NCT04823585
Unique Protocol Id HUS/686/2020

Aggravated airway inflammation: research on biological treatment (Mepolizumab)

AirGOs-biologics

Eudra CT 2020-000421-76
V.4 21.8.2020

Study plan

Aggravated airway inflammation: research on biological treatment (Mepolizumab)

AirGOs-biologics

Eudra CT 2020-000421-76
V.4 21.8.2020

Study plan

1. Summary

Chronic rhinosinusitis is a symptomatic inflammatory disease of the nasal and paranasal mucosa lasting more than 12 weeks (1). It can be divided into a polypotic (CRSwNP) and a non-polypotic (CRSsNP) subform. Asthma is a prolonged bronchial inflammatory disease with an increased and variable tendency for bronchial contraction (2). Chronic rhinosinusitis and asthma are significant and growing health problems in our population, the prevalence of both is about 10% in Finland (3-4). They partially overlap and affect each other´s care balance; their treatment usually consists of topically administered corticosteroids and saline lavage of nasal mucosa (1-2).

About one-fifth of people with chronic rhinosinusitis and/or asthma have a severe form of the disease in which the disease is not completely controllable despite treatment (11-12). The costs of severe chronic rhinosinusitis and asthma account for about 80% of the total costs for the entire disease group (8). Typical findings include eosinophilic airway inflammation and recurrent purulent exacerbations. -Possible changes in the interaction between the genome and the environment that lead to a severe form of the disease remain unknown (9). Patients with severe disease often have concomitant polyposis, chronic rhinosinusitis, asthma, chronic otitis, and non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NERD) with exacerbation caused be acetylsalicylic acid (ASA) or another NSAID. The frequency of surgery, the risk of surgical complications, and the risk of side effects from other treatments (such as recurrent systemic corticosteroids or experimental Aspirin desensitization therapy) are increased in these patients (10).

The function of the mucous membranes of the airways is to transport and regulate the air passing through the airways, as well as to sense and defend against airborne particles. Type 1, 2 and 3 inflammatory responses are normal inflammatory responses in the body. Type 2 inflammatory mediators are IL-4, IL-5 and IL-13, and under normal conditions they defend against helminth infections (3). Patients with NERD experience inappropriate type 2 airway inflammation, which causes symptoms such as mucus production, cough, shortness of breath, congestion, poor sense of smell, fatigue, and recurrent exacerbations. The mechanisms of NERD`s pathogenesis are not yet well known. An unbalanced mucosal microbiota potentially contributes to the development of NERD along with the inflammatory system and hereditary factors. A study in the Icelandic/English population showed that the ALOX15 gene variant is associated with an increased risk of NERD (7), but other risk genes are not yet well known. By studying these factors, high-risk patients could be identified and treated more effectively in the future.

Mepolizumab (Nucala®) is a humanized monoclonal antibody that has been shown to be effective in the treatment of severe eosinophilic asthma (4) and chronic polypotic rhinosinusitis (5). In a retrospective U.S. study, Mepolizumab has been shown to be effective against respiratory symptoms in NERD patients (6), but there is no placebo-controlled study evidence.

The aim of this prospective randomized, placebo-controlled, multicenter study is to investigate whether mepolizumab reduces polyp size, SNOT22 symptom scores, and exacerbations (as measured by systemic corticosteroids and peroral

antibiotics) more than placebo. We will also investigate whether mepolizumab reduces the need for increased drug dosage (topical corticosteroid or bronchodilator dosage) and improves lung and nasal function more effectively than placebo, and we investigate biomarkers that predict disease.

