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Monoclonal Antibodies in Chronic Rhinosinusitis with nasal polips (CRSwNP): our 12 months experience

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Abstract: **Chronic rhinosinusitis (CRS) is a chronic inflammatory disease of the nasal and paranasal cavities. About 20% of chronic rhinosinusitis is represented by rhinosinusitis with nasal polyps (CRSwNP), which in most cases is caused by a type 2 inflammation, with an eosinophilic inflammation.**

Monoclonal antibodies are a targeted therapy that allows you to control the disease by limiting or abolishing the use of systemic steroids.

In this scientific work, the authors tested the efficacy of mepolizumab and dupilumab in patients with nasosinusal polyposis with a 12-month follow-up.

Keywords: **Chronic Rhinosinositis, nasal polyps, monoclonal antibodies, mepolizumab, dupilimab.**

1. INTRODUCTION

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease of the nasal and paranasal cavities that affects 6 to 12% of patients in the Western world. About 20% of chronic rhinosinusitis is represented by rhinosinusitis with nasal polyps (CRSwNP), which in most cases is caused by a type 2 inflammation, with an eosinophilic inflammation.(1)(3)(22). The need for multiple surgical interventions during life and the frequent need for corticosteroid therapies also for the control of concomitant asthmatic pathology aggravate the clinical picture of this disease and worsen the quality of life of affected patients. The introduction of monoclonal antibody therapy has brought a new therapeutic possibility by improving the quality of life and reducing the number and need for repeated surgical interventions.

In 1975 Georges Köhler and César Milstein found a way to "immortalize" the cells that produce an antibody of interest, "fusing" them with particular cell lines capable of multiplying indefinitely in culture. Thus there is a potentially inexhaustible source of an antibody whose specificity, affinity and activity are known. To produce a monoclonal antibody, the antigen is introduced into a rodent (mouse or rat) and, after a sufficient number of days for the immune response to occur, the animal's spleen is isolated. The spleen cells are fused with immortalized cells in culture and then grown in many separate compartments to obtain the single clones. The antibody produced by each clone is then tested in laboratory animals and, if the results are positive, in humans. Once a clone that has the desired characteristics has been identified, it is grown in large quantities in culture, then the monoclonal antibody secreted by the cells in the culture medium is purified. For the development of this technique, Köhler and Milstein were awarded the Nobel Prize for medicine in 1984.

Monoclonal antibodies (MABs) are molecules produced in the laboratory, starting from B lymphocytes extracted from the mouse spleen, and fused with blood cancer cells (myeloma cells) which have the characteristic of being immortal. These fused cells, called hybridomas, are grown singly, in other words they are cloned (one cell in a well). The single cell that has become immortal subsequently divides forming a clone of identical cells capable of producing unlimited quantities of the same antibody called, in fact, monoclonal that can be purified. Monoclonal antibodies are designed to specifically recognize a single, particular antigen and bind to it by neutralizing it.

There are four types of monoclonal antibodies (MABs):

• murine (-omab), entirely derived from mouse cells. They can lead to an allergic reaction in humans

• chimeric (-ximab), obtained using molecular biology techniques that make it possible to replace some parts of the monoclonal antibody derived from mouse cells (the constant region) with the corresponding part of protein of human origin. They can cause allergy

• humanized (-zumab), derived mainly from human cells with the exception of the part of the antibody that binds to the target antigen

• humans (-umab), entirely derived from human cells

MABs can be produced in large quantities against antigens from a range of inflammatory diseases, infections and cancers and are used for both diagnostic and therapeutic purposes. In addition, they are also used to enhance the body's natural defenses. (7)(9)(11)

MABs can be linked (conjugated) to drugs or radioactive molecules (radioimmunotherapy) to convey and direct the active ingredient towards its target with extreme precision. This avoids involving other parts of the body, reducing unwanted effects and increasing the chances of efficacy of the therapy. Radioimmunotherapy is a technique that is mainly applied in the treatment of tumors.

