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Original Research

Biologicals decrease psychological distress, anxiety and depression in severe asthma, despite Covid-19 pandemic

Vincenzo Patella [a,b,*], Corrado Pelaia [c], Roberta Zunno [a], Girolamo Pelaia [c]

[a] Department of Internal Medicine ASL Salerno, "Santa Maria della Speranza" Hospital, Salerno, Italy
[b] Postgraduate Program in Allergy and Clinical Immunology, University of Naples Federico II, Naples, Italy
[c] Respiratory Medicine Unit, University "Magna Græcia" of Catanzaro, Catanzaro, Italy

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ABSTRACT

Patients with respiratory diseases suffer more from problems of severe psychiatric comorbidity than the general population. Asthma might cause psychiatric disorders and affect patients' quality of life negatively. Previous studies reported that mental disorders prevail in asthmatic patients, causing anxiety, depression, and suicidal risk. The aim of this study is to evaluate in real life the prevalence of psychological comorbidities in asthmatics with severe asthma treated by biologicals (Benralizumab, Mepolizumab, Omalizumab). This study starts with the hypothesis that psychological distress, anxiety, depression and suicidal risk in severe asthma patients decreases if treated by biologicals. This study involves a sample of 90 patients (32 males, 58 females and aged 53.92 ± 15.92) suffering from severe asthma and treated with the biological drugs of Benralizumab, Mepolizumab, Omalizumab during Covid-19 pandemic. At the beginning of the treatment (T0) and after 16 weeks (T1), there have been reported results from both clinical disease control, assessed using the ACT, and psychological disorders, assessed with the PSS, HADS and C-SSRS. In the sample of these patients treated with biologicals for severe asthma, the study reported a significant change in all observed parameters, including asthma control (ACT), stress (PSS), anxiety (HADS-A) and depressive symptoms (HADS-D, despite Covid-19 pandemic. In addition, there was a significant improvement in disease management, perceived stress, anxiety and depressive symptoms after a 16 week treatment for severe asthma, independent from the type of biologic drugs used during the pandemic.

1. Introduction

Multiple epidemiological studies have shown that patients with asthma and other respiratory conditions suffer from a higher frequency of psychiatric comorbidities compared to the general population [1–4]. Previous studies and research have highlighted that asthmatic patients suffer from a significant presence of mental disorders, in particular, anxiety, depression, and suicidal risk [5–9,12]. Observational studies in different populations have documented that anxiety and depression are prevalent in patients with asthma and are associated with a higher frequency of exacerbations, increased health care facilities and a worse symptom control [10–18]. Since asthma symptoms might mimic anxiety, asthmatic patients sometimes experience cognitive reactions that can lead to anxiety, especially among the so-called "hyper-perceptors". As a result, asthmatic patients may have a higher incidence of anxiety compared to the general population. Asthmatic patients, who are aware that they have an anxiety-depressive syndrome might, incorrectly, perceive normal asthma symptoms as hyper symptoms of asthma instead. This inaccurate perception of symptoms has negative consequences on the patient's health and their ability to manage their disease, such as inappropriate use of drugs, disproportionate access to healthcare facilities and mortality [19].

Additional research in this specific medical area has focused on the role of stress in the pathophysiology of asthma. In particular, the activity of the hypothalamus-pituitary-adrenal axis and the autonomic nervous system may partially depend on allelic variations in the genes being regulated by the response to psychological stress [20,21]. The key mediators in the neuro-immune interactions are neurotrophin and neuropeptides, which are secreted from the airway nerves in response to brain signals, thus confirming that asthma is an airway inflammatory disease affected by neurological and psychological factors [22].

Clinically, it's essential to provide asthma patients with an optimal

* Corresponding author. Director of Internal Medicine, Department and Division of Allergy and Clinical Immunology, Ospedale Santa Maria della Speranza di Battipaglia – Via Fiorignano, 1 - Battipaglia, 84091, SA, Italy.
E-mail address: info@allergiasalerno3.it (V. Patella).