We will recruit a total of 120 patients with severe NSAID hypersensitivity, i.e., NERD, nasal polyposis and asthma in HUS, KYS, and TAYS in 2020-22. Patients will be randomized to two treatment groups in a 1:1 ratio. Group-1 receives subcutaneous placebo once monthly for 16 weeks and Group-2 receives subcutaneous Mepolizumab 100 mg once monthly for 16 weeks. The study lasts about 6 months. This first visit ensures the inclusion and exclusion criteria of the subject. If necessary, NERD will be verified by an ASA exposure test at a second additional visit. Subjects also have 6 visits, on four of which subcutaneous injection of the study product is administered. During visits, a clinical examination, airway function tests, and nasal, blood, urine, and stool samples are taken. The study aim is to elucidate the treatment and predictive biomarkers of severely symptomatic NERD patients.

2. Methods

2.1. General

The objective of the study is to investigate the effects of Mepolizumab In the treatment of NERD with uncontrolled CRSwNP:

-Does Mepolizumab reduce endoscopic nasal polyp score and SNOT22 symptom score more than placebo?

-Does Mepolizumab reduce exacerbation-rate, reduce need for dosing-up medication, reduce signs of Th2-inflammation (such as eosinophilia) in blood and nasal samples, as well as improve lung and nasal function more effectively than placebo?

The study is performed as a randomized double-blinded prospective controlled multicenter trial. A total of 120 adult NERD patients will be recruited. The NERD with uncontrolled CRSwNP treated in our hospital**s**, will be systematically searched and recruited. About 70-75 NERD patients will be recruited at the Departments of Otorhinolaryngology and Allergy of Helsinki University Hospital (HUH), and the rest will be recruited at the Departments of Otorhinolaryngology, Allergy and Pulmonology of Tampere University Hospital (N=35), Kuopio University Hospital (N=10-15). The study will be monitored by a professional monitor. Electronic CRF and paper/electronic patient questionnaires provided by HUS will be used (eCRF and patient questionnaire, Granitics).

The diagnosis of CRS with nasal polyps (NP) is based on positive history, nasal endoscopy and computed tomography scans (EPOS 2012*).* EPOS-criteria for CRS include: Inflammation of the nose and the paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip): ± facial pain/pressure, ± reduction or loss of smell.

The diagnosis of asthma is based on lung function tests, such as spirometry, methacholine or histamine challenge and peak expiratory flow (PEF). The study patients have been given an asthma drug reimbursement right from the National Health Insurance system. The reimbursement right is granted by certificate that has been made by patient´s physician and includes background information, clinical exam´s results, lung function test results as well as findings and conclusions after asthma treatment test period of 6 months. Allergy is verified with positive history and skin prick test or specific IgE. NERD is verified by typical history and by ASA challenge test unless there is previous reportion of NSAID anaphylaxis or acute airway attack leading to hospitalization, or a previous positive ASA challenge test at a hospital setting. For those who don´t have previous ASA challenge performed, ASA-challenge is performed at a hospital setting

where the patients are administered ASA 50mg. Reaction is monitored by using a standard HUS form 2 hours after the dose. The patients are monitored by airway function tests, questionnaires, and clinical examination. The patients are followed at least for 4 hours.

Those negative to ASA-challenge test will not enter the Clinical Trial. All patients entering the Clinical Trial, have undergone ≥1 earlier CRS surgery and have not gained disease control. Clinical baseline information of the patients is collected including smoking, allergy, asthma, medication, previous operations, co-morbidities, duration of symptoms.

Inclusion criteria:

