Research Article

Center of Excellence in Type 2 Inflammation: an Organizational Model of Multidisciplinarity Management of the Patients Affected by Type 2 Inflammation Diseases

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Abstract

Atopic diseases affect millions of patients worldwide, with the greatest impact on children and young adults. Type 2 inflammation is the underlying mechanism for the development of inflammation and barrier defect in all the atopic diseases as asthma, atopic dermatitis, chronic rhinosinusitis with nasal polyps, eosinophil esophagitis. In our practice we deal every day with a lot of patients in treatment with dupilumab for AD and we realized that almost all of these patients were affected by one or more allergic diseases. Based on this real life experience we decided to create a multidisciplinary group named "Center of Excellence: type 2 disorders" composed by a pneumologist, an allergist, an oculist, an otorhinolaryngologist, a gastroenterologist, a dermatologist, a psychiatrist / psychologist. The group's scientific and research objectives are to optimize the patient's management, to improve multidisciplinary research and to create a specialization pathway to trainee dedicated physicians qualified in type 2 disorders. We created a multidisciplinary questionnaire, the "Red Flag questionnaire", self administered to patient in order to find the presence of type 2 disorders and to orient subsequently clinical evaluations.

Keywords: Allergic diseases; Asthma; Atopic dermatitis; Nasal polyposis

1. Introduction

Atopic diseases affect millions of patients worldwide, with the greatest impact on children and young adults. They have an high public health impact and often multiple atopic conditions coexist in the same patient [1]. These considerations suggest that an integrated approach to diagnosis and treatment may be beneficial for both patients and healthcare practitioners. Type 2 inflammation is the underlying mechanism for the development of inflammation and barrier defect in all the atopic diseases as asthma, atopic dermatitis (AD), chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophil esophagitis (EE) [2].

To date it is known that two key molecules have a central role in the type II inflammation: interleukin (IL) 4 and IL 13. These cytokines facilitate the production of IgE from B cells and are also strongly associated with barrier dysfunction [3,4]. The involvement of this specific immune response allows for the premise of precision medicine to be applied to emerging treatment approaches [5,6]. For this reason a lot of new pharmacological agents direct against type 2 molecules are now on development [7]. Dupilumab, a fully human monoclonal antibody directed against the shared alpha subunit of the IL-4 receptors blocks signaling from both IL-4 and IL-13 [8]. In Italy it has been available from the end of 2018 for adult patients affected by severe atopic dermatitis and from January 2021 it is available also for patients affected by severe asthma, or nasal polyposis and adolescent patients affected by severe atopic dermatitis. Dupilumab works on several fronts and allows us to take a different approach to the patient, abandoning the treatment of a single flare and focusing on the treatment of the underlying type II inflammation in a holistic, long-term patient approach [9]. In our practice we deal every day with a lot of patients in treatment with dupilumab for AD. We realized that almost all of these patients were affected by one or more allergic diseases. Dupilumab could modify the natural history of the other associated diseases. So, we started an informal collaboration with ophtalmologists, allergologists, pneumologists, otorhinolaryngologists, psychiatrist in order to optimize the management of our patients. Based on this real life experience we decided to create a multidisciplinary group named Center of Excellence: type 2 disorders composed by a pneumologist, an allergist, an oculist, an otorhinolaryngologist, a gastroenterologist, a dermatologist, a psychiatrist / psychologist. The statistician collaborates with the group for the collection and processing of data. Each specialist provided a series of questions to be submitted to the patients at the first visit (red-flag) with the goal of identify the presence of other type II diseases.