2. MATERIALS AND METHODS

From June 2020 to February 2022, 20 patients suffering from nasal polyposis underwent surgery at our Operating Unit were enrolled in this study. The minimum follow-up time required for inclusion in the study was 12 months. Within one month of surgery, patients began biological therapy. Twelve patients, all of whom also had bronchial asthma, undertook therapy with mepolizumab. Eight patients, of whom only three also affected by bronchial asthma, undertook therapy with dupilumab.

All patients were screened for endoscopic objectivity classified according to Nasal Polip Score and patient-reported symptoms classified according to SNOT 22 (Sino Nasal Outcome Test 22) immediately before surgery, immediately after surgery and before the start. of biological therapy, 6 months and 12 months from the beginning of biological therapy.

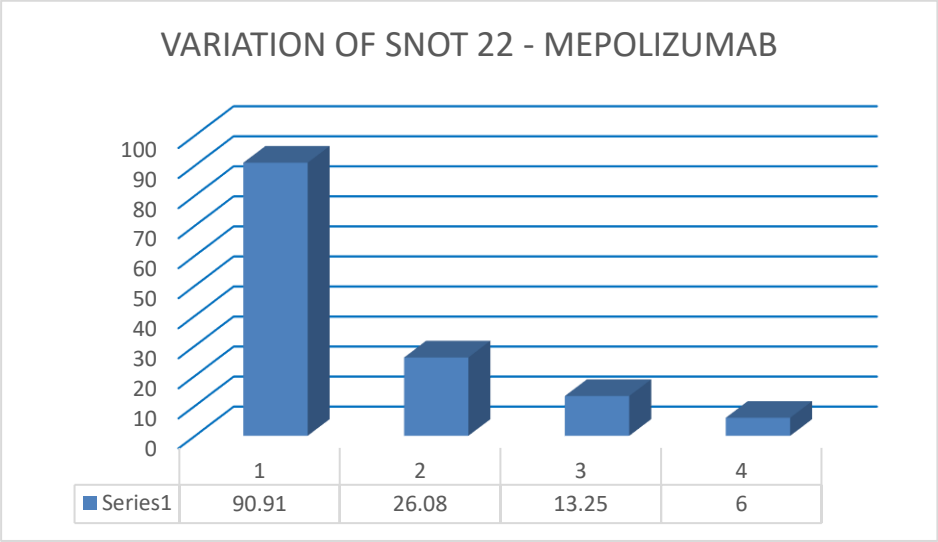
3. OBSERVATION AND RESULTS

Of the 12 patients treated with mepolizumab, 7 were male and 5 were female; the mean age was 50.5 years; the mean number of operations undergone by patients for nasal polyposis was 2.58. All patients had asthma co-morbidities, as mepolizumab is not yet authorized for the treatment of nasal polyposis in its own right and therefore its use is only possible in asthmatic patients with eosinophilia.

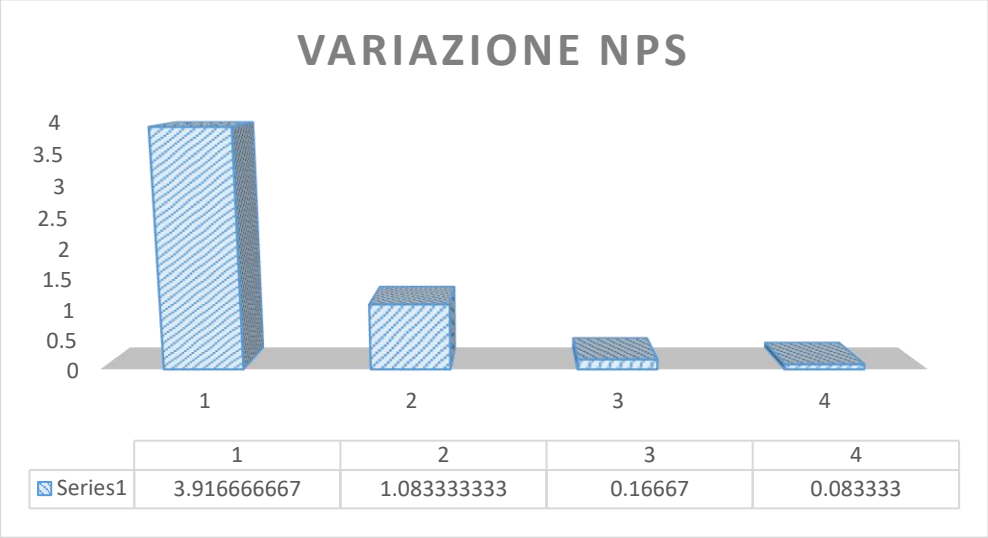
The mean preoperative SNOT 22 value was 90.91 while that found at postoperative follow-up within 1 month and before the start of mepolizumab therapy was 26.08. The SNOT 22 values at six months and at 12 months from the start of therapy were 13.25 and 6, respectively.(Tab.1)