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medical care, including treatments of possible psychiatric disorders, since an accurate diagnosis of anxiety, depression and treatment of these disorders can effectively improve disease outcomes.

During the SARS-CoV-2 pandemic, numerous studies related to the impact of Covid on the management of the patient with asthma have been published [23,24]. Previous studies have already documented a significant increase in patients with asthma at risk of experiencing depressive symptoms, insomnia, perceived stress, post-traumatic stress disorder [25–27], and that longer lasting psychological distress and depression are the risk factors for respiratory tract infections, including the SARS-CoV-2 virus [28]. Recent studies show an increase in anxiety and depression during Covid-19 in asthmatic patients, which was not present in non-asthmatic individuals [29,30]. Therefore, the final data suggest that it is essential to assess and to manage psychological distress among patients with asthma in order to reduce the risk of disease exacerbation and to improve their quality of life.

The aim of this study is to evaluate in real life the prevalence of psychological distress, anxiety, depression and suicidal risk in asthma patients with severe asthma treated with biologicals (Benralizumab, Mepolizumab, Omalizumab), considering the effects of the Covid-19 pandemic too.

This study starts with the hypothesis that psychological distress, anxiety, depression and suicidal risk in severe asthma patients decrease if treated by biologicals.

This analysis, therefore, represents the first observational study on psychological stress, anxiety, depression and suicide risk in patients with severe asthma and treated with the biological drug Benralizumab, Mepolizumab, Omalizumab during the SARS-CoV-2 pandemic.

2. Materials and methods

The study involved 90 patients (32 males, 58 females; aged 53.92 ± 15.92) (Table 1) suffering from severe asthma and treated with the following biological drugs: Benralizumab, Mepolizumab and Omalizumab. These patients were enrolled between the second half of 2020 and the first half of 2021 at two Italian centres during Covid-19 pandemic. The first centre is the G.O.I. of Allergology, Business Centre for Allergic and Immunological Diseases and Psocare/Atopic Dermatitis Business Centre, of the U.O.C. of Internal Medicine of the P.O. of Battipaglia, ASL Salerno and the second centre is the U.O.C. of Pneumology of the Mater Domini University Hospital of Catanzaro. Clinicians made the choice of the type of drug treatment at their discretion.

The sample comprises 33 patients (12 males, 21 females and aged 52.24 ± 20.05) treated with Omalizumab at a dose of 2 vials of 150 mg subcutaneously (SC) every 4 weeks, 30 patients (12 males, 18 females and aged 55.67 ± 11.53) receiving Benralizumab at a dose of 30 mg subcutaneously (SC) every 4 weeks for the first three doses, then every 8 weeks thereafter and 27 patients (8 males, 19 females aged 54.04 ± 14.73) having Mepolizumab at a dose of 100 mg subcutaneously (SC) every 4 weeks.

Table 1
Baseline demographic and disease characteristics of patients.

Characteristic	Patients, No (%)		
	Benralizumab (n = 30)	Mepolizumab (n = 27)	Omalizumab (n = 33)
Sex			
Male	12 (40)	8 (29.63)	12 (36.36)
Female	18 (60)	19 (70.37)	21 (63.63)
Age, mean (SD)	55.67 (11.53)	54.04 (14.73)	52.24 (20.05)
Disease duration since diagnosis, mean (SD)	18.25 (9.64)	21.59 (16.10)	24.64 (14.79)
IgE, mean (SD)	614.30 (737.48)	1071.75 (1524.02)	1430.67 (1061.45)
EOS, mean (SD)	1815.71 (960.62)	1185.70 (1035.43)	1247.74 (1292.96)
FEV1, mean (SD)	970.76 (928.18)	1128.64 (704.60)	1054.77 (803.78)

This table presents the analysis of the clinical and psychological parameters of the population of interest. The examination of the clinical parameters was completed by using the tool of the Asthma Control Test (ACT) to assess the control of asthma symptoms on patients. The investigation of the psychological parameters was completed using the tools of HADS, PSS, and C-SSRS.