The group's scientific and research objectives are:

1.1. Clinical aspect

- Optimize the atopic patient's journey
- Characterize the patients affected by type II inflammation on the basis of the personal features, the environment and the work conditions
- Evaluate the response to the biologic therapy in all the clinical manifestations of type II inflammation
- Optimize and standardize the red flag chart in a real life setting to achieve the best management of our patients

2. Research

- basic and clinical research, with goals for multidisciplinary activities, performing gene profiling and biomarkers studies

2.1. Education and training

- recognized program engaged in dermatology, allergy, asthma, nasal polyposis, ophthalmology and gastroeneterology with goals for multidisciplinary activity and clinical innovation. Participation in national and/or international patient registry
- create a specific specialization path in type 2 inflammation with a final certification for medical residents or postgraduates.

In the first evaluation by one of the physician of the group, a patient suspected to be affected by type 2 disease will be subjected to questionnaires for the evaluation of the "red flags" of all the other specialties. In this way we can identify the necessity for evaluation by other Physicians. Each specialist will carry out his examination by calculating the score necessary for the assessment of the severity, quality of life and trend of the disease. The first specialist who assesses the patient will ask for the following blood tests: eosinophils count, lymphocytary subpopulations (T, B, NK cells), complete liver enzymes; serum protein; serum creatinine; serum reactive C-protein (CRP); serum IgA, IgG, IgM, IgE level;, eosinophil cationic protein serum level (ECP). To enter in the multidisciplinary group a patient must have an high IgE levels and at least 2 type 2 diseases at the moment of the evaluation or in the past. Patients are considered non-eligible if are age under 14 years.

Available to the group there is a shared electronic folder with the group's documentation (red flags and questionnaires of single specialties) and a shared database to fill in for each patient. The patient accesses the multidisciplinary group after signing an informed consent, after which he/she will fill in a structured questionnaire including sociodemografics, anthropometric and lifestyle characteristics and dietary habits. Each specialist provides some visits per week available for the patients of the group. At each visit, clinical data on the course of the disease and other relevant information, will be recorded into the shared electronic database. The group meets every 2 months to take the point of the previous activity with: discussion of particular cases in sharing, criticality on database and data collection, organization of Courses and congresses, evaluation of new publications in progress.

2.2. 1a-Dermatological evaluation

The dermatologist do a complete clinical evaluation and prescribed the necessary tests as blood chemistry tests, patch test, biopsy for histological exams, cultural exams. The results of these tests allow us to confirm the diagnosis of atopic dermatitis to make a differential diagnosis with other disease, as well as lymphoproliferative disorders, contact dermatitis, psoriasis, fungal or bacterial infections When the diagnosis of atopic dermatitis is confirmed, questions are asked (red flags) to assess the presence of other type II comorbidities and then schedule the referral of the necessary specialists for their evaluation. In any case we recommend prescribing an ophthalmologic evaluation with the study of the whole ocular surface at the beginning of the treatment, because patients with atopic dermatitis frequently present ocular surface disorders (atopic keratoconjunctivitis) that are

often asymptomatic, and therefore correct therapeutic management of this problem can prevent the development of Dupilumab-induced conjunctivitis, that is one of the most common side effects of Dupilumab [10]. If the patient has comorbidities, he is sent for a check-up by a colleague in the way prescribed by colleagues and in any case after 4, 12 months and then after every 6 months from the start of biological therapy.

Subsequently, tests are carried out to establish the severity of the disease (EASI and IGA), and tests to assess the patient's emotional aspects and quality of life (NRS pruritus, NRS sleep, POEM, HADS) and Atopic Dermatitis Control Test (ADCT). If the patient is started on topical therapy, subsequent check-ups are scheduled every 4 months (3 visits per year). If the patient is started on systemic biological therapy (dupilumab), a clinical-photographic check-up is carried out at 1 month and then every 4 months. At each visit the above-mentioned follow-up tests are performed. For a better monitoring (especially the development of eosinophilia as a possible side effect), we suggest a restricted panel of blood tests at baseline 1, 4, 8 and 12 months after the beginning of treatment. This panel includes complete blood count with formula, ECP and total IgE. In the case of systemic immunosuppressive therapy, follow-ups after the first month are scheduled every 3 months.