- ≥18 years of age
- Exacerbation of respiratory symptoms by acetylsalicylic acid (ASA) or another NSAID. (NERD will be verified by another visit if necessary).
- chronic rhinosinusitis with bilateral polyps. Endoscopic bilateral nasal polyp score of at least 5 (out of 8), with a minimum score of 2 in each nasal cavity
- Lund Mackay score ≥12 (maximum 24) of sinus computed tomography (CT) or cone beam (CBCT) scans. The new sinus CT/CBCT scans are needed if the previous sinus CT/CBCT scans have been performed over 36 months before recruitment visit and it is clinically indicated, or if there is a suspicion of complication of CRS (f.ex. mucocele, invasive fungal rhinosinusitis). Pregnant and breast-feeding subject will be excluded. Females of Reproductive Potential (FRPs) who are not pregnant or breast-feeding may be enrolled. FRPs need to perform pregnancy test prior to the CT/CBCT scans. If subject is already on contraception prior to the study this should be continued. The data of previous sinus CT/CBCT scans will be used if previous sinus CT/CBCT scans have been performed ≤36 months prior to recruitment visit. The clinical information of sinus CT/CBCT scans is critical to enrolling appropriate subjects for the research and cannot readily be obtained another way. The radiation dose of sinus CT/CBCT scans is less than 0.1 mSv, which corresponds to less than 10 days of natural background radiation in Finland. The increased cancer risk is minimal.
- ≥1 previous CRS-surgery. Note that the last CRS-surgery must have been performed at least 6 months before 1st visit
- SNOT-22 ≥25
- At least one other symptom, such as partial loss of smell (hyposmia), nasal obstruction, total loss of smell (anosmia), or anterior or posterior rhinorrhea
- patient should have a history of at least one exacerbation during the past two years e.g. at least one criterion must be fulfilled of the following list during the past two years ≥1 oral corticosteroids; ≥3 antibiotic courses; ≥1 CRS-operation; ≥ 1 asthma hospitalization. In patients with contraindications of previously listed treatment or continuous oral steroids, additional criteria are not required.
- Asthma diagnosis (patient has the National Social Insurance Institution´s reimbursement right for asthma medication)
- Peripheral blood eosinophils (PBEos) >300 cells/ul at visit 1 OR (PBEos >150 cells/ul at visit 1 AND a history of PBEos >300 cells/ul during the past 12 months). A history of Nasal polyp tissue eosinophilia (NPeos) ≥30% during the past 12 months is a supportive criterion.

The two treatment arms, s.c. Mepolizumab and s.c. placebo injections are randomized in a ratio of 1:1 of the study patients and is scheduled 2-4 weeks before start of trial medication.

Regular use of intranasal corticosteroid (such as intranasal Fluticasone propionate 400 ug per pipette; ½ pipette 1-2 x /day to both nostrils or intranasal corticosteroid spray 1 dose 1-2 x /day to both nostrils if patient is not able to use the drops) is started at least 2 months prior to study entry. Regular CRSwNP and asthma medication is used throughout the whole study.

Exclusion criteria:

- Age <18 years
- CRS-surgery < 6 months before 1st visit
- pregnancy/ breastfeeding**.** FRPs need to perform pregnancy test prior to the CT/CBCT scans. If subject is already on contraception prior to the study this should be continued.
- complication of CRS (f.ex. mucocele, invasive fungal rhinosinusitis). Take sinus CT/CBCT scans, if needed!
- acute rhinosinusitis/respiratory infection
- severe disease related to airways/ immunology: cystic fibrosis, primary ciliary dyskinesia (PCD), sarcoidosis, immunosuppression, diagnosed Specific antibody deficiency (SAD), CVI, HIV, fungal rhinosinusitis; Young syndrome; Kartagener syndrome;
- other severe disease such as active cancer
- Received biologic therapy/systemic immunosuppressant/ASA desensitization therapy/experimental monoclonal antibody treatment to treat inflammatory or autoimmune disease within 2 months of study entry or 5 half-lives, whichever is longer. The patient is allowed to use ASA dose <100 mg/day due to cardiovascular reasons after ASA desensitization.
- current immunotherapy
- communication problems (f.ge. neurological/psychiatric disease, language skills)
- unlikely to comply
- ASA-challenge negative.
- History of hypersensitivity to mepolizumab or excipients in the formulation

Power calculation: The mean postoperative difference in the Sinonasal Outcome test (SNOT-22) was assumed to be at least 9 between the treatment arms. In a previous study the response within each subject group was normally distributed with standard deviation 17. If the true difference in the experimental and control means is 13, we will need to study 57 experimental subjects and 57 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. The total number recruited is 120 (estimated rate of discontinuation is 5%).