There was a subsequent collection of data on physical and psychological parameters at baseline (T0) and after 16 weeks of treatment with biologics (T1) for all patients that started their treatment with biologics before the SARS-CoV-2 pandemic and completed 16 weeks of treatment during the pandemic. We developed a qualitative interview based on 4 questions which was administered to the same patients during psychological counselling to explore the impact of Covid-19 on asthma.

2.1. HADS - Hospital anxiety and depression scale

The Hospital Anxiety and Depression Scale (HADS) is a self-administered questionnaire developed by Zigmond and Snaith in 1983 [31] and aims to identify states of anxiety and depression in patients suffering from organic diseases. Since its initial validation, HADS has been used in both cross-sectional studies to compare patient subgroups for screening and in longitudinal studies. This tool is made of 14 items related to the person's global distress (HADS-T) plus two subscales comprising 7 items each, one scale that evaluates anxiety symptoms (HADS-A) and the other scale indicative of the presence of depressive symptoms (HADS-D). For each statement, each patient has to choose between four options to better describe their emotional state relative to the previous last one, and each response of the patient has a score ranging from 0 (absence of the symptom) to 3 (significant presence of the symptom). The total score is from 0 (the absence of global distress) to 42 (the maximum of discomfort). According to Zigmond & Snaith recommended cut-off scores are: 0–7 for not compatible cases to anxiety and depression diagnosis; 8–10 for doubtful cases of anxiety and depression; ≥11 for definite cases of anxiety and depression.

2.2. PSS - Perceived Stress Scale

The Perceived Stress Scale (PSS) is a self-administered questionnaire developed by Cohen in 1983 [32] and in 2010 translated into Italian by Andrea Fossati of the Vita-Salute San Raffaele University of Milan. It is a scale that comprises 10 PSS items, measuring the degree to which the person perceives the situations of own life as stressful, unpredictable, uncontrollable and overloaded.

The PSS items focus on feelings and thoughts linked to the last month. For each item, a person has to show how often they felt a certain way by assigning a specific score. Scores range from 0 (never) to 4 (very often). The items are easy to understand and generally presented, free from specific content of a subpopulation. A score of 1–10 shows a good management of stressful events and adaptation to the unexpected, associated with a perceived level of stress below average. The next score of 11–14 reveals an average stress level. The last score of 15 above evidences a medium-high level of stress, especially with scores greater than or equal to 19, revealing a high level of accumulated stress with its significant influence on the body, thoughts, emotions, and behaviour.

2.3. C-SSRS - Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale (C-SSRS) is a scale made by Posner et al., In 2008 [33] to assess the severity of suicide risk in children, adolescents and adults. C-SSRS is a tool meant to be administered by clinicians through their analysis of definitions of events.

C-SSRS comprises two sections: Suicidal Ideation and Suicidal Behaviour. The first section ranks an individual's degree of suicidal ideation on a scale from one to five, ranging from a "generic desire to die" to an "active suicidal ideation with specific suicide planning and

intention". The second section identifies behaviours that could show an individual's intention to commit suicide.

There are different perspectives to be considered when committing suicide. Referring to a suicidal behaviour, a suicidal self-harm act is linked to at least a minimal intention of dying because of the self-harm act itself, even in the absence of actual injuries. Whilst a non-suicidal, self-injurious behaviour is when a person only adopts a self-injurious behaviour for other reasons not aiming to take their own life. Therefore, it is very important to evaluate separately suicidal ideation and suicidal behaviour, as it is not possible to exclude that a person who denies their suicidal ideation might carry out suicidal behaviour.

In conclusion, interviewers should complete an effective assessment of suicidal behaviours because an individual who exhibits even a single behaviour on the rating scale is eight to ten times more likely to commit suicide. To guide the interviewers, and facilitate their effective assessment, the corresponding definitions are shown for each item of the C-SSRS and standardized questions are provided for each category.