2.3. 1b-Gastroenterological evaluation:

Complete clinical evaluation; appropriate blood tests, also to look for oesinophilia (which is unfrequent); upper gastrointestinal endoscopy with biopsies to look for number of eosinophils/HPF (in the esophagus, stomach or duodenum according to symptoms) [11-15]. When the diagnosis of oesinophilic esophagitis/gastroenteritis is confirmed, questions are asked (red flags) to assess the presence of other type II comorbidities and then schedule the referral of the necessary specialists for their evaluation. Furthermore, treatment with proton pump inhibitors and topical steroids will be evaluated. Need of esophageal dilation in eosinophilc esophagitis will be assessed [11-15].

2.4. 1c-ENT evaluation

The first ENT examination aims at detecting the presence of CRSwNP and defining the endotype based on international guide lines [16]. To do so, each patient undergoes complete ENT assessment with flexible high-definition narrow-band imaging (HD-NBI) nasal videoendoscopy (with definition of the nasal polyps score –NPS-) [17-19], SNOT-22 questionnaire [17-20], and sense of smell assessment [17-19]. Computed-Tomography (CT) scans (performed no more than three months earlier) are evaluated and the Lund-McKay score (LMS) is defined [17]. In patients with severe and resistant type 2 CRSwNP, Dupilumab treatment is proposed (if not yet ongoing). At this stage, the patients also perform the measurement of the levels of exhaled (FeNO) and nasal (nNO) nitric oxide, and nasal cytology. All the patients candidates to Dupilumab treatment are addressed to perform an ophthalmologic evaluation with the study of the whole ocular surface just before the beginning of the treatment.

Then, the patients are clinically re-evaluated every two months until six months after the first administration (then every six months), in order to assess the effectiveness and tolerability of the treatment. During each visit we determine SNOT-22, NPS scores based on flexible HD-NBI nasal videoendoscopy, and sense of smell assessment; nasal citology, and FeNO-nNO assessment are repeated 4 and 12 months after the beginning of treatment, and a restricted panel of blood tests (including complete blood count with formula, ECP and total IgE) are performed 4 and 8 months after the beginning of treatment. Low radiation cone beam CT scan (with definition of the LMS) is performed 12 months after the first administration. If the patient has comorbidities, he is sent for a check-up by a colleagues in the way prescribed by colleagues and in any case at the baseline and 12 months after.

2.5. 1d-Allergy evaluation

The first step of the allergist evaluation is a complete history and physical examination. According to data collected the allergist prescribe skin prick tests (inhalant, food and/or occupational allergens). When necessary, serum total IgE, specific IgE and IgE to recombinant proteins are measured. We determine also blood cells count, eosinophil cationic protein (ECP) and exhaled nitric oxide levels (FeNO). Patients with suspected asthma undergo pulmonary function testing (spirometry with bronchodilatator reversibility test) and, if necessary, a nonspecific bronchial challenge with methacholine. The results of these tests allow us to confirm the diagnosis of allergic asthma and/or rhinoconjunctivitis, based on international guidelines, as well as the definition of the endotype [22,25]. Two questionnaires, the Asthma Control Test (ACT) and/or the Asthma Control Questionnaire (ACQ-7) [26], are completed in asthmatic patients, and SNOT-22 [27] questionnaire in patients with rhinosinusitis with or without nasal polyps.

When the diagnosis of allergic rhinoconjunctivitis and/or asthma is confirmed, questions are asked (red flags) to assess the presence of other type II comorbidities and then schedule the referral of the necessary specialists for their evaluation. In patients with type II severe asthma and/or type II severe CRSwNP, Dupilumab treatment is proposed (if not yet ongoing) [28]. All the patients candidates to Dupilumab treatment are addressed to perform an ophthalmologic evaluation with the study of the whole ocular surface just before the beginning of the treatment. Therefore, the patients are re-evaluated after 1 month, 4, 8 and 12 months after the first administration, in order to assess the effectiveness and tolerability of the treatment. During each examination the above-mentioned follow-up tests are performed, expecially in every patient we determine serum total IgE, blood cells count, exhaled nitric oxide levels (FeNO), pulmonary function testing and the questionnaires ACT, ACQ-7 and/or SNOT-22.

