Sponsor: SIP/IRS – Italian Society of Pneumology / Italian Respiratory Society
Prof. Francesco Blasi
SIAAIC – Italian Society of Allergology, Asthma and Clinical Immunology
Prof. Giorgio Walter Canonica

Title: Mild/Moderate Asthma Network of Italy Observatory

Code: MANI Project

Short title: MANI real-life Perspective Observatory

Study Description

Study Type:	Observational
Estimated enrolment:	20.000 participants
Estimated number of recruiting centers:	200
Observational model:	Cohort
Time prospective:	Cross-sectional, Perspective
Official title:	Mild Moderate Italian Network Study (MANI)
Estimated study start date:	Sept 2020
End of enrollment date:	From Sept 2020 until the established sample is reached.
End of the study:	Follow-up procedures will last 10 years from the date of the last patient enrolled.

Abbreviation:

MANI: Mild Moderate Asthma Network of Italy

GINA: Global Initiative for Asthma

SIAAIC: Italian Society of Allergology, Asthma and Clinical Immunology

SIP: Italian Society of Pneumology

IRS: Italian Respiratory Society

FEV1: Forced Expiratory Volume in One Second

AQLQ(S): Asthma Quality of Life Questionnaire (Short)

ACT: asthma control test

ACQ: asthma control questionnaire

FeNO: fractional exhaled nitric oxide

CCIQ: Chronic Cough Impact Questionnaire

RAPP: Rhinitis and asthma Patient perspective

PHE-S: Patient Health Engagement

TAI: Test of the Adherence to Inhalers

INDICE

1) Background

Describing the natural history of asthma is challenging for several reasons. First of all data source is often questionable; it is matter of fact that information mainly comes from studies of patients with predominantly severe or difficult-to-treat asthma [1] rather than on milder cases; often incomplete data are retrieved from hospital, prescription and mortality; at times, general population cohort studies can be criticized for an uncertain diagnosis and poor definition of the participants and they do not always include clinically ,important variables such as lung function, daily symptoms and biomarkers. The heterogeneity of the airway diseases unified under the "asthma" label [2] makes it right of the different paths and intensity of disease progression, including lung function decline, remission, reoccurrence, morbidity and mortality [3]. Beside diseases related factors claimed as predictors of diseases worsening (long-standing disease, severe symptoms, frequent exacerbations, smoking, exposure to allergens/pollutants and occupational agents, chronic mucus hypersecretion, and high levels of AHR, IgE and eosinophils) [4] , drugs (use of SABA, controllers, OCS, etc), schedule (symptoms driven, continuous) and administration tools (device, smart inhaler, digital) can influence disease evolution as well as individual biological (comorbidities, concomitant disorders, inflammatory pattern) and sociodemographic profile (education, income, etc). Some current clinical outcomes and behavior in facing with mild/moderate asthma need to be improved. Although asthma mortality has reduced substantially over the last few decades in most countries, it still remains significant and substantially affects also mild asthmatic [5]. Furthermore, the effects of an over-reliance on inhaled short acting β2-agonists increases the risk of asthma mortality. An increased understanding that patients considered to have mild asthma, have greater morbidity than previously appreciated [6] brought GINA document to recommend the use of ICS/rapid-onset β2-agonist as a reliever medication for all patients with asthma, in preference to SABA alone [7]. Although it has been shown that even low doses of ICS reduce the risk of severe asthma exacerbations and death from asthma [8] the use of oral steroid in non-severe asthma is relevant and related to significant costs and comorbidities [9]. Finally, albeit disease control [10] is the goal of asthma management, severe exacerbations in mild asthma represent 30-40% of asthma exacerbations requiring emergency consultation [11]. The understanding of the biology and pathophysiology of mild/moderate cases need to be improved, with the identification of a number of distinct phenotypes, how it is happening in severe asthma [12]. The prevalence of asthma in Italy is estimated to be around 4%, it affects around 2,000,000 citizens. Considering the minimum treatment needed to achieve control, epidemiological studies estimate that 50-75% of patients suffer from mild asthma, 15-45% from moderate asthma and 5-10% from severe asthma. The individual burden of the pathology is strictly related to the level of control and the severity while the social and welfare burden (number of events x number of patients) of mild and moderate asthma is not second to that of severe asthma. If the latter engages more than 50% of the relative resources, the remaining 50% of them are absorbed by milder patients. The development of a long-term observation plan of a large patient population represents an unparalleled source of data for defining the most appropriate management measures.

