offer the highest efficiency in these patients. In this way, the treatment will be directed to a personalized medicine.

Keywords: severe asthma, inflammation, phenotype, treatment, monoclonal antibodies

1. Introduction

Asthma is a heterogeneous disease characterized by chronic airway inflammation. The GINA guidelines indicate that inflammation control is a key for management goals and as such is considered a treatment priority. Severe asthma represents a good part of the health spending, with significant impact on patients’ quality of life. Hence, the identification and correct treatment of severe asthma may help to control exacerbations and the inflammatory process, thus improving the personal, social, and economic impact of the disease [1]. In the
pathophysiology of asthma, there are multiple processes mediated by various cytokines and cells that cause inflammation. Management goals have been directed toward these molecules and cell targets through the use of corticosteroids, which have meant a dramatic change in the control of the disease. However, these drugs act in a nonspecific way. Furthermore, the development of new monoclonal antibodies could represent a significant milestone for treatment of asthma, reinforcing the essential idea of personalized medicine. In 1984, researchers Jerne, Köhler, and Milstein received the Nobel Prize in Medicine for their work on plasma cell and multiple myeloma cell fusion, which allowed the generation of specific antibodies with the appropriate genetic information, but at high speed. In subsequent years, immunoglobulins synthesized from this new technology, with specific target molecules, such as the endotoxin of Gram-negative bacteria in sepsis, demonstrated an initial benefit. Subsequently, the concept of personalized medicine began to take shape, and in recent years, biomedical research has focused on deepening the molecular mechanisms underlying various pathologies, parallel to the production of new drugs that act at crucial points of specific immunological cascades. Therefore, monoclonal antibodies are an effective and safe therapeutic alternative in many chronic diseases such as rheumatoid arthritis, cancer, and asthma and are seen as a hopeful option in many other diseases. The challenge now is not to get lost in the wide variety of clinical studies that can be found in the literature, as well as in connecting a particular patient with the appropriate management based on the evidence.

2. Critical view of current guidelines and treatment

Large studies on severe asthma have expanded our knowledge about the characteristics of the disease. Severity is defined as the requirement for systemic corticosteroids more than twice a year, the need for at least one hospitalization, previous admission to an intensive care unit, the need for mechanical ventilation in the previous year, impaired pulmonary function determined by a forced expiratory volume in the first second (FEV1) less than 80% of the predicted in the presence of forced vital capacity (FVC) below normal limits after the administration of bronchodilator, or the use of high doses of corticosteroids inhaled and long-acting beta-2-agonists without achieving control of symptoms [2]. In fact, it is estimated that 50% of patients are not well-controlled despite receiving optimal treatment, and that 5–10% do not respond to treatment. Also, receiving high doses of inhaled or systemic corticosteroids increases the risk for adverse effects, which implies an affectation of the additional quality of life due to the sum of other secondary diseases [3]. The GINA guidelines include evidence-based diagnostic and therapeutic recommendation derived from studies that meet all criteria of scientific validity. However, it is possible that in selected patients, guidelines do not accurately reflect what a clinician is trying to address.

The guidelines suggest management according to severity and control, symptom dynamics and pulmonary function, but these are directed to the total population of patients with asthma [1]. In this sense, there will always be a percentage of patients who either receive a suboptimal treatment or who remain unresponsive despite being in the most serious step. Finally, the guidelines are not based on the characteristics of the specific inflammation related to the different phenotypes, which are the ones that could define with greater precision what
would be the ideal treatment to stop a specific pathophysiological mechanism [4]. It is not sufficient then to establish a management based only on severity, since there are several aspects that arise from the very concept that asthma is a heterogeneous disease and with different molecular and genetic bases, so if a patient should be typecast within a general parameter, reduce their therapeutic options [5]. On the other hand, the control of severe asthma represents a challenge for specialists in allergology and pneumology due to the high impact of this disease on the quality of life of patients. The GINA guidelines establish levels of disease control according to the response to treatment as follows: well-controlled, partially controlled, and uncontrolled. However, it can differ as patients cataloged in one of the degrees, in reality corresponding to another, taking into account that probably a partially controlled asthma is actually an uncontrolled asthma and that this has therapeutic implications. In daily practice, middle terms cannot be established to define management. Some patients persist without control despite established therapeutic recommendations, which allows us to infer that as with severity, there are other aspects that should be evaluated from the pathophysiology of the disease and not only based on the degree of control of the disease. Additionally, the classification based on control is very strict and poorly documented.