2.6. 1e-Pneumological evaluation

The pulmonologist does a complete clinical evaluation and prescribes the necessary tests as blood chemistry tests (complete blood count with formula, ECP and total IgE), spirometry test with pletismografic test and DLCO and bronchodilation or bronchoprovocative challenge if the spirometry is normal, an XRay chest or Thorax CT scan, levels of FeNo on exhaled, depending on the clinical characteristics and on the history of the patient [20-24].

The results of these tests allow us to confirm the diagnosis of asthma, to make a differential diagnosis with other disease, and to evaluate the presence of a Type 2 inflammation asthma [20-24]. When the diagnosis of asthma is confirmed, a questions are asked (red flags) to assess the presence of other type II comorbidities and then schedule the referral of the necessary specialists for their evaluation. Then, depending on the results of tests and on the symptoms, the pulmonologist prescribes an inhaled therapy, which is based on inhaled corticosteroids plus a bronchodilator (LABA) and, if needed, inhaled tiotropium [20-24]. The ACT (asthma control test) will be evaluated on every visit, so the asses the real control of the disease and , if necessary, a step-up or step-down of the therapy.

2.7. 1f-Ophthalmological evaluation

The ophthalmological evaluation includes the visual acuity assessment, biomicroscopic examination of the ocular adnexa and anterior segment including the ocular surface evaluation, tonometry and fundus examination. As part of the ophthalmological visit, all patients are required to complete the Ocular Surface Disease Index (OSDI) questionnaire, a standardized evaluation scale of dry eye-related symptoms.

The following clinical procedures for ocular surface examination have been performed according to the technique and order of the tests suggested by the Tear Film and Ocular Surface Society (TFOS) Dry Eye

Workshop (DEWS) II Diagnostic Methodology Subcommittee guidelines [25-34].

This examination included a slit lamp evaluation of:

1. The lids and lid margins to identify erythema, plasticity, thickening with irregular posterior margins, notching, keratinization, scurf and telangiectasia. The presence of even one of these findings was considered pathological.
2. The conjunctiva. We used the Sullivan grading criteria for bulbar and tarsal hyperemia. Foster staging system was used to assess conjunctival fibrosis; 0= no fibrosis, 1= subconjunctival scarring and fibrosis, 2= manifest scarring with fornix shortening, 3= symblepharon, 4= ankyloblepharon and keratinization of the ocular surface.
3. The tear film breakup time (BUT), indicator of tear film stability. A BUT of <10 seconds was considered abnormal.
4. Fluorescein and Lissamine greenstaining were performed. This procedure is essential to diagnose and asses the severity of the ocular surface disease.

a. Corneal and bulbar conjunctival staining were evaluated using Oxford grading scheme

b. The upper and lower lid and lid margin staining with lissamine green were also assessed . Lid Wiper Epitheliopathy (LWE) was evaluated and graded from 0 to 3 for horizontal length and sagittal width according to the Korb scale.

c. Meibomian Gland morphology and function were evaluated according to "The International Workshop on MG dysfunction: report of the diagnosis Subcommittee"

d. Tear production. Schirmer test without anesthesia was performed, providing an estimation of stimulated reflex tear flow. A reading of <5mm was referred to as aqueous deficiency.

5. Corneal sensitivity was measured wit Cochet-Bonnet aesthesiometry.

The ocular involvement in atopic dermatitis is underestimated. All patients who are to be treated with dupilumab should undergo ophthalmological follow-up before starting therapy.