2.4. Impact of Covid-19 on asthma

The impact of Covid-19 on asthma was explored through a qualitative interview based on 4 questions administered during psychological counselling, related to the concern about Covid-19 and access to treatment and management of the disease. The questions administered were:

1. My concern about COVID-19 makes my asthma symptoms worse.
2. I am afraid of contracting COVID-19 because of my asthma.
3. COVID-19 makes it difficult for me to access the treatment service.
4. I cannot undergo regular asthma treatments because of COVID-19.

The result shows that many patients were afraid of contracting Covid-19 because of asthma. Despite this result, all patients, who had started therapy before Covid and continued their treatment with biologic drugs during the Covid-19 pandemic, stated that they had no difficulty in accessing care services and they were still able to undergo regular asthma treatments. In addition, patients reported that their concern about Covid-19 hadn't made their asthma symptoms worse because they felt protected by being treated for asthma. These patients also stated that they had got used to managing asthma in their new daily life with regards to the restrictions to contain the Covid-19 pandemic.

3. Results

Comparing the mean values of the measured parameters from T0 and T1, we used t-student test.

a. Results of Asthma Control Test and Biologic treatments

Results obtained with control test (ACT) in patients receiving biologic treatments for asthma at T0 (baseline) 12.40 ± 4.92 and T1 (at 16 weeks) 21.67 ± 3.24 for Benralizumab ($p < 0.0001$); ACT at T0 12.48 ± 2.67 and T1 20.37 ± 3.59 for Mepolizumab ($p < 0.0001$); ACT at T0 14.15 ± 3.30 and T1 21.21 ± 3.67 for Omalizumab ($p < 0.0001$). At the T1, most patients [66/90 (73,3%)] achieved a well-controlled disease activity (ACT>19).

b. The results of psychological disorders are presented through the following scales and their respective indexes (Fig. 1).

3.1. Perceived Stress Scale

Baseline PSS was evaluated for 90 patients divided into four PSS groups. Five patients (5,38%) were in PSS1, a low perceived stress group, 7 patients (7,53%) were in PSS2, a medium perceived stress group, 13 patients (13,98%) patients were in PSS3, a medium-high perceived stress and finally 65 patients (72%) patients were in PSS4, a high perceived stress group.

PSS mean values considerably differ from T0 to T1 [T0 = 23.33 ± 8.52; T1 = 12.93 ± 6.60; −10.4 (−44.57%); $p < 0.0001$]. At baseline, most patients were in the medium-high levels of perceived stress PSS3 and PSS4 [78/90 (87%)]. At T1, a considerable part of patients were in the low-medium levels of stress PSS2 and PSS1 [56/93 (60%)]. Referring to the drug treatment of these patients, 18/30 (60%) patients had a treatment with Benralizumab, 15/27 (56%) with Mepolizumab and 23/33 (70%) with Omalizumab.

3.2. Anxiety

Baseline HADS-A was assessed in 90 patients divided in three groups: 22 patients (23,66%) were in a "not compatible cases for anxiety" group (NoA), 14 patients (15,05%) were in a "doubtful case for anxiety" group (DoA) and 54 patients (60%) were in a "definite case for anxiety" group