2.1. Approach by phenotypes

It is clear that some characteristics can be identified in some asthmatic patients and not in others; from this arises the concept of “phenotype,” which is defined as the presence of different characteristics that are the product of the interaction of genes with the environment. There may be overlap between them and that the same patient can migrate transiently or definitively from one phenotype to another. The challenge, therefore, is to determine in each patient the individual characteristics.

Several years ago, Chung and Adcock [6] published a review about phenotyping of asthma. The first systematic study of severe asthma carried out in Europe by the group ENFUMOSA (European Network for Understanding Mechanisms of Severe Asthma) [7] consolidated the concept that asthma has a heterogeneous expression, and thus, severe asthma should be considered a different form of the disease, more than simply an increase in the symptoms of it. Subsequent studies included in the Severe Asthma Research Program (SARP) of the United States, together with the results of the ENFUMOSA group, and subsequently of the BIOAIR (Longitudinal Assessment of Clinical Course and BIOMarkers in severe chronic AIRway Disease) [8], have extended the knowledge of clinical expressions and generated new hypotheses about the pathophysiology of severe asthma. In this way, five phenotypes have been established:

1. Early onset atopic asthma with airway dysfunction, eosinophilic inflammation, and high number of hospitalizations.
2. Asthma with noneosinophilic inflammation, obesity, and present in the female sex.
3. Early onset asthma, with few symptoms and minimal eosinophilic inflammation.
4. Asthma with eosinophilic inflammation, with few symptoms and delayed onset.
5. Asthma with neutrophilic inflammation.
2.1.1. Severe asthma early onset

It comprises 40% of all severe asthmatics. Patients develop the disease in childhood and have a history of atopy, increased bronchial hyperresponsiveness, higher levels of total immunoglobulin E (IgE), and a higher eosinophil count both peripherally and in sputum, as well as a tendency to subendothelial fibrosis and overexpression of the mucin gene. In general terms, they respond to management with inhaled corticosteroids. Family history suggests a genetic component; in fact, multiple studies have reported associations between genes related to the expression of the Th2 phenotype and multiple polymorphisms related to greater severity. The Th2 pattern of cytokines, including interleukins (IL) 2, 4, 5, 9, and 13, is expressed in the bronchial submucosa of these patients. These cytokines contribute to the allergic inflammation of the airway, generating the activation and the recruitment of B lymphocytes producing specific IgE, mast cells, basophils, and eosinophils. IL-13 also acts as an inducer of the genes of regulator 1 of the chlorine channels, periostin, and the inhibitor of serpin peptidase.

Recently, the role of thymic stromal lymphopoietin (TSLP) has been described as an inducer of IL-4, -5, and -13 production in the initiation of cellular response mediated by Th2 pattern cells, as well as IL-25 and -33, which are produced in response to exposure to allergens, contaminants, and viruses. IL-33, which is a member of the cytokine family of IL-1, possesses potent induction and chemotactic activity of Th2 lymphocytes. Elevated levels of IL-33 and TSLP have been observed in patients with asthma, especially in severe cases [9].

2.1.2. Phenotypes with and without eosinophilia

An increased presence of eosinophils in induced sputum and in peripheral blood can identify the eosinophilic subgroup. The cutoff points are at least 3% of eosinophils in the sputum and peripheral eosinophilia greater than 350 (absolute number). The noneosinophilic phenotype has been defined as asthma with eosinophils in induced sputum less than 3% and increased neutrophilic infiltration. The mechanisms that explain neutrophilia in the airway are not very clear. It has been suggested that this phenotype reflects a “non-Th2” pattern with all its molecular implications. In addition, it is associated with a poor response to treatment with inhaled corticosteroids (even inducing even more neutrophilia), suggesting a Th1 pattern orchestrated by the tumor necrosis factor alpha (TNFa), which is assumed to have an important role. Both Th17 cells and bacterial colonization of the airway secondary to defects in phagocytosis have been implicated as causes of neutrophilia [10].