ASA challenge is conducted during the second visit if needed, according to modified international protocol (15-16). FEV1 should be at least 1.5 L and > 60% of predicted before challenge or desensitization. Patient will receive 25 mg ASA at a hospital setting. If no remarkable symptoms are seen, patient will receive 1-2 hours later another 25 mg ASA at a hospital setting.

ASA challenge positive result:

1. Naso-ocular alone: a 30 % or > increase in at least one of the following VAS (0-10 cm) scores: nasal obstruction, nasal discharge, postnasal drip, eye itching. These may exist with or without objective signs of increased nasal turbinate swelling/discharge or eye redness in examination.
2. Naso-ocular (please see 1.) and a 15% or > decline in FEV1 or in PEF (Classic reaction)
3. Lower respiratory reaction only (FEV1 or PEF declines by >20%)
4. Laryngospasm with or without 1-3 (flat or notched inspiratory curve)
5. Systemic reaction: hives, flush, gastric pain, hypotension

Patients Randomization and the treatment arms I-II occurs after 1st (or 2nd for ASA challenged) visit. The patients are randomized to two treatment arms: I) subcutaneous injections of placebo once per month for 16 weeks II) subcutaneous injections of Mepolizumab once per month for 16 weeks. Mepolizumab 100 mg / Placebo (NaCl solution)

is injected subcutaneously once per month, for a total of 16 weeks. GSK provides the randomization codes to each center.

Table1 the study protocol

Time	-4 weeks	~~-2~~ weeks	0 weeks	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks
Visit	1	2	3	4	5	6	7	8
	Rekrytointi	ASA-asltistus	1. pistoskerta	2. pistoskerta	3. pistoskerta	4. pistoskerta	Seurantakäynti	Loppukäynti
Name of the visit	Recruitment	ASA-challenge	1st injection	2nd injection	3rd injection	4th injection	Follow-up visit	End of Trial
Informed Consent	x							
Review Inclusion / Exclusion Criteria	x	x No flu 2 we before	x					
Medical History comorbidities	x							
Randomization	x	x						
Visiting Doctor	x	~~x~~	x	x	x	x	x	x
Visiting Nurse	x	x	x	x	x	x	x	x
Review of Concomitant Medication	x	x	x	x	x	x	x	x
Visits, hospitalisations, exacerbations, sick leave, productivity	Previous year							
Allergy test = serum specific IgE test (pölyerittely)	x							
	x						x	
ASA challenge test (to subjects without previous challenge-test-confirmed NERD dg)		x						
Treatment with IMP			x	x	x	x		
Check side-effects		x	x	x	x	x	x	x
ENT visit (+ lung examination)	x	x	x	x	x	x	x	x
Check CRS control	x	x	x	x	x	x	x	x
Pulmonologist visit	x						x	
Check asthma control	x	x	x	x	x	x	x	x
Questionnaire-packet: SNOT-22, 15D, AQLQ, Asthma control	x	x	x	x	x	x	x	x

test, 2xNetherlands-Q								
VAS symptoms		x						
Baseline characters questionnaire (esitietokaavake)	x							(x) if changed
Acoustic rhinometry (ARM)	x	xx	x	x	x	x	x	x
nNO	x	xx					x	
eNO	x						x	
Olfaction Sniffin' sticks	x		x	x	x	x	x	x
sinus CT scans	x							
Blood analysis for Biobank	*				-	-		-
Blood samples (5 EDTA tubes) for metabolomics & genomics	x	xx	x	x	x	x	x	x
Urine samples for metabolomics	x	xx	x	x	x	x	x	x
Fecal sample for microbiome	x		x	x	x	x	x	x
Nasal samples (microbiome, transcriptomics, histology)	x	xx					x	
Spirometry	x						x	
PEF 1 week	x	x					x	
microspirometry		x						
PEF at visit	x	x	x	x	x	x	x	x
PNIF at visit	x	x	x	x	x	x	x	x
Check disease relapse	x	x	x	x	x	x	x	x
Consider additional therapy /referral to operation	x	x	x	x	x	x	x	x

Study endpoints

Primary, Change from baseline

endoscopic nasal polyp score (total score ranges between 0-8 of both sides), SNOT22 symptom score, VAS score (of smell loss, obstruction, postnasal drip, nasal discharge, facial pain/pressure) and, exacerbation-rate. Exacerbation means that patient has at least one of the following due to airway symptoms: oral corticosteroid course; antibiotic courses; sinus lavation; hospitalization.