A special population is represented by asthmatic women during pregnancy. It is well known that asthma control can change during pregnancy and that a poor asthma control can cause several maternal, fetal and perinatal pour outcomes. Nevertheless, the Global Initiative for Asthma (GINA) international guidelines do not suggest the most effective and safe interventions for managing asthma in pregnancy. We will suggest the use of a specific application for android- and iOS-based smartphones developed for asthmatic women during pregnancy, allowing a regular electronic monitoring of asthma control and adherence to anti-asthmatic treatment, then reducing asthma related risks during pregnancy and poor perinatal outcomes.

2) **Design**: A cluster-based, real world, cross-sectional perspective, observational cohort study

3) **Study objectives**

Primary Outcomes:

Perspective observation of epidemiological evolution of mild and moderate asthma

Secondary Outcomes:

- Real life assessment of control, exacerbation and PROs in patients treated with different drugs and schedule
- Asthma control in asthmatic pregnant women by means of a specific application for android- and iOS-based smartphones, in comparison with the traditional current management
- Burden of Oral Corticosteroid in Mild Moderate asthma
- SABA use in Mild Moderate asthma
- Role of in Infection & vaccination in influencing diseases outcomes and progression
- Role of Upper airways disease in influencing diseases outcomes and progression
- Device and Smart Inhalers impact on diseases outcomes and progression
- Environmental exposure in influencing diseases outcomes and progression
- Evolution of Inflammatory pattern over time and its relationship with diseases outcomes and progression
- Role of Smoke and life style on Lung function and disease progression
- Patients reported outcomes over times
- Awareness and engagement in mild moderate asthma
- Impact of Digital therapy on Disease management and outcomes
- Direct, Indirect and intangible costs of mild moderate asthma
- Cost-efficacy of mild/moderate asthma treatments and management plan
- Sociodemographic issues related to disease progression and burden

4) **Eligibility**

Ages Eligible for Study: 18 Years to 99 Years (Adult)

Sampling Method: Non-Probability Sample

Sexes Eligible for Study: All

Sample distribution: National

Inclusion Criteria

Adult patient

Asthma diagnosis according GINA 2020 algorithm (Annex 1)

Patients enrolled in other previous or ongoing observational studies

Exclusion Criteria

- Severe asthma patients according International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Kian Fan Chung, KF et Al. European Respiratory Journal Feb 2014, 43 (2) 343-373; DOI: 10.1183/09031936.00202013 (Annex 2)

- Subjects are excluded from this cohort if they exhibit interstitial lung diseases, pulmonary neoplasms, current lung infections, immunological disorders leading to the use of immunosuppressants or continuous treatment with oral steroid.

5) Study Procedures

To represent real-world mild moderate Italian asthmatics, all adults with diagnosed asthma by specialist, according GINA document, attending respiratory or allergy clinic for a scheduled visit are eligible for study enrollment. If inclusion/exclusion criteria are satisfied, a written consent to participate in the study will be obtained and an informative leaflet for the patient and his/her GPs will be delivered.

Subjects follow up will be scheduled according with GINA document and center plan. (6 or 12 months follow up visit).

The researchers will gather history, asthma features, comorbid diseases, as well available results of spirometry and imaging. Questionnaires regarding subjects' baseline characteristics, self-rating of asthma control, and laboratory tests for allergy and airway inflammation will be collected at the time of enrollment. Follow-up data regarding asthma control, lung function, and environmental questionnaires will be collected at least every 6-12 months to assess outcome and exacerbation-related aggravating factors.