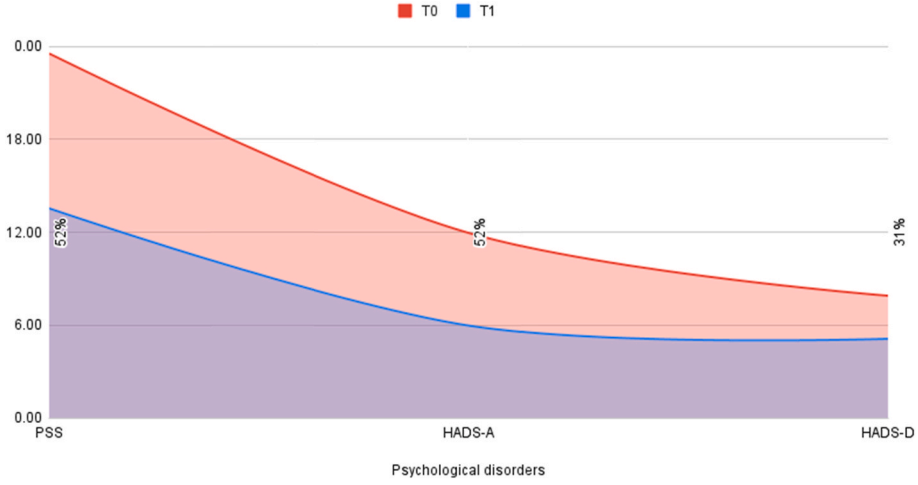

Fig. 1. *Summary of statistical data of psychological disorders*
At the beginning of the treatment (T0) and after 16 weeks (T1), psychological disorders were evaluated both using the Perceived Stress Scale (PSS) to examine perceived stress, and the Hospital Anxiety and Depression Scale (HADS-A and HADS-D, respectively) to examine depression and anxiety. Perceived Stress Scale (PSS) mean values evidenced a relevant fall from T0 to T1 (T0 = 23.33 ± 8.52; T1 = 12.93 ± 6.60; −10.4 (−44.57%); $p < 0.0001$); a little less than a half of the patients (47 of 90 [52%]) reached, at least, a medium or low level of perceived stress. The results of the Hospital Anxiety and Depression Scale-Anxiety (HADS-A) are also presented; the HADS-A mean value was almost halved from T0 to T1 (T0 = 11.58 ± 5.30; T1 = 5.59 ± 3.85; −5.99 (−47.27%); $p < 0.0001$); 47 of 90 [52%] patients, at T1, did not fit for a diagnosis of anxiety anymore. The results of Hospital Anxiety and Depression Scale-Depression (HADS-D) means considerably differed from T0 to T1 (T0 = 7.54 ± 3.13; T1 = 5.07 ± 2.85; −2.47 (−32.75%); $p < 0.0001$); many patients (28 of 90 [31%]), at T1, were not suitable anymore for a diagnosis of depression.

(DeA).

HADS-A mean halved almost its value from T0 to T1 [T0 = 11.58 ± 5.30; T1 = 5.59 ± 3.85; −5.99 (−47.27%); p < 0.0001]. Among the patients belonged to the DoA and DeA groups at baseline, 47/90 (52%) were evaluated at T1 and specifically 14/30 (47%) patients in treatment with Benralizumab, 12/27 (44%) with Mepolizumab, and 21/33 (64%) with Omalizumab.

3.3. Depression

Baseline HADS-D was rated in 90 patients divided in three groups; 54 patients (60%) were in a "not compatible cases for depression" group (NoD), 11 patients (13,98%) were in a "doubtful case for depression" group (DoD) and 25 patients (27,77%) patients were in a "definite case for depression" group (DeD). Among patients belonging to DoD and DeD groups at baseline, 47/90 (52%) were evaluated at T1 and specifically 8/30 (27%) patients in treatment with Benralizumab, 7/27 (26%) with Mepolizumab, 13/33 (39%) with Omalizumab.

3.4. C-SSRS

C-SSRS was assessed in 90 patients. Only 1 patient (1.1%) showed a suicidal risk (expressed as a suicidal ideation or a suicidal behaviour), both at T0 and T1.

We included a regression study to check the correlation between the ACT and stress, anxiety and depression scale: patients with more uncontrolled disease at baseline or less response with biologics would be expected to have worse scoring in psychological parameters. The results show that the ACT and psychological parameters have a negative correlation: an increase in the ACT is associated with a decrease in PSS, HADS-A and HADS-D. The regression model shows significant data at T1 [PSS T1 ($R^2 = 0.116$; $p = 0.001$); HADS-A T1 ($R^2 = 0.054$; $p = 0.027$); HADS-D T1 ($R^2 = 0.231$; $p < 0.0001$)] (Table 2). Data analyses were conducted with Epi Info.