The identification of phenotypes results in a large number of treatments with specific objectives, which have been developed for some years. The challenge is to unify the physiopathology with clinical phenotypes and use that knowledge to discover other phenotypes that have not yet been recognized. None of the clinical phenotypes established to date has a detailed identification of their pathophysiology, biomarkers, genetic elements, stability over time, or the response to a specific treatment. Probably, all the factors that influence a phenotype will need to be incorporated into an endotype, which is nothing else than the subtype defined by the functional or pathophysiological mechanism of the disease for a particular individual.

The support of the evidence regarding the conformation of phenotypes and endotypes continues to be limited by the lack of large-scale longitudinal studies that may intertwine the
pathophysiology with the clinical findings. However, there are already phenotypes that seem to be clearly defined in terms of their clinical and molecular bases, and in which the pharmacological intervention with monoclonal antibodies constitutes an important starting point in the management of severe asthma [2].

3. Monoclonal antibodies

Monoclonal antibodies are specialized glycoproteins produced by B cells from a stem cell, forming identical clones of it. They can recognize specific molecules, such as cytokines or receptors.

3.1. Chimeric monoclonal antibodies

They are artificial molecules in which the constant portions of the heavy and light chains come from a human immunoglobulin and the variable regions VL and VH (variable region of the light and heavy chain, respectively) are obtained from an antibody of murine origin. The goal with the construction of a chimeric antibody is to reduce immunogenicity without affecting the selectivity of the antibody for the antigen. These molecules have 66% of human component and 33% of murine origin; they are less immunogenic than the first-generation monoclonal antibodies, but they can still induce an immune response against them. Antibodies of this type end with the prefix ximab (e.g. infliximab, rituximab).

3.2. Humanized antibodies

These molecules have 90% of human origin, so when it is injected into the patients, there is no response from the immune system. Only the antigen binding site (paratope) is of murine origin and is formed from the spatial combination of the hypervariable loops. The rest of the variable region (called M) only works as a scaffold whose function is to serve as structural support to the paratope. In this way, the epitopes associated with the murine M regions, which are present in the chimeric antibodies, are not found in the humanized antibodies. This type of antibody ends with the prefix zumab (e.g., omalizumab, trastuzumab).

3.3. Human antibodies

Almost 100% of its structure is human. However, while the production of mouse monoclonal antibodies is routinely carried out by hybridoma technology, the production of human monoclonal antibodies by this technology has been difficult, because the human hybridomas and cell lines derived from multiple myeloma have been difficult to develop and immunization in vivo is not feasible for many antigens. However, several techniques make it possible to generate human monoclonal antibodies, such as the expression of immunoglobulin fragments, the single-chain variable fractions, and the single strands of the variable fraction. Currently, the development of recombinant monoclonal antibodies by phage library technology with genes that encode the immunoglobulin variable regions has proven useful in basic and clinical research. This type of antibody ends with the prefix mumab or numab (e.g. adalimumab, secukinumab) [11–13].

The traditional production process of monoclonal antibodies is outlined in Figure 1.
3.4. Development and production

The production of monoclonal antibodies is based on the method of fusion of B lymphocytes from an immunized animal (usually a mouse), with an immortal myeloma cell line and the culture of the cells in a medium in which the nonfused normal and tumoral cells cannot survive. The resulting fused cells that are obtained are called hybridomas and each hybridoma produces only one immunoglobulin, derived from a B lymphocyte of the immunized animal [11]. The method as such consists of the fusion of spleen cells from a mouse immunized to an antigen or mixture of known antigens, with a myeloma cell line, with the subsequent formation of hybrid cells that preserve many chromosomes of the fused pairs. These cells are then placed in a selection medium that allows the survival only of immortalized hybrids, which in turn are cultured as cell clones that secrete the antibody of interest. This method of selection includes hypotaxine,
aminopterin, and thymidine, and is therefore called HAT [14]. Antibody-producing hybridomas are expanded in larger capacity culture vessels, and the cells are harvested by centrifugation, suspended in culture medium supplemented with fetal calf serum and dimethyl sulfoxide (DMSO) to freeze, first at −70°C and then in liquid nitrogen. The production of the monoclonal antibody is made from the supernatant of bulk cultures or after intraperitoneal inoculation of the hybridoma in histocompatible animals. In the latter case, an antibody-producing tumor is produced that generates an ascitic fluid rich in these. In both cases, the monoclonal antibodies are separated and purified by conventional methods [15] (Figure 2).