The information collected in the CRF coincides with the patient data routinely reported in the medical record. Information relating to the first visit and subsequent visits carried out according to the doctor's instructions will be transferred to the web platform reserved for data collection (REDCAP), accessible from the MANI project website. The transfer of data from the medical record to the platform is carried out by the doctor who manages the therapy.

In case of a blood draw for routine clinical practice, a blood sample will be acquired and stored to assess biomarkers currently under investigation.

Description of the APP for asthmatic pregnant women.

The application for smartphone will include a first page in which the main complications that may occur in asthmatic patients during pregnancy, as well as the effect of a correct asthma management on natal and perinatal outcome, will be discussed.

The second page is related to the monitoring of asthma control and is composed by:

- Asthma control questionnaire-6 (ACQ6) section with the specific questions of asthma control that each patient must complete every week

- An asthma control test (ACT) questionnaire to complete the test questionnaire every month. We will use a specific asthma control test validated for pregnant asthmatic women (7)

- An automatic message will be sent to the referral pulmonologist in case of an ACQ score higher than 1.5 and/or ACT lower than 20.

- The pulmonologist will contact the patient to organize a visit.

The third page is dedicated to improving the compliance to inhaled therapy. The patient will sign off the treatment and receive a message to remember to take therapy at the specified time(s) of the day.

In this section the patient will also report also the use of rescue medication.

In the fourth page, the principal drugs that may be used during pregnancy for respiratory problems will be reported: oral and inhaled corticosteroids, bronchodilators, antileukotrienes, antihistaminic, antibiotics, AIT (allergic immunotherapy) and omalizumab or other biologic drugs.

In this section the patient can send a message to the physician to ask information about drugs not included in this list.

Finally, the fifth page contains a pollen calendar to help patients with allergic asthma to use antihistaminic treatment or local therapy for allergic symptoms related to pollen concentration in a specific Italian region (screenshot of the APP)

6) List of information to be collected

The data collection form at enrolment and follow-up visits will include:

• ✓ anthropometric characteristics (age, height, gender, body mass index);

• ✓ clinical features (allergies, respiratory function, presence of comorbidities, need for hospitalizations and / or access to the emergency room in recent years);

• ✓ asthma control level in the last month (according to ACT);

• ✓ presence of elements of possible future risk, as recommended by the GINA Guidelines;

• ✓drugs doses and schedules of maintenance and on-demand drug treatment;

• ✓drugs doses and schedules of maintenance and on-demand drug treatment for the treatment of comorbidities (rhinosinusitis, EJN, etc.);

• ✓ reporting and classification of adverse reactions during treatment with traditional drugs;

• ✓ Indicators of systemic and local inflammation (i.e. blood and eosinophilia);

• ✓ Indicators of systemic and exhaled nitric oxide (FeNO);

• ✓ AQLQ (S) Quality of Life questionnaire for Asthmatics which must be completed by the patient without the help of family members or medical or nursing staff in the clinic;

• ✓ Asthma Control Test which must be completed by the patient without the help of family members or medical or nursing staff in the clinic;

• ✓ Patient reported outcomes questionnaires (Chronic Cough Impact Questionnaire – CCIQ; Rhinitis and asthma Patient perspective – RAPP; Patient Health Engagement (PHE-S); Test of the Adherence to Inhalers (TAI).