Secondary, *Change from baseline*
Other medication such as dosing-up medication, and medication of exacerbations (antibiotics, bronchodilators, nasal decongestants, systemic corticosteroids)
BEos, NPeos
signs of Type2-inflammation in blood and nasal samples
nasal and lung function test results (FEV1, peak expiratory flow rate, eNO, nNO and/or MCA in Acoustic rhinometry, PNIF, Sniffin' sticks 12)
Number of patients who met criteria for requiring surgery for polyposis at each time point
Questionnaire-packet: 15D, mini-AQLQ, Asthma control test, iMCQ, iPCQ, WPAI, EQ-5D-5L
Consideration/planning of a CRS-operation due to airway symptoms
Cost-effect and productivity (iMCQ,iPCQ questionnaires, sick leaves due to airway symptoms)
Safety (adverse effects)

The following clinical data are also collected:
Lund-Mackay score of Sinus CT scans/Cone beam CT, performed ~~12 months~~ prior to the study.
Questions concerning uncontrolled CRS according to EPOS12 and EPOS20 -criteria

The patient will know the treatment arm when the trial has been terminated. The patient can discuss with the doctor of the need to continue or start with advanced or another therapy or referral to consideration of operation, if needed. Results of the samples will be compared with the results of other studies (AirGOs-oper and AirGOs-medical).

Reporting and monitoring of adverse events and -reactions

Reporting of adverse events and -reactions is performed as follows: immediate announcement to the healthcare personnel, the patient and the principal investigator, and by recording and transferring the data to an electronic follow-up form (eCRF). The report will be forwarded to the supervisory authorities if necessary.

The subject's condition is monitored and treatment is carried out properly. eg. (medical care, treatment calls, medical appointments, if necessary), and all contacts between the study patient and the study unit are recorded in the patient records and eCRF-form and the necessary reports are submitted to the supervisory authorities if necessary.

Pharmaceutical manufacturer GlaxoSmithKleine will also receive a safety report from the research unit on the incident.

Adverse event and reaction reporting-, monitoring and registration is performed in accordance with Finnish legislation. We follow EU-standards and guidelines as well as the Declaration of Helsinki of the Word Medical Assembly.

Pregnancy:

· Details of all pregnancies in female participants will be collected after the start of study intervention and until 16 weeks after the last dose.

· If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

· Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

· The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor.

· Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

SAE and pregnancy reporting:

Sponsor will promptly notify GlaxoSmithKline of all SAEs and pregnancies (if applicable) that have occurred for participants enrolled in this Study Drug Appendix, in accordance with the timelines and procedures specified in the Protocol/appendix. In addition, the sponsor will reasonably obtain and provide follow-up information as available, to GSK upon request.

Follow-up of the patient after the study

There is no follow-up after the study in the research protocol. However, the follow-up monitoring is performed according to normal clinical routine, as the recruited patients are under continuous monitoring and treatment by HUS, KYS and TAYS, in which the study centers are also located.

Patients who are discontinuing their participation are asked the permission to use the data collected.