4. Current and future targets in the management of asthma

4.1. Current targets

4.1.1. Nonspecific blockade of inflammation (corticosteroids and leukotriene antagonists)

At present, asthma control focuses on the use of inhaled corticosteroids, either alone or in association with leukotriene antagonists, and/or long-acting beta-2 agonists. Numerous studies have documented the efficacy of corticosteroids in reducing inflammation, both in children and adults and at any degree of severity. Currently, they are considered the most effective drugs to achieve control in most cases. Its action requires binding to a cytoplasmic receptor (alpha GR), which is associated with heat shock proteins (Hsp90-Hsp60). The binding of the corticoid to its receptor induces the dissociation of these proteins and the translocation of the complex toward the nucleus where several events occur that lead to the activation of the transcription of anti-inflammatory genes and the blocking of those pro-inflammatory. Additionally, corticosteroids interact directly with transcription factors, such as the nuclear factor kB, further blocking the expansion of the inflammatory process.

The use of these drugs has made it possible to reduce both the symptoms and the frequency and severity of the exacerbations, improving quality of life, lung function, and reducing bronchial hyperreactivity. However, their lack of specificity makes them susceptible to generating adverse effects in different organs. In addition, there is a percentage of patients resistant to corticosteroids, a phenomenon explained, among other causes, by the presence of a receptor isoform unable to bind to the glucocorticoid [16].

It is difficult to know if in the medium or long term, corticosteroids will continue to be the standard asthma therapy. Likewise, it is uncertain whether the advent of monoclonal antibodies will allow the reduction of the dose of corticosteroids and/or their total clearance in patients with severe asthma. The cysteiny1 leukotrienes comprise C4, D4, and E4 leukotrienes. They are mediators that play an important role in inflammation, mucus secretion, bronchospasm, and remodeling. The antagonists of the type 1 receptors of cysteiny1 leukotrienes (montelukast) are potent and selective and block their action in a competitive manner, generating an interruption of the pro-inflammatory intracellular cascade with a subsequent reduction of its effects. Clinical studies show that antagonism of these receptors is beneficial to some degree and percentage of the population. However, it is never superior to the effects
achieved with corticosteroids used as monotherapy or in combination with long-acting beta-2 agonists. The precise indications for use in asthma have not been completely defined. It seems that its administration in transient early wheeze triggered by virus and without atopy works to a certain extent [17].

4.1.2. Long-acting β-agonists (LABA) combined

The agonist stimulation of the beta 2 adrenergic receptors generates smooth muscle relaxation of the central and peripheral airways, reversing the bronchial obstruction in asthmatics. The effect is given by the activation of adenylate cyclase (it catalyzes the conversion of adenosine triphosphate—ATP—into cyclic adenosine monophosphate—AMPc), generating the decrease in intracellular calcium, and thus causing muscle relaxation. This treatment always associated with a corticoid is a choice when control is not achieved with the inhaled corticosteroid alone [18].

4.1.3. Anti-IgE therapy

IgE is a clear therapeutic goal in allergic diseases. It is released by the plasmocyte, binds to its receptor of high affinity in the mast cell, and later, upon exposure to the allergen involved, induces several effector responses including the release of mediators responsible of allergic reaction. Omalizumab, a recombinant humanized monoclonal antibody, binds specifically to free serum IgE in its CH3 domain, near the high-affinity receptor binding site, thereby blocking its interaction with mast cells, basophils, antigen-presenting cells, and other inflammatory cells that express the receptor. That binding results in the decrease of free IgE, generating a negative feedback of the receptor of high affinity, and therefore, an interruption of the inflammatory cascade evident by the reduction of the levels of tissue eosinophils and peripheral blood, as well as of the GM-CSF, and IL-2, -4, and -13. They also decrease the presentation of allergens to T cells and the production of cytokines that stimulate differentiation toward the Th2 phenotype [19] (Figure 3).