4. Discussion

In this study, we observed a large sample of 90 patients that had only severe asthma and who had started their treatment with biologics before the SARS-CoV-2 pandemic and completed 16 weeks of treatment during the pandemic. Previous studies have so far shown that the pandemic has resulted in high psychological distress and symptoms of anxiety and depression, even among patients with severe asthma, which was not present in non-asthmatic individuals [29,30]. We used a qualitative interview based on 4 questions, that was administered to our asthmatic patients being treated with biologics, to explore the impact of Covid-19 on severe asthma. These results have shown a high impact in line with the data already presented in the previous studies and related literature. Interestingly, our results have shown that there has been a significant change in all observed parameters, related to both asthma control (ACT) and stress (PSS), anxiety (HADS-A) and depressive (HADS-D) symptoms (Fig. 1), despite Covid-19 pandemic. The regression model shows that the ACT is a good predictor of stress, anxiety and depression. The ACT and psychological parameters are negatively related: an increase in the control of the disease, measured by the ACT, is associated with a decrease in stress, anxiety and depression scores (Table 2). As evidenced by the responses to the qualitative interview on Covid-19, all patients continued biological therapy during the Covid-19 pandemic, probably because they can be self-administered at home. Indeed, there were no differences in the response to Omalizumab, Mepolizumab and Benralizumab.

These data are in line with our hypothesis that improvement in clinical asthma control following therapy with biologics reduces psychological stress, anxiety and depression in patients with severe asthma, despite the impact of Covid-19.

Table 2
Correlation between psychological tests and asthma control test.

ACT				
	r Correlation	95% CI	R squared	P value
T0				
PSS	−0.082	−0.284 to 0.128	0.007	0.444
HADS-A	0.017	−0.191 to 0.223	0.000	0.874
HADS-D	−0.122	−0.321 to 0.009	0.015	0.252
T1				
PSS	−0.340	−0.511 to 0.143	0.116	0.001
HADS-A	−0.233	−0.42 to 0.027	0.054	0.027
HADS-D	−0.481	−0.626 to −0.304	0.32	<0.0001

The ACT and psychologicals parameters are negatively related: an increase in the ACT is associated with a decrease in PSS, HADS-A and HADS-D.

5. Conclusions

The main results highlighted a significant improvement between T0 (baseline) and T1 (16 weeks of treatment with biologics) in terms of asthma control, perceived stress, anxiety and depressive symptoms. In addition, no significant change in the suicidal risk was shown between T0 and T1, probably because of the small size of the sample (1/90 pcs).

Further results have confirmed the hypothesis that, despite the high impact of the pandemic on asthma described in literature, all patients who had started therapy before Covid continued their treatment with biologics during the Covid-19 pandemic. It was shown that there was a significant improvement in disease management, perceived stress, anxiety and depressive symptoms, following treatment of 16 weeks with biological therapy during the pandemic, independent from the type of biologics used (Fig. 1). Our results confirm that biologicals might additionally contribute to a decrease in psychological distress, anxiety and depression.

In conclusion, it is important to highlight psychological counselling as a valuable treatment for respiratory diseases. During our study, patients were also followed through psychological support interviews since psychological counselling could itself help patients to improve the treatment of respiratory diseases. Therefore, this therapeutic option can be indeed considered in the management of asthma, in line with the most recent field research [34–36].

CRediT authorship contribution statement

Vincenzo Patella: Conceptualization, Methodology, Software, Supervision. **Corrado Pelaia:** Software, Validation. **Roberta Zunno:** Data curation, Writing – original draft. **Girolamo Pelaia:** Visualization, Investigation, Writing – review & editing.

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