The preoperative value of the NPS was on average 3.91, the postoperative one 1.08, the one after therapy at 6 months and at 12 months respectively 0.16 and 0.08 (Tab.2)

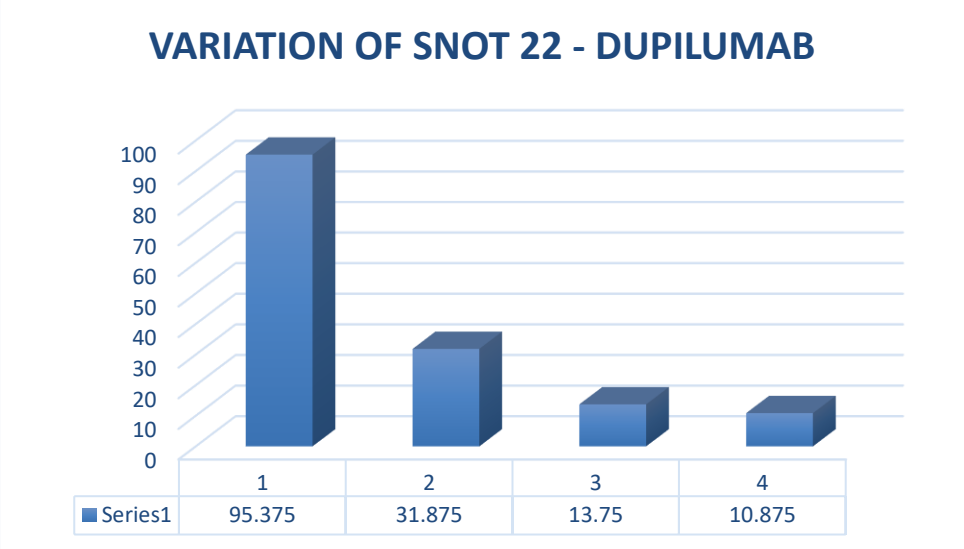
Dupilumab-treated patients were five males and three females, with a mean age of 44.87 years; the average number of interventions underwent was 1.75. Of these patients, 3 had asthmatic comorbidities and 5 were exclusively affected by nasal polyposis. Dupilumab has been authorized in Europe since January 2021 for the treatment of nasal polyposis even without concomitant asthma. The preoperative SNOT 22 value was on average 93.37, the postoperative one 31.87, the one after 6 months of therapy with dupilumab 13.75 and the one after 12 months 10.87.(Tab3) The NPS values were 3.62 preoperatively, 0.37 postoperatively, 0.12 at both 6 months and 12 months of therapy.(tab.4)