The efficacy and safety of omalizumab treatment in severe asthma has been demonstrated in several controlled studies, showing a significant reduction in exacerbations, a steroid-sparing effect, and improvement in quality of life. The greatest benefit has been observed in patients with allergic asthma, particularly those of greater severity, who failed to respond to conventional treatment [20]. Since 2003, this continues to be its main indication, when it was approved by the Food and Drug Administration (FDA). In 2005, it was approved by the European Medicines Agency (EMA) as an additional therapy in adult patients and in children older than 6 years with persistent severe uncontrolled allergic asthma, with decreased lung function (FEV1 less than 80% of predicted), despite the chronic management with high doses of inhaled corticosteroids plus long-acting beta 2-agonists and with evidence of sensitization to at least one aeroallergen in the skin test or by determination of specific IgE in blood [21]. In Colombia, Invima has approved it since 2005 with the same indication.

4.1.4. Interleukins 4 and 13

IL-4 and -13 are considered the most important cytokines in allergic inflammation in the respiratory tract for a long time; they are essential for the differentiation of CD4+ lymphocytes toward the Th2 phenotype. In addition, they are the promoters of the Ig class switch toward the production
of IgE, of the differentiation of the B cells in plasma producing specific Ig E, and of the recruitment of eosinophils to the airway through the receptors for them that are expressed in them. They also stimulate mast cells and other pro-inflammatory cells. IL-13 favors the development of airway fibrosis and mucus hypersecretion, and in conjunction with IL-4, induces inflammation, remodeling, and the proliferation of bronchial fibroblasts and smooth muscle cells [22].

4.1.5. Interleukin 5

It is produced mostly by Th2 cells, mast cells, basophils, and eosinophils. This cytokine mainly conditions the population of eosinophils, from their medullary differentiation to their maturation, survival, and activation. It is a potent inhibitor of eosinophilic apoptosis [23].

4.2. Future targets

4.2.1. Interleukin 9

It is produced by Th2, Th9, basophil, eosinophil, and mast cells, and is thought to be also by neutrophils. This cytokine acts by binding to its IL-9R alpha receptor, generating an increase in the proliferation and attraction of mast cells. It plays a very important role in the differentiation and activation of Th2 cells. Together with interleukins 4 and 13, it acts on the smooth muscle and the airway epithelium, contributing to bronchial hyperreactivity [23].

4.2.2. Granulocyte macrophage colony-stimulating factor

It is a growth factor involved in the differentiation and survival of eosinophils [23].
4.2.3. Thymic stromal lymphopoietin

It is an epithelial cytokine similar to IL-7, produced in response to a pro-inflammatory stimulus. It acts by inducing the release of cytokines from the Th2 pattern. Patients with asthma have elevated levels of this cytokine in their airway, showing a correlation between the degree of elevation and the severity of the disease. In fact, several studies have shown that some polymorphisms in the locus for the TSLP gene have a protective effect for the development of asthma and bronchial hyperreactivity [24].

4.2.4. Prostaglandin D2 receptor (PTGDR)

It is a receptor located in Th2 cells, innate lymphoid type 2 cells (ILC2), and in eosinophils. Prostaglandin D2 is its natural ligand. PTGDR activation stimulates the synthesis of Th2 cytokines.

4.2.5. Interleukin 25

It is produced by epithelial cells in response to different stimuli. Through the induction of GATA 3, it favors the differentiation toward Th2 and ILC2 cells. It has an essential role in inflammation of the airway and in the remodeling process [25].