Data management

Statistics. Data analysis will be carried out on the relationship between Mepolizumab and placebo treatment. Variables tested in the statistical models include age, gender, symptoms, exacerbations, infections, medications, endoscopic findings, sick leave, allergy, side-effects of treatment, hospitalizations, and other factors at different time-points. Student´s t test (or KW, MWU tests, in case of not normally distributed sample), as well as adjusted linear regression models are used for continuous measures. A statistical analysis plan (such as correction for multiple testing) will be drawn up with advice from the statistical department at the University of Helsinki**.**

We will use several software: R 3.0.2, SPSS 22.0 Statistical Software Package (SPSS, Chicago, IL) and STATA (Release 13.1 software, StataCorp, Texas, USA). For comparisons, the results will be analyzed by Logistic regression, Student´s t-, Chi-square, (nonparametric) Fisher´s exact and Mann Whitney U test. P-values less than 0.05 are considered statistically significant. Results of logistic regression are reported as odds ratios (OR) with 95% confidence intervals. All models will be adjusted by selected covariates (potential confounding factors).

Sample handling

The samples will be stored at Helsinki Biobank or at the University of Helsinki.

Table 2. Samples and their schedule. The sample protocol is reduced in KYS and TAYS.

Time	-8 weeks	-4 weeks	0 weeks	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks
Visit	1	2	3	4	5	6	7	8
Name of the visit	Recruitment	ASA-challenge (if needed)	1st injection	2nd injection	3rd injection	4th injection	Follow-up visit	End of Trial
Nasal cotton/swab samples (Microbiome, RNA)	x	xx					x	
Nasal biopsies under local anesthesia	X2	x					X2	
Nasopharyngeal aspirate (Microbiome)	x		x	x	x	x	x	x
Fasting blood sample 18 ml[1]	x EDTA, plasma 9 ml	xx EDTA, plasma 9+9 ml	x EDTA, plasma 9 ml	EDTA DNA 4 ml, CPT 8 ml	x EDTA, plasma 9 ml	x EDTA, plasma 9 ml	x EDTA, plasma 9 ml; EDTA DNA 4 ml, CPT 8 ml	x EDTA, plasma 9 ml
Biobank 0-blood sample (voluntary)	X							
Blood sample (CBC, WBC differential, S-IgE allergen profile) + ECG	X						x	
Urine sample (first morning urine, bladder time ≥ 4h, fasting from 22:00 previous night)	x	xx	x	x	x	x	x	x
Stool sample (microbiome, placed in room-temperature transport tube, voluntary)			x				x	

X = routine sample, collected at all centers (HUS, TAYS, and KYS);

x = specialized sample, collected only at HUS.

[1] Plasma & cells (DNA, RNA) are taken from the same sample, collected cold (protected from light if possible), and divided into 2–5 tubes (EDTA and CPT tubes).

[2] At KYS/TAYS, only the routine PAD is collected; at HUS, a biopsy microbiome/frozen sample is also collected.

We aim at performing exome sequencing, mRNA sequencing and metatranscriptomics, immunohistochemistry, western-blot and ELISA, metabolomics in order to search for biological key-factors relevant for aggravated CRS and asthma and NERD. For exome sequencing DNA is isolated from peripheral blood leucocytes, PCR enriched, and libraries are processed and sequenced on an Illumina HiSeq. For microbiome 16S-RNA sequencing and metatranscriptomics are performed to several sample types (nasal, nasopharynx, fecal) (17). Reads are mapped to rRNA reference sequences and outputs are summarized for each phylotype. For DNA profiling, raw bisulphite

treatment is performed on DNA. Oligonucleotide primers are synthesized. Libraries are processed and sequenced. SNPs and indels are called and annotation is performed by ANNOVAR. For transcriptomics total RNA from nasal cell brushings is extracted, enriched RNA-seq library is prepared and Nextera Primers are used. miRNA is PCR enriched and smallRNA libraries sequenced. Reads are corrected and aligned to the reference human genome. For quality control original cDNAs and RT-qPCR are used in the validation. cDNAs are amplified using TaqMan Universal PCR Master Mix. The expression levels are normalized with TBP or GAPDH. Small interfering RNAs targeting candidate genes are used. For metabolomics we will perform chromatography, mass spectrometry, immunohistochemistry, western-blot and ELISA to specimens. Genetic calculations on Hardy–Weinberg equilibrium and linkage disequilibrium will be performed with Arlequin (version 3.5) using SPSS Statistics (version 20.0, IBM).