7) Pharmacovigilance

Data on the frequency and grading of immediate and delayed local and systemic adverse reactions related to the administration of drugs will be collected, and the consequent therapeutic conduct will also be recorded. In agreement with current legislation on pharmacovigilance, including the rules of Good PharmacoVigilance Practice, GVP, in the field of non-interventional studies, the natural person in charge of conducting the clinical study (Investigator) is responsible for the prompt communication to the competent Authorities of all adverse events relating to the conduct of the Observational Study, similarly to the provisions of the rules in force for spontaneous reporting (post-marketing). The Promoter will ask the Investigator to be made aware of such adverse events and, in turn, the Promoter will take care of promptly communicating to the Lender any significant safety issues that may be related to drugs marketed by the Lender himself. The Promoter guarantees to the Lender the fulfillment by the Investigator of the obligations referred to in this

paragraph and undertakes more and more towards the Lender to prepare adequate contracts with the Investigator for this purpose. (Guidelines for the classification and conduct of observational drug studies, Official Gazette No. 76 of March 31, 2008).

8) Study duration

Patients will be enrolled from September 2020 until the established sample is reached. Follow-up procedures will last 10 years from the date of the last patient enrolled.

9) Data management

An ad hoc CRF on the web platform REDCAP has been created (see appendix 1). Each center involved has a user and password with which it can access a reserved area of the web application. Authentication is secure thanks to an https connection that encrypts the user and password. The passwords of each center are automatically stored in the database with MD5 coding. The web application is protected by SQL, therefore it is not possible to evade the authentication system or to return data other than that which the application can return. A center cannot in any way display sensitive data from another center. Each patient registered in the database is assigned a unique ID number, an identifiable code is used only by the doctor who has it in therapy by entering only the first three letters of the name followed by the first three letters of the surname, the date of birth, the gender, the province of residence in the form of a cadastral code. Sensitive patient data can be viewed/edited only from the reserved area of the center that is treating him. Each center has the possibility to view the clinical data of its patients and only elements of general descriptive statistics (number of patients entered) of the other centers that share the platform.

10) Statistical analysis

The qualitative variables will be described by absolute and relative frequencies (percentages), while the quantitative variables will be synthesized by means (standard deviations) or medians (interquartile ranges) on the basis of their parametric and non-parametric distribution, respectively. The primary outcome of the incidence of evolution of the forms of asthma will be calculated by punctual and interval estimation (95% confidence intervals) and asthma severity was defined according GINA document and already developed study[14] The role of demographic, clinical and epidemiological variables will be assessed by means of Cox proportional regression models in the evolution of asthma. The statistical software STATA 16 (StatsCorp, Texas, US) will be used for descriptive and inferential analyzes. Based on bibliographic reference [15], a number of 667 subjects were assumed for the entire cohort for an estimated incidence of 8% for the primary outcome in the cohort, with beta error equal to 0.1 and alpha error equal to 0.05.

11) Ethical issues

The latest revision of the Helsinki declaration as well as the Oviedo declaration are the basis for the ethical conduct of the study.

The study protocol is designed and will be conducted to ensure adherence to the principles and procedures of Good Clinical Practice and to comply with Italian laws, as described in the following documents and accepted, with their own signature, by the study investigators:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.

2. Directive 91/507 / EEC, The Rules Governing Medicinal Products in the European Community.

3. Italian Legislative Decree No. 211 of June 24, 2003.

4. Italian Legislative Decree No. 200 6 November 2007.

5. Italian Ministerial Decree December 21, 2007.

12) Discussion

Based on the assumption that asthma is heterogeneous and each subject exhibits a different subset of risk factors for asthma exacerbation, as well as a different disease progression, the MANI study aims to identify mild/moderate asthma clusters on the basis of sociodemographic data, clinical data and PROs.
The study results may suggest cluster-specific strategies by focusing on subjects' personalized aggravating factors during each exacerbation episode and by focusing on disease progression.
GINA 2020 provides a new approach for the management of mild asthma. As recently underlined by Boulet at al[16] despite relevant advances in asthma care, several research gaps need to be addressed through clinical research. Longitudinal real life studies will be will be of exceptional importance for providing information on the translatability of clinical research results, on long-term efficacy of currently recommended strategies and on ability to intervene on disease evolution.

Keywords: Asthma, Adult, Cluster, Cohort study, Italy, Prospective.

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