Figure 4. Different monoclonal antibodies with their respective therapeutic targets within the inflammatory cascade of asthma. The neutralization of the different receptors and mediators blocks the intracellular cascade of kinases that amplify the inflammatory process. IL-4Ra: alpha receptor for interleukin 4; IL-13 Ra1: alpha 1 chain of the interleukin 13 receptor; rIL-4: inactive recombinant interleukin 4; S-U: subunit.
<table>
<thead>
<tr>
<th>Antibody (references)</th>
<th>Type</th>
<th>Target</th>
<th>Study phase</th>
<th>Clinic outcomes</th>
<th>Inflammatory outcomes</th>
<th>Dose/route/interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benralizumab [27–31]</td>
<td>Humanized</td>
<td>IL-5Rα</td>
<td>II–III</td>
<td>- Reduction of exacerbations, and hospitalization - Improvement of FEV1 - Improvement of the quality of life</td>
<td>- ↓ eosinophilia - ↓ sputum eosinophils - ↓ ECP</td>
<td>20–100 mg SC/4–8 weeks</td>
</tr>
<tr>
<td>Mepolizumab [32–35]</td>
<td>Humanized</td>
<td>IL-5S</td>
<td>II–III</td>
<td>- Reduction of exacerbations - Reduction of dose of oral corticosteroids - Improvement of the ACT - Improvement of FEV1</td>
<td>- ↓ eosinophilia - ↓ sputum eosinophils</td>
<td>75 mg IV/month 100 mg SC/month</td>
</tr>
<tr>
<td>Reslizumab [36, 37]</td>
<td>Humanized</td>
<td>IL-5S</td>
<td>III</td>
<td>- Improvement of FEV1 - Improvement of the ACT - Improvement of symptoms - Reduction of exacerbations</td>
<td>- ↓ sputum eosinophils</td>
<td>3 mg/kg IV/month</td>
</tr>
<tr>
<td>Dupilumab [38, 39]</td>
<td>Human</td>
<td>IL-4Rα</td>
<td>II–III</td>
<td>- Reduction of exacerbations - Improvement of FEV1 - Improvement of the quality of life</td>
<td>- ↓ FeNO - ↓ total IgE - ↓ eotaxin 1</td>
<td>200 mg SC/2 weeks</td>
</tr>
<tr>
<td>Pitrakinra [40, 41]</td>
<td>rIL-4</td>
<td>IL-4Rα</td>
<td>II</td>
<td>- Reduction of exacerbations* - Reduction of night awakenings* - Reduction of activities limitation by asthma* - Reduction of exacerbations in patients with eosinophilia - Reduction of need for beta-2’s rescue - FEV1 improvement</td>
<td>- ↓ FeNO</td>
<td>3–10 mg inhaled/12 h</td>
</tr>
</tbody>
</table>
4.2.6. Interleukin 33

IL-33 origin and actions are very similar to IL-25. Its effect is even greater and more potent on innate lymphoid cells compared to IL-25. In addition, it activates mast cells and basophils and is a survival factor for eosinophils [26].

4.2.7. Tumoral necrosis factor (TNF-α)

It is produced by epithelial cells, Th1 and Th17 cells. TNF-α promotes the recruitment of eosinophils and neutrophils to the airway by dysregulation of adhesion molecules. It activates macrophages for the production of growth factors and GM-CSF [25].

4.2.8. Intervention in the Th2 pathway with monoclonal antibodies

The possible therapeutic interventions with monoclonal antibodies for the treatment of asthma are outlined in Figure 4. The characteristics of the main molecules and the current evidence available for each of them are detailed in Table 1[27–45]. Other monoclonal antibodies have fewer studies and possibly have a residual role in the treatment of asthma [46–50].

5. Conclusion(s)

A significant percentage of patients with severe asthma do not achieve control of the disease despite receiving adequate treatment. Current guidelines are outdated and will be even more
if biomarkers and specific molecular susceptible of an intervention are not included in future guideline versions.

For now, omalizumab, the only biological treatment available for the management of severe asthma, continues influencing future studies aiming to evaluate new molecules and possible newer targets in selected patients. Linking the characteristics of each patient’s disease, with the effects of a specific monoclonal antibody, will surely imply a much more effective and timely control of the disease.

The detailed approach of the phenotypic characteristics and their molecular basis should lead to a personalized treatment of great precision and effectiveness. A very promising new era in the treatment of asthma is approaching.

Conflict of interest

The authors declare no conflict of interest.

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