3. Implementation of the study plan The clinical trials will be performed in 9/2020-3/2022. The statistical analyses, data management, search for literature, and manuscript(s) will be performed in 1/2022-6/2022. The wetlab will be performed during the years 2-6 and data management & manuscripts of wetlab are performed during the years 3-9.

4. References1. Fokkens WJ, Lund VJ, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl. 2012. (23):3,1-298. Update 2020 in press.

2. Reddel HK, Bateman ED, Becker A, Boulet LP, Cruz AA, Drazen JM, et al. A summary of the new GINA strategy: a roadmap to asthma control. Eur Respir J 2015 Sep;46(3):622-639.

3. Bachert C, Akdis CA. Phenotypes and Emerging Endotypes of Chronic Rhinosinusitis. J Allergy Clin Immunol Pract. 2016; 4:621-8.

4. Albers FC, Papi A, Taillé C. et al. Mepolizumab reduces exacerbations in patients with severe eosinophilic asthma, irrespective of body weight/body mass index: meta-analysis of MENSA and MUSCA. Respir Res. 2019; 20: 169.

5. Gevaert P. Van Bruaene N. Cattaert T. et al. Mepolizumab, a Humanized anti-IL-5 mAb, as a Treatment Option for Severe Nasal Polyposis. JACI 2011.

6. Tuttle KL. Buchheit KM. Laidlaw TM. Cahi KN. A Retrospective Analysis of Mepolizumab in Subjects With Aspirin-Exacerbated Respiratory Disease. JACI in Pract. 2018. 6(3), 1045-1047

7. Kristjansson RP. Benonisdottir S. Davidsson OB. et al. A Loss-Of-Function Variant in ALOX15 Protects Against Nasal Polyps and Chronic Rhinosinusitis. Nat gen. 2019. 51 (2), 267-276

8. Noon E, Hopkins C. Review article: outcomes in endoscopic sinus surgery. BMC Ear, Nose and Throat Disorders 2016; 16:9 DOI101186/s12901-016-0030-8

9.Kowalski ML, Asero R, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. Allergy. 2013. 68(10):1219-32

10. Koskinen A, Salo R, Huhtala H, Myller J , Rautiainen M, Kääriäinen J, Penttilä M, Renkonen R, Raitiola H, Mäkelä M, Toppila-Salmi S. Factors affecting revision-rate of chronic rhinosinusitis Laryngoscope Investigative Otolaryngology DOI: 10.1002/lio2.27. 5.7.2016.

11. Hellings 2013: Uncontrolled allergic rhinitis and chronic rhinosinusitis: where do we stand today? Allergy 68 (2013) 1-7.

12. van der Veen J, Seys SF, Timmermans M, Levie P, Jorissen M, Fokkens WJ & Hellings P. Real-life study showing uncontrolled rhinosinusitis after sinus surgery in a tertiary referral center. Allergy 2017:72:282–290

13. Lund VJ and Mackay IS. Staging in rhinosinusitis. Rhinology 1993; 31:183-184.

14. Psaltis AJ, PhD; Li G, MD; Vaezeafshar R; Cho K-S, MD; Hwang PH. Modification of the Lund-Kennedy Endoscopic Scoring System Improves Its Reliability and Correlation With Patient-Reported Outcome Measures. Laryngoscope 2014; 124:2216–2223.

15. Woessner KM, White AA. Evidence-based approach to aspirin desensitization in aspirin-exacerbated respiratory disease. J. Allergy Clin Immunol. 2014, 133;1:286–287e9.

16. Esmaeilzadeh H, Nabavi M, et al. Clin Immunol. Aspirin desensitization for patients with aspirin-exacerbated respiratory disease: A randomized double-blind placebo-controlled trial. 2015; 160(2):349-57.

17. Ojala T. Ahlroos T. et al. Functional genomics provides insights into the role of Propionibacterium freudenreichii ssp. shermanii JS in cheese ripening. Int J Food Microbiol. 2017.