2.8. 1g-Psychiatry evaluation

The psychiatrist performs a complete clinical evaluation to make or to exclude a diagnosis of psychiatric disorders for those with relevant symptomatology in accordance to the above mentioned questionnaires. She/he will prescribe the necessary tests to eventually exclude general medical conditions (e.g. TSH for hypothyroidism) if recent evaluation is lacking. Further exams could be prescribed if the start of a pharmacological treatment is required (e.g. electrocardiografy for the beginning of a therapy with atypical antipsychotics). The severity of symptoms will be assessed by the administration of targeted rating scales such as Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Depressive Rating Scale (HDRS) for depressive symptoms, Hamilton Anxiety Rating Scale (HARS) for anxiety and Brief Psychiatric Rating Scale (BPRS) for general psychopathology [35-42].

1a-Dermatology		
Have you ever suffered from	YES	NO
● from atopic dermatitis?		
● from eczema (even localized)'		
● from itching ?		
● from itching when sweating?		
● from dry skin and needed to apply a moisturising cream ?		
● from intolerance to wool or synthetic textiles		
● from sleep disorder (problems falling asleep or waking up at night)		

Any family member has suffered or is suffering from atopic dermatitis?		
Have you ever suffered from	YES	NO
● Trouble in swallowing food?		
● Pain while swallowing?		
● Coughing or choking while swallowing food or liquids?		
● Food getting stuck in your throat or esophagus for a period longer than 30 min?		
● Had to visit the emergency room because of food stuck in your throat or esophagus?		
● Unexplained recurrent dyspepsia, nausea or vomit?		
Have you ever suffered from	YES	NO
● from chronic rhinosinusitis with or without nasal polyps?		
● from persistent nasal obstruction?		
● from smell impairment?		
Have you even undergone surgery for chronic rhinosinusitis with or without nasal polyps?		
-Any family member has suffered or is suffering from chronic rhinosinusitis with nasal polyps?		
Have you ever suffered from	YES	NO
● from allergic rhinitis and/or allergic conjunctivitis?		
● from allergic asthma?		
● from food allergy?		
● from oral allergy syndrome with fresh fruit and vegetable?		
Have you suffered or are suffering from seasonal or perennial symptoms such as nasal obstruction, nasal itching, rhinorrhea, sneezing, eye itching, watering eyes, swollen eyes, tired or sore eyes?		
Have you suffered or are suffering from coughing, wheezing, chest tightness and/or shortness of breath?		
Any family member has suffered or is suffering from allergic diseases?		
Have you ever suffered from	YES	NO
conjunctivitis ?		
red eye ?		
eyelid itching ?		
excessive tearing ?		
photophobia ?		
discomfort: computers, digital devices , tv ?		
used or using eye drops ?		
Have you ever suffered from	YES	NO
● From weezing?		
● from dry cough?		
● from chest tightness?		
● From dyspnea after a physical exercise?		
● From sudden dyspnea at rest or at night?		

Any family member has suffered or is suffering from asthma?		
1g-Psychiatry		
-Have you ever suffered from prolonged insomnia (more than 2 weeks of sleep disorders without any specific stressful situation)?		
-Do you consume alcohol? If yes, how many drinks in one week?		
- Have you ever suffered from prolonged depression that hampered your social life (e.g. staying all day in bed)?		
-Have you ever suffered from intense and prolonged anxiety regarding health,work, finance and family and interfering with your daily life activities?		
-Have you currently death ideas or have you ever thought about a plan to end your life?		
-Have you ever consumed substance of abuse (e.g. cocaine) also to alleviate symptoms?		
-Have you ever experienced some days of euphoric mood during which you spent more money or you did not need sleeping the hours you used, even working during the night?		
-Have you the sensation that strangers want to harm you?		
Notes: If the patient answers yes to any of the questions, he or she should be referred to the specialist for evaluation.		

Table 1: Red Flags: questionnaire to be done by the patient in the first visit to evaluate the presence of other disorders.

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