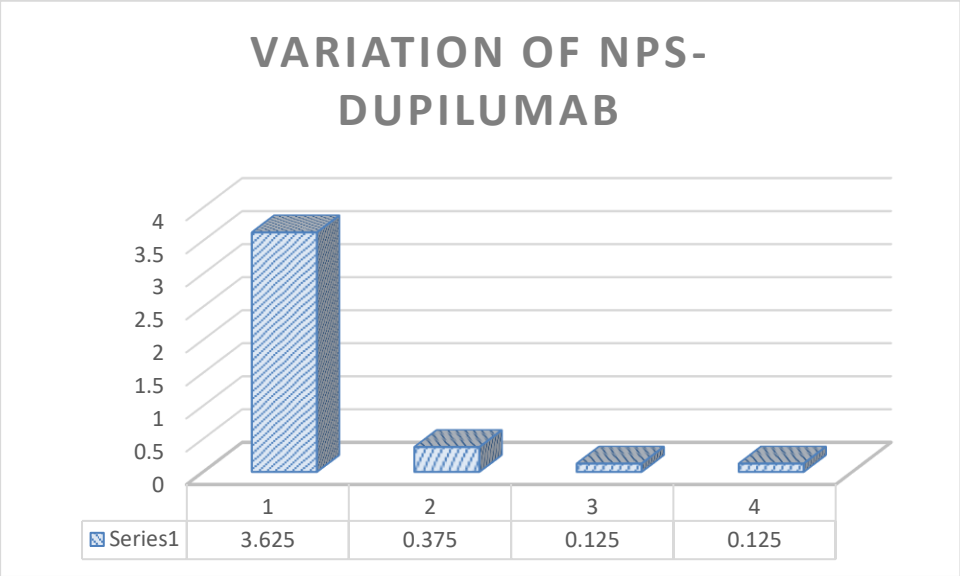
Tab. 1 – Mepolizumab. Variation of SNOT 22 1) preoperative 2)post-operative within one month 3) within six months 4) within twelve months



Tab. 2 – Mepolizumab. Variation of NPS 1) preoperative 2)post-operative within one month 3) within six months 4) within twelve months



Tab. 3 – Dupilumab. Variation of SNOT 22 1) preoperative 2)post-operative within one month 3) within six months 4) within twelve months



Tab. 4 – Dupilumab. Variation of NPS 1) preoperative 2)post-operative within one month 3) within six months 4) within twelve months

4. CONCLUSIONS

Our experience is based only on patients treated with dupilumab and mepolizumab. We still do not have enough patients treated with omalizumab and benralizumab to be able to report scientifically meaningful data.

Mepolizumab is a humanized monoclonal antibody (IgG1, kappa), whose target is human interleukin-5 (IL-5) for which it has high affinity and specificity. IL-5 is the main cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils. Mepolizumab inhibits the bioactivity of IL-5 with nanomolecular potency by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the surface of eosinophil cells, consequently, inhibits the IL-5 signal and reduces production and the survival of eosinophils.(2)(4)(5)(6)(7)(8))10).

Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits interleukin 4 and interleukin 13 signal transduction. Dupilumab inhibits IL-4 signal transduction via the type I receptor (IL-4Ra / yc), and both IL-4 and IL-13 signal transductions through the type II receptor (IL-4Ra / IL-13Ra). IL-4 and IL-13 are fundamental factors of type 2 human inflammatory diseases such as atopic dermatitis, asthma and CRSwNP. Blocking the IL-4 / IL-13 pathway with dupilumab in patients reduces many of the mediators of type 2 inflammation (12)(13)(14)(15)(16)(17)(18)(19)(20)(21).

The results at 6 and 12 months are very good both as regards the endoscopic objectivity and as regards the symptom score. Only patients with recent surgery were considered in this work. In the future it will be very important to evaluate both patients who have undergone not recent surgery and who have an ongoing relapse, and patients with major nasal polyposis without surgical therapy, in order to evaluate the effectiveness of biological therapies in these subgroups. Mepolizumab seems to have a better final result in clinical satisfaction of the patient at 12 months (6 against 10.87) but both results should be considered excellent as well as those of the NPS. It should be noted that in the group of patients treated with mepolizumab 8 out of 12 were affected by intolerance to NSAIDs, configuring the picture of the aspirin-exacerbated respiratory desease (AERD) or Widal's triad which represents, as is known, one of the forms at greatest risk of relapse and greater difficulty in treatment, so the therapeutic success obtained appears to be of great value.

In conclusion, we believe that therapy with biological drugs is already an important therapeutic reality in the management of nasal polyposis and we hope, in light of the results obtained, a more frequent and constant use both in patients with chronic sinusitis with nasal polyposis (CRSwNP) and in patients with CRSwNP and asthma.

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